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Title: Pain Responses of Pascal® 20 ms Multi-spot and 100 ms Single-spot Panretinal Photocoagulation: *MA*nchester *PAS*cal® *S*tudy, *MAPASS* report 2.

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Key words: Pascal® panretinal photocoagulation; pain responses; conventional laser; proliferative diabetic retinopathy; nociception

Word count: 2500

Abstract

Aims:

To evaluate pain responses following Pascal® 20ms multi-spot and 100ms single-spot panretinal photocoagulation (PRP).

Methods:

Single-center randomized clinical trial. 40 eyes of 24 patients with treatment-naive proliferative diabetic retinopathy randomized to 20ms-PRP and 100ms-PRP under topical 0.4% oxybuprocaine. A masked grader used a pain questionnaire within one-hour (Numerical pain score: NPS) and one-month after treatment (Numerical headache score: NHS). Primary outcome measure was NPS immediately post-PRP. Secondary outcome measures were mean NHS scores and levels of photophobia reported within 4-weeks of primary PRP.

Results:

Mean laser fluence was significantly lower using 20ms-PRP (4.8 J/cm^2) compared to 100ms-PRP (11.8 J/cm^2; $p<0.001$). Mean NPS scores for treatment were 2.4±2.3 (mild) for 20ms-PRP group compared to 4.9±3.3 (moderate) in 100ms-PRP group, a significant difference (95%CI –4.3 to -0.68;$p=0.006$). Mean NHS score within 1-month was 1.5±2.7 in 20ms-PRP group compared to 3.2±3.5 in 100ms-PRP group ($p<0.05$). The median duration of photophobia after 20ms-PRP was 3-hours, and significantly less compared to 100ms-PRP after which 72-hours of photophobia was reported ($p<0.001$).

Conclusions:

Multi-spot 20ms-PRP was associated with significantly lower levels of anxiety, headache, pain, and photophobia compared to 100ms single-spot PRP treatment. Possible

reasons include lower fluence, shorter-pulse duration, and spatial summation of laser nociception with multi-spot Pascal® technique.

Laser panretinal photocoagulation (PRP) standards for treating proliferative diabetic retinopathy (PDR) were established by the Diabetic Retinopathy Study 20 years ago. [1] The conventional long pulse durations (100-200 milliseconds,ms) used for PRP may be associated with significant pain and laser-intolerance by patients. [2]

A number of pre-laser injection strategies have been investigated. Subconjunctival and sub-Tenon injections may be effective, but sharp needle peri/retrobulbar anesthesia is rarely used due to potential sight-threatening complications. [2-5]

Oral acetaminophen, diazepam, diclofenac, mefenamic acid, and paracetamol have all been studied. [4,6,7] Entonox and intramuscular ketorolac tromethamine have also been studied pre-laser. [4,8] To date, oral diclofenac has been shown to be effective in reduction of post-laser pain response. [6] Randomized trials of pretreatment analgesia for PRP using pain scales report mean placebo group pain scores that range from 37.3 to 53.1. [4,6,9,10] Pain scores of 31-69 fall within the moderate range of pain. [11]

Recently, clinicians have undertaken conventional laser PRP parameters with reduced 50ms pulse duration. [12] Reductions in pain response have been reported with different pulse waveforms and 20ms pulse duration PRP. [13,14] The Pascal® (Pattern Scanning Laser) Photocoagulator uses a brief pulse duration combined with rapid raster scan that allows effective multi-spot applications. [15,16] Furthermore, this technique may be less damaging to inner retina with reduced collateral thermal diffusion. [17]

The conception of this study was based on the following observations: pain may reduce laser uptake during photocoagulation, pain-related anxiety post-PRP may reduce compliance and further delay application of laser in sight-threatening diabetic retinopathy, and reduced pulse laser may reduce pain.

The primary aim of this study was to compare the pain responses under topical anesthesia of multi-spot 20ms-PRP and single-spot 100ms-PRP burns in PDR. Our secondary aims included an evaluation of the characteristics of pain responses, subjective responses post-laser, and evaluation of patient's experiences related to laser-induced inflammation.

Materials and Methods

A prospective, randomized clinical trial was carried out with patients treated at Manchester Royal Eye Hospital (MREH) over a 1-year period. The study protocol received Research Ethics Committee approval, and informed written consent was obtained from all participants. Data and safety monitoring was provided by an independent panel at both the University of Manchester and the Research Office at MREH. The inclusion and exclusion criteria are outlined in Table 1.

Literature searches were carried out in the PubMed and MEDLINE databases between January 1993 and June 2009 to uncover all previously published articles describing pain modification techniques for PRP using the search terms *panretinal photocoagulation, laser photocoagulation, pain*, and *laser pulse duration.*

The randomization sequence was generated using randomly permuted blocks, and a randomization table was created for the 40 subjects. After computerized randomization procedure, sequentially-numbered, opaque, sealed envelopes were generated by the masked trial statistician. The treatment allocation envelopes remained concealed until interventions were assigned. Once a participant consented to the study, a research trial coordinator who was blinded to the treatment opened the sealed envelope and assigned participants to each group. The treatment was not blinded to the treating investigator or

study participant. Patients underwent either unilateral or bilateral PRP according to randomization treatment allocation. In cases of bilateral study eye eligibility, the right eye was randomized first with treatment allocation, followed by independent randomization and allocation of the left eye. Eyes were randomized into one of two groups, 20ms-PRP or 100ms-PRP.

The primary efficacy endpoint was the NPS score for each group immediately post-PRP. Main secondary efficacy endpoints included duration of pain responses during PRP, NHS score at 1-month, affective changes post-treatment, and levels of photophobia post-PRP.

Safety endpoints included all adverse events reported spontaneously by study participants, elicited by investigators, or observed by investigators. Adverse events were graded as mild, moderate, or severe and were assessed as being either related to the laser intervention or unrelated to the laser treatment. We recorded all serious adverse events whether deemed related to the treatment or not, as per ethical and good clinical practice.

Pre-laser anaesthesia used up to 5 drops of topical 0.4% oxybuprocaine hydrochloride applied over 5 minutes. Photocoagulation was applied using techniques outlined in Table 2 with a Mainster 165 PRP lens. Before trial commencement, two experienced retinal specialists at MREH externally validated the laser technique of the treating investigator (MM), and laser training was certified according to the study laser protocol and good clinical practice guidelines. Threshold laser burn intensity was standardized for all eyes, and this was checked at 1-hour post laser using fundus photographs.

This pain assessment was part of MREH guidelines for nurses and was adapted

from McGill Pain Questionnaire. [18] This measurement tool has been externally validated previously, and is routinely used at MREH as a reliable and sensitive measure of pain responses. [16,19] An examiner, masked to the treatment, used a standard questionnaire to assess the pain responses, characteristics of responses, and levels of affect.

Participants were asked to rate the level of pain related to the treatment session using the numerical pain scale (NPS). The NPS allows the patient to rate the pain intensity on a numbered scale, from 0 to 10. Zero is absence of pain, 1-3 is mild pain, 4-6 is moderate pain, and 7-10 is designated severe pain. In subjects undergoing multiple-session PRP, we recorded the mean NPS score over 3 treatment sessions. The duration of pain responses was reported using a 3-point scale: first half of treatment, second half of treatment, and full duration of treatment.

The laser illumination lamp intensity was adjusted to minimise unnecessary photophobia or discomfort. For patients receiving bilateral PRP, the first eye was treated followed by pain assessment, and after a delay, the second eye was treated followed by pain assessment. This method ensured that treatment of second eyes did not elicit an exaggerated or diminished pain response depending on the nature and fluence of the first eye's treatment.

At one-month post-PRP the same masked examiner carried out a second questionnaire-based interview to assess headache responses, and used a numerical headache scale (NHS), analogous to the NPS. Patients were asked about presence of photophobia, photopsia, and affective responses (anxiety, mood disturbances) within the preceding 4-weeks. The responses were recorded as increased, reduced, or unchanged compared to the day of primary PRP laser. We scored these responses using the ratio of

increased versus decreased responses as the (I:R) ratio.

We performed statistical analyses using STATISTICA version 6 (StatSoft, Inc [2003], www.statsoft.com). We used the 2-tailed *t* test to explore mean NPS and NHS scores, and duration of photophobia following treatment at specified time-points. The null hypothesis was rejected for P values less than 0.05.

The sample size was based on the following assumptions: the test of significance should be 2-sided, with a significance level of 5%. Using a standard deviation of 2.0, if the true difference in the mean NPS response of matched pairs is 1.5, we will need to study 20 pairs of subjects (20 experimental and 20 control subjects) to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. A 1.5-point mean NPS difference was chosen since this represented a realistic value within the ranges of pain scores published in the literature for laser PRP studies to achieve significance. [6,7,9,10]

Results

A total of 40 eyes of 24 patients (20 in each arm) were recruited into the study between June 23rd 2008 and July 10th 2009 (Figure 1). Complete data capture from study questionnaires were obtained for 40 eyes all visits. The age profiles were similar in both groups with mean 46 years. No patient required additional PRP treatment within 1-month of the primary PRP. Patient demographics and laser parameters are presented in Table 3.

Examples of threshold laser burns intensities at 1-hour are shown in Figure 2. Laser fluence was significantly greater in 100ms-PRP compared to 20ms-PRP (average values 11.8 and 4.8 J/cm^2; p=0.0001), however the intensity of photocoagulation burns was

equivalent in both groups.

The mean NPS score immediately post-laser was 2.4 ± 2.3 for 20ms-PRP group, compared to 4.9 ± 3.3 (100ms-PRP) categorized as moderate severity of pain (Figure 3).[11] The pain following multi-spot 20ms-PRP was mild, and this was significantly lower than the single-spot 100ms-PRP (95% CI –4.3 to -0.68; p=0.006). The mean NHS score within one month of treatment was 1.5 ± 2.7 in the 20ms-PRP group compared to 3.2 ± 3.5 (100ms-PRP group, Figure 4). The difference in NHS scores between groups was significant (95% CI –3.7 to 0.3; p=0.045).

During treatment, the mean contact lens-related NPS score was 3 in 4 eyes (20%) for 20ms-PRP group, and mean NPS was 6 in 4 eyes (20%) for the 100ms-PRP group. Pain related to the laser contact lens was reported in 20% total study eyes, and this source of pain was reported as either a “gritty” or “foreign-body” sensation in all cases. The characteristics of side-effects related to pain responses are presented in table 4. As shown in table 2, subjects in 100ms-PRP group reported significantly increased levels of anxiety compared to Pascal® 20ms-PRP treatment ($p<0.05$). At 1-month, patients in both arms reported equivalent anxiety and mood changes, related to apprehension regarding the future beneficial outcomes of laser treatment rather than any pain responses.

Pain responses reported by group 20ms-PRP occurred during the first half of treatment in 11 (55%) and during the full duration in 3 (15%). In the 100ms-PRP group, pain responses were reported to last the full duration of treatment in 16 eyes (80%). The remainder did not report any pain during treatment (30% 20ms-PRP, 20% 100ms-PRP).

The data for levels of photophobia reported within 1-month of PRP in both groups was skewed, and median values were analyzed for comparison to achieve a better central

tendency than arithmetic mean scores (Table 5). Median duration of photophobia after 20ms-PRP was 3 hours, and this was significantly less compared to 100ms-PRP (72 hours, $p<0.001$). The effects of PRP on driving and work performance, reading ability, watching television, and navigation during night-time did not show any significant differences or results between either group (Table 5). There were no significant differences in physiological responses designated by I:R ratios for either treatment group.

There were no ocular complications during the immediate or short-term, and no reported adverse or serious adverse events. In the 20ms-PRP group, there were no signs of intraretinal haemorrhage or blood vessel damage from photocoagulation burns.

Discussion

Our results have demonstrated that single-session, multi-spot 20ms-PRP using topical 0.4% oxybuprocaine is significantly more comfortable for patients with PDR compared to conventional multiple-session 100ms-PRP.

Although the retina is devoid of pain sensitivity, ocular pain and photophobia are frequently reported post-laser. Laser-induced eye nociception may be related to thermal effects within choroid, stimulation of ciliary nerves within suprachoroidal spaces, thermal diffusion to nerve fiber layer, or perhaps direct photocoagulation of the long posterior ciliary nerve. [20]

Laser photocoagulation may produce a thermal rise in outer retina. Leukocyte-endothelial cell interactions can lead to inflammatory maculopathy post-PRP in animal models, with increased cytokine release and retinal capillary hyper-permeability. [21] Recent work with rabbit retina demonstrated that 100ms pulse duration burns produced full-thickness retinal injury on pathological sections. [22]

Laser photocoagulation may stimulate ocular nociception through inflammatory, mechanical, and thermal stimulation. A significantly higher fluence was required for 100ms-PRP that will produce higher levels of intraretinal inflammation. Longer standard pulse duration was associated with higher pain scores and greater photophobia post-laser. Local ocular inflammatory responses may enhance outer retinal neurogenic inflammation in ocular nociceptive terminals and higher order neurons. [20]

The conventional 100ms-PRP produced pain for the full duration of PRP, whereas the multi-spot Pascal® 20ms pattern arrays triggered pain responses during the first half of PRP. This temporal aspect of pain may be related to spatial summation of pain associated with shorter-pulse Pascal®. A 20ms pulse reduces the time required for intraretinal tissue thermal changes to occur. Better localisation of 20ms burns within outer retina will minimise heat diffusion towards the retinal nerve layer and choroid. [17] Furthermore, the 1.5 burns spot-spacing means each 20ms burn within the array is applied to the retina in a scatter technique. The Pascal® rapid raster application of multiple spots may lead to habituation of pain associated with the laser arrays during PRP. The interactions between these spatial summation and temporal aspects of repetitive noxious stimulation have been studied in skin. [23] A shorter stimulus duration has been shown to reduce nociceptor activation times and produce a stronger spatial–temporal summation at central synapses. [24]

The pain scores reported by Al-Hussainey and co-workers were better than our NPS scores for 20ms and 100ms photocoagulation, although far less laser burns were used in their study and a single eye received two different types of laser that would confound the overall perception of pain by the patient. [14] The mean age of patients and the laser power

parameters for the 100ms group was higher compared to our study. We found no correlation between NPS and NHS scores and age or sex. Higher fluence laser in an older age-group with less retinal pigmentation may explain the differences between pain scores in both studies. The pain responses demonstrated in our study are more closely related to clinical practice, as 1500 burn PRP is within ETDRS recommendations for treatment. Previous PDR studies have not as yet studied physiological, psychological, and spatial-temporal effects of retinal laser photocoagulation at different pulse durations.

Our study did not demonstrate any significant effects or differences between 20ms and 100ms PRP on physiological aspects of pain. Depressed mood and anxiety was reported in 10-20% of patients in both laser groups, and photopsia was problematic in 25% cases following 100ms-PRP. At home, patients reported no significant impairment of reading and television tasks, with similar and equivalent responses when either navigating at night or driving. Our small sample size may explain the difficulty in associating any physiological responses with different PRP techniques.

The main limitations of our study include the absence of conventional argon laser (514nm) PRP as a comparative group. However the Pascal® system (532nm) allows 100ms burns in single-spot mode, and we used a single laser system with standard illumination and optical apparatus for both arms of the study. It may be questionable as to the exact source of pain during the laser treatments. Patients reported any discomfort from the laser illumination source at the onset of laser titration before the PRP had commenced, and light intensity was adjusted accordingly until patients were comfortable and able to fixate with the fellow eye during the PRP. There were no reports of increased discomfort or pain associated with the multiple aiming beams of the multi-spot Pascal®

raster patterns. Pre-laser topical anaesthesia minimised any surface discomfort from the contact lens, and pain related to contact lens was reported in only 20% of all eyes.

Multi-spot 20ms-PRP laser under topical 0.4% oxybuprocaine is associated with significantly lower levels of anxiety, headache, pain, and photophobia compared to single-spot 100ms-PRP treatment. This may be explained by a combination of lower fluence, shorter-pulse duration, and spatial summation of laser nociception.

Competing interests: GR Marcellino is an employee of Optimedica Corporation. PE Stanga has received financial support from Optimedica Corporation

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References

1. **Diabetic Retinopathy Study Research Group**. Photocoagulation treatment of proliferative diabetic retinopathy. The second report of diabetic retinopathy study findings. *Ophthalmology* 1978; **85**: 82-106.

2. **Royal College of Anaesthetists and the Royal College of Ophthalmologists**. Local Anaesthesia for Intraocular Surgery. RCA, RCOphth: London 2001.

3. **Stevens JD**, Foss AJ, Hamilton AM. No-needle one-quadrant sub-tenon anaesthesia for panretinal photocoagulation. *Eye* 1993; **7(6)**: 768-71.

4. **Wu WC**, Hsu KH, Chen TL et al. Interventions for relieving pain associated with panretinal photocoagulation: a prospective randomized trial. *Eye* 2006; **20(6)**: 712-9. Epub 2005 Jul 8.

5. **Hay A**, Flynn HW Jr, Hoffman JI, Rivera AH. Needle penetration of the globe during retrobulbar and peribulbar injections. *Ophthalmology* 1991; **98**: 1017–24.

6. **Zakrzewski PA**, O'Donnell HL, Lam WC. Oral versus topical diclofenac for pain prevention during panretinal photocoagulation. *Ophthalmology* 2009; **116**: 1168–74.

7. **Vaideanu** D, Taylor P, McAndrew P, Hildreth A, Deady JP, Steel DH. Double masked randomised controlled trial to assess the effectiveness of paracetamol in reducing pain in panretinal photocoagulation. *Br J Ophthalmol* 2006; **90**: 713-7.

8. **Cook HL**, Newsom RSB, Mensah E, Saeed M, James D, Ffytche TJ. Entonox as an analgesic agent during panretinal photocoagulation. *Br J Ophthalmol* 2002; **86**: 1107-8.

9. **Weinberger D**, Ron Y, Lichter H, et al. Analgesic effect of topical sodium diclofenac 0.1% drops during retinal laser photocoagulation. *Br J Ophthalmol* 2000; **84**: 135-7.

10. **Esgin H**, Samut HS. Topical ketorolac 0.5% for ocular pain relief during scatter laser

photocoagulation with 532 nm green laser. *J Ocul Pharmacol Ther* 2006; **22**: 460-4.

11. **Kelly AM**. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? *Acad Emerg Med* 1998; **5**: 1086-90.

12. **Diabetic Retinopathy Clinical Research Network**, Brucker AJ, Qin H, et al. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol* 2009; **127(2)**: 132-40.

13. **Friberg TR**, Venkatesh S. Alteration of pulse configuration affects the pain response during diode laser photocoagulation. *Lasers Surg Med* 1995; **16(4)**: 380-3.

14. **Al-Hussainy S**, Dodson PM, Gibson JM. Pain response and follow-up of patients undergoing panretinal laser photocoagulation with reduced exposure times. *Eye* 2008; **22(1)**: 96-9. Epub 2007 Nov 23.

15. **Blumenkranz MS**, Yellachich D, Anderson DE, et al. New Instrument: Semiautomated Patterned Scanning Laser for Retinal Photocoagulation. *Retina* 2006; **26**: 370-5.

16. **Sanghvi C**, McLauchlan R, Delgado C et al. Initial Experience with the Pascal® Photocoagulator: a Pilot Study of 75 Procedures. *Br J Ophthalmol* 2008; **92**: 1061-4.

17. **Muqit MMK**, Gray JCB, Marcellino GR et al. Fundus Autofluorescence and Fourier-Domain Optical Coherence Tomography Imaging of 10 and 20 millisecond Pascal® Retinal Photocoagulation Treatment. *Br J Ophthalmol* 2008; **93(4)**: 518-25. Epub 2008 Dec 15.

18. **Melzack R**, Wall PD. Textbook of Pain. 5th ed. Churchill Livingstone, 2005: 1-1280.

19. **Mc Caffery M**, Pasero C. Pain: Clinical Manual.2nd ed. St. Louis, MO: Mosby 1999.

20. **Belmonte C**, Garcia-Hirschfeld J, Gallar J. Neurbiology of ocular pain. *Prog Ret Res* 1997; **16(1)**: 117-56.

21. **Nonaka A**, Kiryu J, Tsujikawa A et al. Inflammatory response after scatter laser photocoagulation in nonphotocoagulated retina. *Invest Ophthalmol Vis Sci* 2002; **43**: 1204-9.

22. **Paulus YM**, Jain A, Gariano RF et al. Healing of retinal photocoagulation lesions. *Invest Ophthalmol Vis Sci* 2008; **49(12)**: 5540-5.Epub 2008 Aug 29.

23. **Defrin R**, Pope G, Davis KD. Interactions between spatial summation, 2-point discrimination and habituation of heat pain. *European Journal of Pain* 2008; **12(7)**: 900-9.

24. **Iannetti G**, Leandri M, Truini A, Zambreanu L, Cruccu G, Tracey I. A delta nociceptor response to laser stimuli: selective effect of stimulus duration on skin temperature, brain potentials and pain perception**.** *Clin Neurophysiol* 2004; **115(11)**: 2629-37.

Legends:

Figure 1: Consort flow chart of study

Figure 2: Appearances of threshold laser photocoagulation burns at one hour post-laser. (A) Pascal ® single-session with 4x4 array, and (B) single-spot multiple session PRP laser applications.

Figure 3:

Title: Numerical Pain Scale Scores Immediately after Treatment

y-axis: Numerical Pain Scale (0-10)

Footnotes: Grade of pain scores-0, absent; 1-3, mild; 4-7, moderate, 8-10, severe

Figure 4:

Title: Numerical Headache Scores One Month after Treatment

y-axis: Numerical Headache Scale (0-10)

Footnotes: Grade of headache scores 0, absent; 1-3, mild; 4-7, moderate, 8-10, severe

Table 1. Study Eye Major Inclusion and Exclusion Criteria

Inclusion Criteria

• Older than 18 years of age
• Male or female patients with diabetes mellitus type I or type 2 who meet the WHO or ADA criteria for diabetes
• ETDRS visual acuity between 35 and 85 letters (Snellen equivalent of 6/60 or better).
• Newly diagnosed PDR
• Mean CRT of less than 300 microns as measured by OCT scans with absence of intra and/or subretinal fluid
• Adequate pupil dilatation and clear media to perform laser photocoagulation, digital photography and OCT scans
• Ability to perform accurate Humphrey visual field test
• If both eyes are eligible, then both eyes will be randomized as per protocol and treated independently

Exclusion Criteria

• Recent (last 6 months) or ongoing poor glycemic control. HbA1C greater than 10.0mg/dL
• Uncontrolled hypertension. Blood pressure greater or equal to 180/110 mmHg
• History of chronic renal failure or renal transplant for diabetic nephropathy
• Lens opacity/cataract that could influence vision and results
• Any previous surgical or laser treatment to the study eye or fellow eye
• Planned YAG peripheral iridotomy
• Previous laser photocoagulation or macular laser treatment to study eye or fellow eye.
• History of DME in study or fellow eye
• Any previous ocular condition that may be associated with a risk of macular oedema
• Active lid or adnexal infection
• Previous retinal treatment: laser, drug or surgery
• Planned intra-ocular surgery within one year

WHO=World Health Organization; ADA=American Diabetic Association; ETDRS= Early Treatment Diabetic Retinopathy Study; PDR=proliferative diabetic retinopathy; CRT=retinal thickness within central subfield; OCT=optical coherence tomography; HbA1C=glycosylated hemoglobin; YAG= yttrium aluminum garnet; DME=diabetic macular edema

Table 2. Pascal® Laser Parameters

	Single-Session Group	Multiple-session Group
Number of sessions	One Day 0	Three Day 0 Day 14 Day 28
Number of burns	1500	500 per session (total-1500)
Type of laser	Pascal® (532nm)	Pascal® (532nm)
Type of laser spot	Pattern-spot 5x5, 4x4 arrays	Single-spot
Spot-size	400µm	400µm
Pulse duration	20ms	100ms
Laser burn spacing	1.5 burn-widths	1.5 burn-widths
Laser burn intensity	Grade 2+, 3+ ETDRS Mild gray-white	Grade 2+, 3+ ETDRS Mild gray-white

Table 3: Demographics for each group

	Single Session Pascal® 20ms	Multiple Session 100ms
Mean age (years) ± SD	45.7 ± 9.7	45.8 ± 10.5
Male: female ratio (% male)	14:6 (70%)	13:7 (65%)
Mean total laser power (milliWatts) ± SD	142 ± 22	287 ± 71
Mean laser fluence (Joules/cm^2)	11.8	4.8

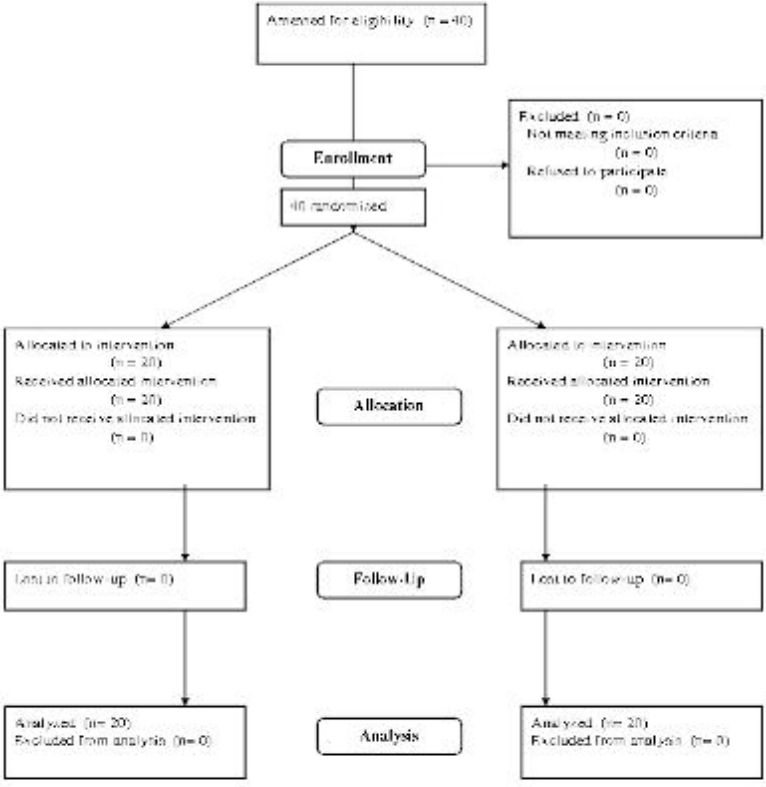
Table 4: Number of patients reporting side-effects immediately after Laser

Side-effect	Single Session (n=20)	Multiple Session (n=20)
Ache	5	9
Pinprick	5	2
Sharp	1	3
Burning	2	
Tingling	1	
Electric shock-like		1
Intense		1
Discomfort		1
Anxiety	4	10
Nausea		1

Table 5: Physiological side-effects during first month following laser treatment

Side-effect	Single Session (n=20)	Multiple Session (n=20)
Photopsia	2	5
Reduced mood	3	3
Increased anxiety	2	4
Driving performance (I:R) ratio*	(3:0)	(0:1)
Performance at work (I:R) ratio*	(2:0)	(1:2)
Reading ability (I:R) ratio*	(2:4)	(2:2)
Watching television (I:R) ratio*	(2:0)	(1:3)
Night-vision navigation (I:R) ratio*	(1:3)	(2:0)

* (I:R) ratio: increased versus decreased ratio;


Assessed for eligibility (n = 40)
Enrollment
Excluded (n = 0)
Not meeting inclusion criteria
(n = 0)
Refused to participate
(n = 0)
40 randomized
Allocated to intervention
(n = 20)
Received allocated intervention
(n = 20)
Did not receive allocated intervention
(n = 0)
Allocation
Allocated to intervention
(n = 20)
Received allocated intervention
(n = 20)
Did not receive allocated intervention
(n = 0)
Lost to follow-up (n = 0)
Follow-Up
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Analysis
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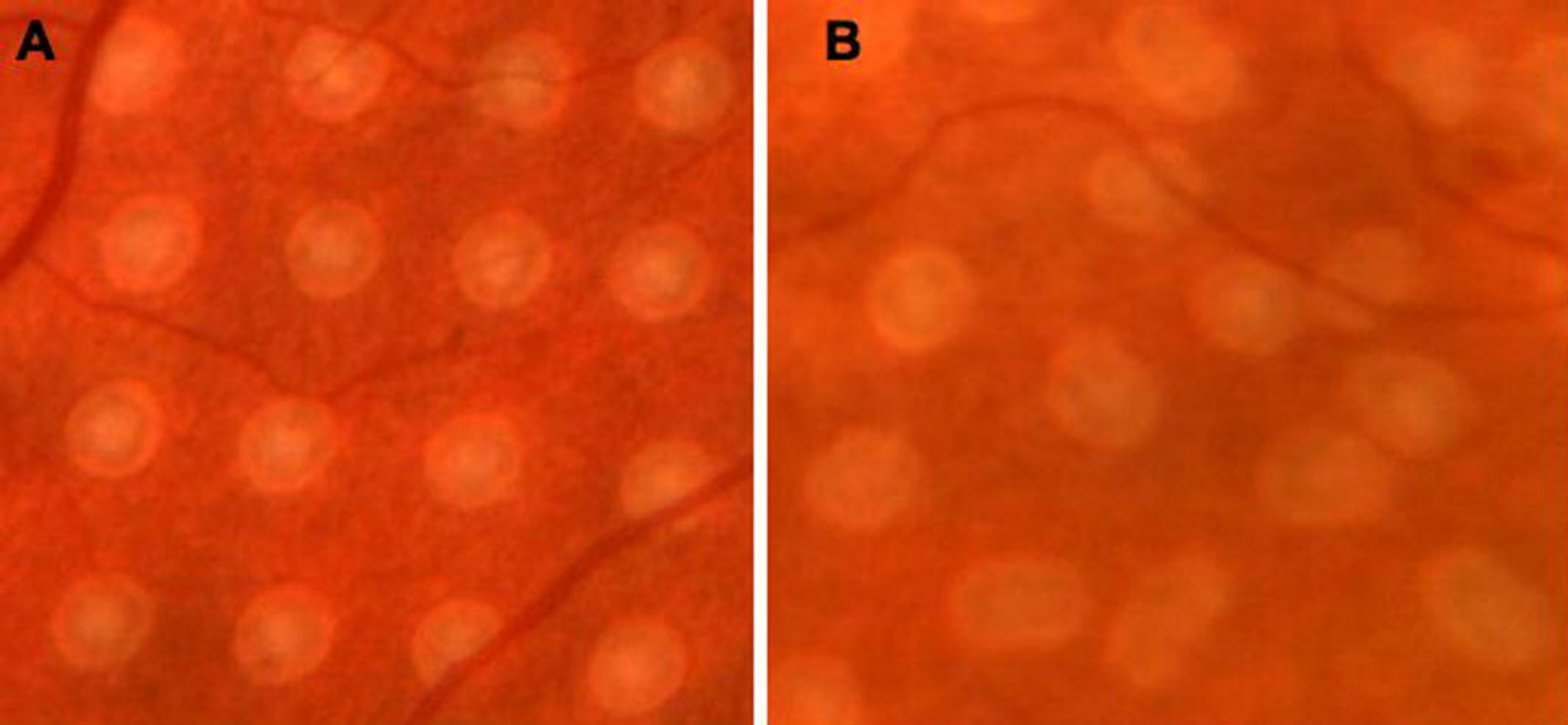
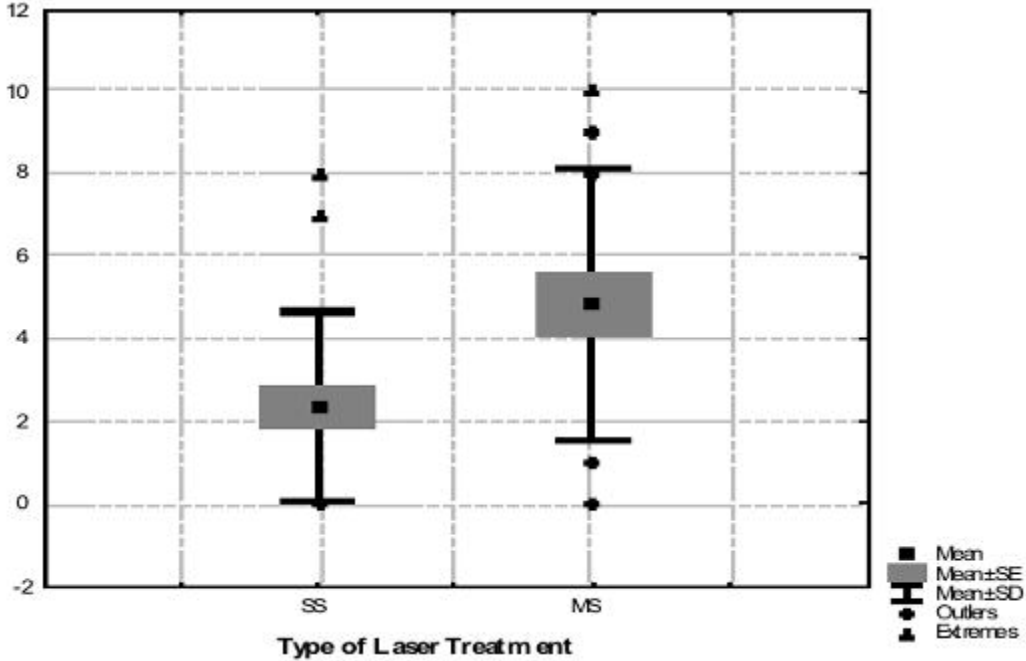
Excluded from analysis (n = 0)


A
B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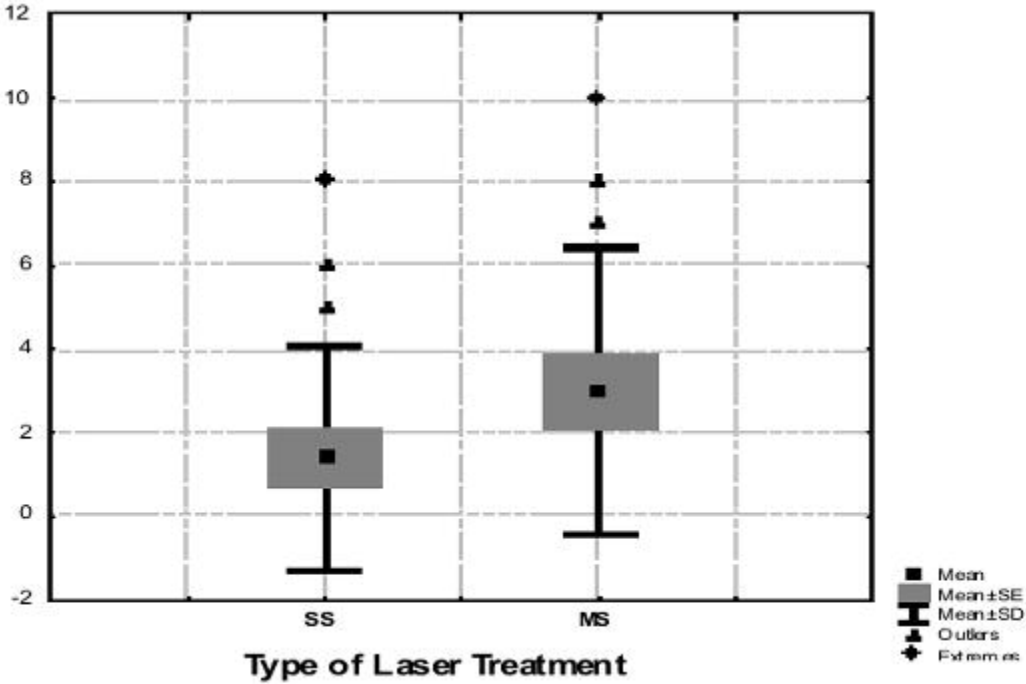
SS
MS
Type of Laser Treatment
Mean
Mean±SE
Mean±SD
Outlers
Extremes


12
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SS
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Type of Laser Treatment
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Mean±SE
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Outlers
Extremes