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REVIEW

Comparison of Pain Scores Among Patients Undergoing Conventional and Novel Panretinal Photocoagulation for Diabetic Retinopathy: A Systematic Review

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Corrina P Azarcon [1]
Jose Carlo M Artiaga [2,3]

[1]Department of Ophthalmology and Visual Sciences, Philippine General Hospital, University of the Philippines – Manila, Manila, Philippines; [2]International Eye Institute, St. Luke's Medical Center Global City, Taguig City, Philippines; [3]Department of Ophthalmology, Ospital ng Muntinlupa, Muntinlupa City, Philippines

Purpose: To summarize key findings from a systematic review focusing on pain as an adverse outcome of panretinal photocoagulation (PRP) among patients with diabetic retinopathy.

Design: Systematic review.

Methods: We systematically searched articles in major databases from July to September 2020. Studies that compared pain outcomes of PRP among diabetic patients who underwent conventional single-spot laser (SSL), conventional multi-spot laser (MSL), and/or novel navigated laser (NNL) were included. The Cochrane RoB 2 tool and ROBINS-I tool were used to evaluate the risk of bias of the included randomized controlled trials (RCTs) and controlled clinical trials (CCTs), respectively.

Results: We included 13 RCTs and 4 CCTs. Thirteen studies were included for Comparison 1 (Conventional SSL versus Conventional MSL), 3 studies were included for Comparison 2 (NNL versus Conventional MSL), and 3 studies were included for Comparison 3 (NNL versus Conventional SSL). A total of 783 patients and 1961 eyes were included in this review. The review showed that NNL yielded the lowest pain scores, followed by conventional MSL, then by conventional SSL.

Conclusion: This review summarizes findings of multiple studies that reported pain as an adverse outcome of PRP among patients with advanced diabetic retinopathy. Data from RCTs with mostly some concerns for bias (RoB 2 tool) and CCTs with mostly moderate risk of bias (ROBINS-I tool) show benefit of using MSL over SSL, and NNL over conventional systems for PRP in diabetic retinopathy, considering pain as the primary outcome.

Keywords: pain, panretinal photocoagulation, diabetic retinopathy, PASCAL®, NAVILAS®

Introduction

Diabetes mellitus is a global epidemic that affects nearly half a billion people worldwide.[1] This disease is a significant health and economic burden, as patients with diabetes are at risk for multiple disabling and life-threatening complications.[2,3] Among the most common complications of diabetes is diabetic retinopathy.[2] Global estimates in 2010 indicated that around 4.5 million people were visually impaired or blind as a consequence of this condition.[4]

Diabetic retinopathy is characterized by microvascular damage leading to retinal ischemia, neovascularization, and edema.[2,5] The earlier stage, non-proliferative diabetic retinopathy (NPDR), is classified based on the presence and the number

Correspondence: Corrina P Azarcon
Department of Ophthalmology and Visual Sciences, Philippine General Hospital, University of the Philippines – Manila, Manila, Philippines
Email corrinaa.md@gmail.com

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of microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities, and venous beading. The advanced stage, proliferative diabetic retinopathy (PDR), is characterized by preretinal neovascularization.[2,6]

Panretinal photocoagulation (PRP) has been considered as the standard of care in the management of advanced diabetic retinopathy since its introduction in the late 1970s.[7,8] In PRP, laser burns are applied at the retinal periphery using slit lamp or indirect ophthalmoscope-based systems.[9] Laser energy is primarily absorbed by melanocytes located at the retinal pigment epithelium layer. The energy, which is converted to heat, causes a localized increase in temperature.[10] Local destruction of retinal tissue brought about by the heat decreases oxygen demand and improves oxygenation of the surrounding retina.[11] In conventional laser therapy, a total of 1200 to 1600 moderate-intensity burns measuring 200 µm to 500 µm are delivered in 100 to 200 millisecond pulses. The treatment is traditionally administered using single-spot laser (SSL) systems and completed over 2 to 3 sessions.[9] The effectiveness of this protocol in prevention of vision loss has been demonstrated in large multicenter trials - the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS).[12,13]

Multi-spot lasers (MSL) are semi-automated, fully integrated, slit lamp-based laser systems that can deliver multiple laser spots in a single depression of the foot pedal. Using these machines, ophthalmologists can select and deliver various patterns, shapes, and sizes of laser burns.[14] The Pattern Scanning Laser (PASCAL®) photocoagulator (OptiMedica, Inc., Santa Clara, CA, USA) was introduced in 2006. It makes use of a frequency-doubled Neodymium:Yttrium Aluminum Gallium (Nd:YAG) laser to deliver single or multiple shots in arrays, circles, arcs, or lines. The Valon Multispot Laser (Valon Lasers Oy, Vantaa, Finland) is similar with PASCAL® but adds an important function that allows display of the settings over the retinal image. The VISULAS 532s VITE (Carl Zeiss Meditec AG, Jena, Germany) is a 532-nm solid-state photocoagulator that also delivers pre-programmed short-pulse multi-spot patterns on the retina. The NAVILAS® (OD-OS GmbH, Teltow, Germany) is a novel retinal navigation system and laser device that incorporates a digital fundus imaging system to a 532-nm and 577-nm diode pumped solid-state laser (DPSS). The fundus camera generates a large, glare-free image that allows live red-free, infrared, and fluorescein angiography imaging useful for treatment planning.[15] Pulse durations of these MSL's are usually in the 10 to 20 millisecond range, compared to the 100 to 200 millisecond duration used in conventional SSL systems.[14] Total treatment times with MSL's are approximately one-fifth of the time required to complete PRP using conventional SSL.[15]

One of the undesirable side effects of PRP is pain. With the conventional procedure, Visual Analog Scale (VAS) scores have been reported to range from 37.3 to 53.1 using a 100-millimeter scale.[16] Word descriptors included the following: sharp, flashing, pricking, tiring, blinding, intense, annoying, piercing, and nagging.[17] Previous reports show that pain may be controlled by adjusting laser parameters, which include wavelength, duration, and fluence.[10,14,17] Other factors that may influence pain perception are sex, culture, previous experiences, and anxiety levels.[17]

Pain is an important undesirable side-effect of any medical intervention. Up to 64.1% of patients are unable to tolerate pain associated with laser therapy.[18] Experience of pain may affect compliance to therapy and result to deterioration of vision.[15,19–21] In addition, pain may increase the patient's risk for complications during the procedure if it stimulates sudden movement of the eye.[22] Ophthalmologists should employ methods to minimize the amount of pain experienced by their patients during ocular procedures. The use of retrobulbar, peribulbar, and sub-Tenon's block have been suggested, but these methods pose the patient toadditional risk for complications.[10,23] Several drugs, which include oral non-steroidal anti-inflammatory drugs, topical diclofenac, inhalational nitrous oxide, oral diazepam, intramuscular ketorolac tromethamine, have been also described in different studies.[10,16,17,23–25] To date, there are no systematic reviews on PRP for diabetic retinopathy that have focused on pain as a primary adverse outcome. This systematic review shall compare pain scores obtained from patients undergoing conventional SSL, conventional MSL (PASCAL®), and novel navigated laser (NNL, NAVILAS®).

Methods

Guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed.[26] Randomized clinical trials (RCTs) and controlled clinical trials (CCTs) were included in the study, regardless of the setting and sample size. Trials wherein randomization was not explicitly stated in the text but compared outcomes of the two eyes of one patient using different types of laser on

each eye were considered as CCTs. Retrospective studies, observational studies, and reviews were excluded. We intended to include studies comparing pain scores of patients undergoing PRP by conventional SSL, conventional MSL (PASCAL®) and NNL (NAVILAS®). We only included studies involving patients diagnosed with diabetic retinopathy whose condition warranted PRP. Studies focusing on other retinal pathologies were excluded. Reports about focal laser therapy for diabetic macular edema were also excluded, except for studies which separately analyzed and reported data for patients who underwent PRP.

Search Methods

Two authors (CA and JA) independently conducted an electronic search from July to September 2020 using a pre-defined search strategy. No language restrictions were imposed. Search terms included "multi-spot", "pattern", "navigated," "panretinal photocoagulation," and "pain." Synonyms, alternate spellings, prefixes, and suffixes were also used. The following databases were searched: MEDLINE, CENTRAL, EMBASE, ClinicalTrials.gov, LILACS, and Herdin.ph. We sought for grey literature in OpenGrey and Google Scholar using similar search terms. Hand-searching was also performed through reference lists of retrieved studies.

Trial Selection

Two authors (CA and JA) independently screened titles and abstracts of the search yield. Differences in assessment were resolved through discussion between the first two authors. A third ophthalmologist served as the arbiter for disagreements. Two authors (CA and JA) selected studies based on the defined inclusion and exclusion criteria.

Outcomes of Interest

Primary outcomes were measured using pain scales which include the visual analog scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS) and other ordinal and continuous arbitrary pain scales for pain. Secondary outcomes included laser parameters (average laser power, average laser fluence, number of laser shots administered) and number of treatment sessions.

Data Collection and Assessment of Trials for Risk of Bias

Data was extracted into a pre-formatted electronic data collection sheet (Microsoft Excel) by the two investigators. All authors of the selected studies were e-mailed for clarifications regarding their protocols and reports. Studies of authors who were not able to respond were evaluated based on published data. The Cochrane RoB 2 tool and the ROBINS-I tool were used to assess the risk of bias of the RCTs and CCTs, respectively.[27,28] The robvis tool[29] was used to generate the risk of bias plots. Data from the RCTs were encoded into the Review Manager 5.4 software of the Cochrane Collaboration.

Data Synthesis and Analysis

Mean pain scores and standard deviations were extracted for each study. We used Microsoft Excel to calculate for means and standard deviations for studies that provided raw data. For articles that did not provide the standard deviation (SD) but provided the range of the scores, the estimate of the SD was computed using the method described by Walter.[30] Results of the RCTs and CCTs were included in the qualitative analysis, with consideration of its risk of bias. Pain scores from RCTs were encoded into the Review Manager 5.4 software for quantitative analysis. Pain scores were treated as continuous outcomes; standardized mean differences (SMD's) were obtained to account for differences in the pain scales used. Confidence intervals were set at 95%. A random effects model (Mantel-Haenszel) was applied. The p-value cut-off for significance was set at 0.05. Heterogeneity was assessed by individual evaluation of the methodologies and by using the I^2 statistic. Sensitivity analysis was done by checking if results and conclusions would change if studies with high or serious risk of bias were removed. Standardized mean differences and ranges were back-transformed to mean differences in the 10-point visual analog scale (VAS) following the method described in the Cochrane Handbook.[31] The protocol of this study was registered in PROSPERO (ID: CRD42020203047).

Results

The search process is detailed in Figure 1. Nineteen (19) full-text articles were retrieved for review. Of the 19 papers, a paper by Röckl et al[32] was excluded since the population included patients with retinal pathologies other than diabetic retinopathy, and a breakdown of the data was not available. Two reports written by Chhablani et al published in 2014 and 2015 consisted of the same set participants; only the updated article was included in our analysis.[33,34] Of the 17 articles remaining, 13 articles

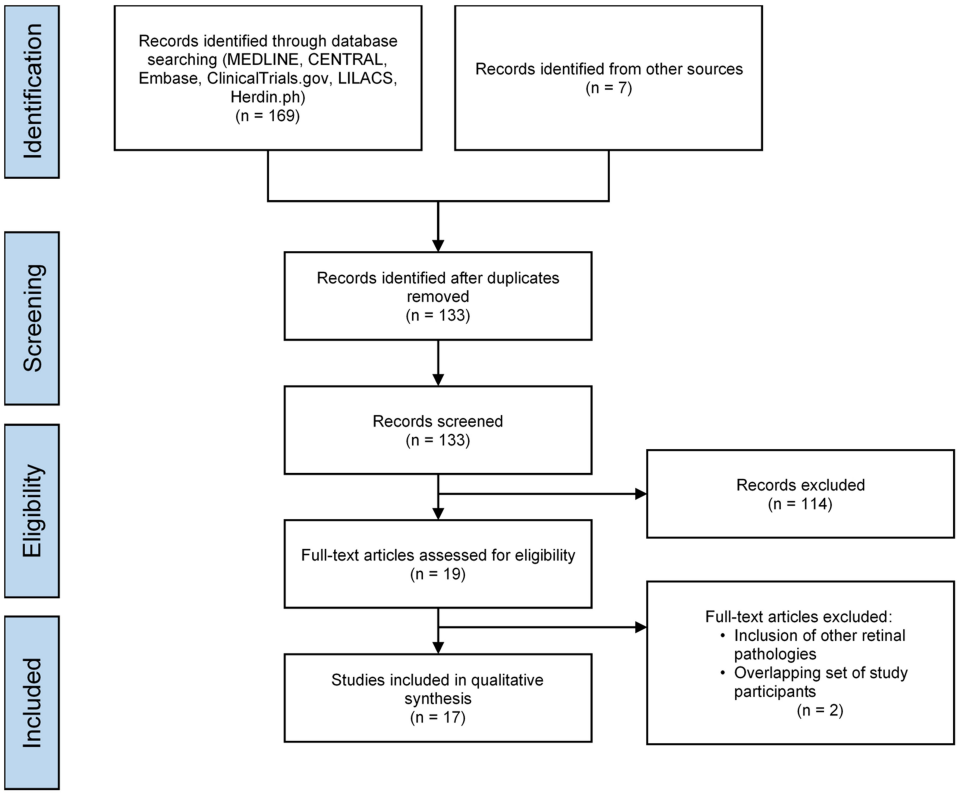

Figure 1 Search yield.

were included for Comparison 1 (conventional MSL versus conventional SSL), 3 articles were included for Comparison 2 (NNL and conventional MSL), and 3 articles were included for Comparison 3 (NNL versus conventional SSL). The search did not yield any studies that investigated the use of NNL systems other than NAVILAS®. Table 1 lists the characteristics of included studies. The inclusion and exclusion criteria used in the review are presented in Table 2.

Thirteen of 17 included studies were RCTs, whereas the remaining 4 were CCTs. Majority of the studies were performed in single centers, except for the study of Chhablani et al,[34] which was done in 2 hospitals, and the study of Ahmed,[18] which was performed in multiple sites from a single center. Six studies studied only 1 eye per patient, 6 studies used the other eye of the patient as a comparison, and 5 studies intervened on a mix of unilateral and bilateral cases. The sample size ranged from 15 to 150 eyes. From the studies that provided the age of participants, Muqit et al[35] studied the youngest age group (MSL: 45.8 ± 9.7 years old; SSL: 45.8 ± 10.5 years old) and Polat et al[36] studied the oldest age group (63.14 ± 9.23 years old). Majority of the studies utilized 532-nm wavelength for both laser groups. Passos[37] compared 577-nm conventional MSL and 532-nm conventional SSL, Zhang[38] compared 577-nm conventional MSL and 577-nm conventional SSL; Amoroso[8] used 577-nm lasers for both NNL and conventional MSL. Significant differences in laser methodology among patients across all studies were observed. Table 3 summarizes the list of laser machines, settings and parameters used in all included studies.

VAS was the most commonly utilized pain scale; it was used in 10 of the 17 studies included. The report of Muraly et al[39] was the only study where pain outcomes were reported by the physician based on observations of the patient's reactions. Ahmed[18] used the mean value of the numerical rating pain score and the Wong-Baker Faces Pain Rating Scale. Nemcansky et al,[40] Salman et al,[41] and Zhang et al[38] used numerical scales with range of 0 to 8, 0 to 5, and 0 to 3, respectively. Muqit et al[35] used a Numerical Pain Scale from 0 to 10. Seymenoğlu et al,[21] Inan et al,[11] Inan et al,[19] and Polat et al[36] also reported VRS separate from the VAS score. Only the study of Muqit et al[35] measured duration of pain and recorded word descriptors for pain.

Table 1 Characteristics of Included Studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Comparison 1: Conventional Multi-spot versus Conventional Single-Spot					
Muqit 2010[35]	RCT	Setting: Manchester Royal Eye Hospital Participants: 24 patients (40 eyes) Mean age (years): 45.7 ± 9.7 (MSL) 45.8 ± 10.5 (SSL)	MSL: PASCAL® 532 nm SSL: PASCAL® 532 nm Anesthetic: 0.4% oxybuprocaine eye drops Other notes: • Independent randomization of right and left eyes for bilateral cases • Delay between treatment of one eye and the other	Primary: **Pain score (NPS, mean of 3 sessions, 3 measurements per session)** Secondary: Duration of pain responses, NHS score at 1 month, affective changes post-treatment, levels of photophobia post-PRP, adverse events	Funding: Optimedica Corporation, Santa Barbara, USA Conflict of Interest: One author is an employee of the Optimedica Corporation, one author received financial support from Optimedica Corporation
Nagpal 2010[7]	RCT	Setting: No information Participants: 60 patients (120 eyes) Mean age (years): 52 (45 - 61)	MSL: PASCAL® 532 nm SSL: Solid-state green Laser/ GLX 532 nm Other notes: • Each patient experienced both modalities on the same day; time interval in between not specified	Regression of retinopathy, complications of PRP, change in laser spot size, retinal visual field sensitivity, total time required for complete PRP, **pain score (VAS)**	Funding: No financial disclosures Conflict of Interest: None
Yang 2010[20]	RCT	Setting: No information Participants: 80 patients (150 eyes) Mean age (years): 60.03 ± 13.66 (MSL) 58.78 ± 11.30 (SSL)	MSL: PASCAL® 532 nm SSL: PASCAL® 532 nm	Laser parameters, progression of diabetic retinopathy, visual acuity, central macular thickness, **pain score (VAS)**, complications	Funding: No information Conflict of Interest: No information
Muraly 2011[39]	RCT	Setting: Aravind Eye Hospital Participants: 50 patients (100 eyes) Mean age (years): 57.44 ± 8.98	MSL: PASCAL® 532 nm SSL: Nd-YAG laser 532 nm	**Pain score (graded by physician – mild, moderate, severe)**, retreatment, regression and persistence of neovascularization, vitreous hemorrhage	Funding: No financial disclosures Conflict of Interest: None
Salman 2011[41]	RCT	Setting: No information Participants: 120 patients (120 eyes) (50% of study population excluded from this review) Mean age (years): 48.9 ± 9.3	MSL: PASCAL® 532 nm SSL: Novus Spectra Green-light Diode Pumped Solid State Photocoagulator (Lumenis) 532 nm	Treatment parameters, treatment efficacy, visual acuity, procedure length, **pain score (0 to 5)**, adverse events	Funding: Ophthalmology Department, Ain Shams University Conflict of Interest: None

(*Continued*)

Table 1 (Continued).

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Chhablani 2015[34]	RCT	Setting: L V Prasad Eye Institute, Hyderabad, India and King Khaled Eye Specialist Hospital Riyadh, Saudi Arabia Participants: 47 patients (74 eyes) Mean age (years): 52.8 (42 - 63)	MSL: PASCAL® 532 nm SSL: PASCAL® 532 nm	Laser parameters, visual acuity, regression and/or development of neovascularization, need for additional treatment, **pain score (VAS)**, treatment time	Funding: No funding Conflict of interest: Two authors have disclosed potential conflicts of interest
Zhang 2017[38]	RCT	Setting: Affiliated Eye Hospital of Nanjing Medical University Participants: 32 patients (40 eyes) Mean age (years): MSL: 46.5 ± 9.6 SSL: 50.2 ± 11.2	MSL: SupraScan® 577 nm SSL: SupraScan® 577 nm Other notes • Standardized instruction in ranking pain scores	Changes on fundus fluorescein angiography, duration of session, **pain score (0 to 3)**	Funding: No information Conflict of Interest: No information
Inan 2018[11]	RCT	Setting: No information. Participants: 28 patients (56 eyes) Mean age (years): 61.36 ± 9.10	MSL: PASCAL® 532 nm SSL: ELLEX 532 nm Other notes: • PASCAL on one eye and conventional SSL on the other eye on the same day (random order) • Pain scores collected in 1 of 4 sessions wherein both eyes were treated with a 30-minute interval in between; the total duration of treatment was shorter than the others; # of laser shots were less than the usual	**Pain score (VAS and Verbal Score)** Note: Authors reported that the VAS scale was used, but the figures in the paper showed that they actually used a Numerical Rating Scale and a Faces Pain Scale.	Funding: No financial support Conflict of Interest: None
Nemcansky 2019[40]	RCT	Setting: Ophthalmology Clinic, Faculty Hospital Ostrava Participants: 30 patients (60 eyes) Mean age (years): No information	MSL: PASCAL® SSL: PASCAL® Other notes: • PASCAL first on one eye and conventional SSL on the other eye	Laser parameters, stability of clinical findings, DME progression, **pain score (0-8)**, complications	Funding: No financial support Conflict of Interest: None
Passos 2019[37]	RCT	Setting: Single-center Participants: 41 patients (41 eyes) Mean age (years): MSL: 56.2 ± 10.4 SSL: 61.2 ± 7.4	MSL: SupraScan® 577 nm SSL: PASCAL® 532 nm	Primary: BCVA, central retinal thickness, laser parameters, **pain score (0 – 10 scale from McGill Pain Questionnaire)** Secondary: OCT changes, FA findings	Funding: No financial support Conflict of Interest: Two authors received travel grants from Quantel Medical

Ahmed 2020[18]	RCT	Setting: Aswan university hospital (MSL); Aswan eye & laser center (SSL) Participants: 60 patients (80 eyes) Mean age (years): 54.47 ± 8.72	MSL: PASCAL® 532 nm SSL: Green-light Diode Solid State photocoagulator laser 532 nm (ELLEX) Anesthetic: 0.5% proparacaine hydrochloride drops	Primary: **Pain score (mean value of numerical rating pain score (0 to 10) and the Wong-Baker Faces Pain Rating Scale)**, laser parameters Secondary: Complications	Funding: No information Conflict of interest: No information
Seymenoğlu 2013[21]	CCT	Setting: Celal Bayar Üniversitesi Participants: 70 patients (70 eyes) Mean age (in years): MSL: 61.9 ± 7.98 SSL: 64.22 ± 5.85	MSL: PASCAL® 532 nm SSL: GYC 1500 532 nm Anesthetic: 0.5% proparacaine hydrochloride drops	Primary: **Pain scores (VAS, verbal pain score (0-4))** Secondary: Relationship between pain level and patient characteristics, neovascularization	Funding: No information Conflict of interest: No information
Yilmaz 2016[42]	CCT	Setting: Beyoglu Eye Training and Research Hospital, Istanbul, Turkey Participants: 40 patients (40 eyes) Mean age (in years): MSL: 63.7 ± 3.2 SSL: 62.5 ± 3.3	MSL: PASCAL® SSL: VISULAS 532 nm Anesthetic: Unspecified topical anesthesia	Primary: Pupil diameters in scotopic, mesopic, and photopic conditions before and after the PRP Secondary: **Pain scores (0 to 10 on a 10 cm scale; equivalent to VAS)**	Funding: No information Conflict of interest None
Comparison 2: Novel Navigated Laser versus Conventional Multi-Spot Laser					
Chhablani 2015[34]	RCT	Setting: L V Prasad Eye Institute, Hyderabad, India and King Khaled Eye Specialist Hospital Riyadh, Saudi Arabia Participants: 47 patients (74 eyes) Mean age (years): 52.8 (42 - 63)	NNL: NAVILAS® 532 nm SSL: PASCAL® 532 nm	Laser parameters, visual acuity, regression and/or development of neovascularization, need for additional treatment, **pain score (VAS)**, treatment time	Funding: No funding Conflict of interest: Two authors have disclosed potential conflicts of interest
Inan 2016[19]	RCT	Setting: No information Participants: 60 patients (60 eyes) Mean age (in years): Age 62.22 ± 9.19	NNL: NAVILAS® MSL: PASCAL®	**Pain scores (VRS and VAS)**	Funding: No funding Conflict of interest: None

(*Continued*)

Table 1 (Continued).

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Amoroso 2019[8]	CCT	Setting: University Eye Clinic of Creteil (France) Participants: 16 patients (32 eyes) Mean age (in years): 57 ± 13	NNL: NAVILAS® 577 nm MSL: SupraScan 577 nm Other notes: • Session with each laser treatment carried out on the same day, 30 minutes apart	**Pain score (VAS)**, duration of PRP, laser parameters, spot coverage and characteristics	Funding: No funding Conflict of interest: None
Comparison 3: Novel Navigated Laser versus Conventional Single-Spot Laser					
Chhablani 2015[34]	RCT	Setting: L V Prasad Eye Institute, Hyderabad, India and King Khaled Eye Specialist Hospital Riyadh, Saudi Arabia Participants: 47 patients (74 eyes) Mean age (years): 52.8 (42 - 63)	NNL: NAVILAS® 532 nm SSL: PASCAL® 532 nm	Laser parameters, visual acuity, regression and/or development of neovascularization, need for additional treatment, **pain score (VAS)**, treatment time	Funding: No funding Conflict of interest: Two authors have disclosed potential conflicts of interest
Polat 2019[36]	RCT	Setting: No information Participants: 70 patients (140 eyes) Mean age (in years): 63.14 ± 9.23	NNL: NAVILAS® 532 nm SSL: ELLEX 532 nm Other notes: Session with each laser treatment carried out on the same day, 30 minutes apart	**Pain scores (VAS, VRS)**, laser parameters	Funding: No information Conflict of interest: None
Kim 2014[22]	CCT	Setting: Sanggye Paik Hospital, Seoul, Korea Participants: 15 patients (15 eyes) Mean age (in years): 58.3 (47 - 76)	MSL: NAVILAS® SSL: OcuLight® 532 nm Anesthetic: 0.5% proparacaine	**Pain score (VAS)**, duration of treatment Note: "VAS" used appears to be "NRS" based on the publication	Funding: No information Conflict of Interest: No information

Note: Bold: Pain outcome.

Abbreviations: RCT, randomized controlled trial; MSL, multi-spot laser; SSL, single spot laser; nm, nanometers; NPS, numerical pain score; NHS, numerical headache scores; PRP, panretinal photocoagulation; PASCAL, Pattern Scanning Laser; VAS, visual analog scale; Nd:YAG, Neodymium-doped:Yttrium Aluminum Garnet; BCVA, best-corrected visual acuity; VRS, verbal rating score; CCT, controlled clinical trial.

Table 2 Inclusion and Exclusion Criteria of Included Studies

Study ID	Inclusion Criteria	Exclusion Criteria
Comparison 1: Conventional Multi-Spot Laser versus Conventional Single-Spot Laser		
Muqit 2010[35]	Newly diagnosed PDR, Type 1 or 2 DM, > 18 years old, VA 6/60 or better, mean CRT < 300 μm by OCT with no intraretinal or subretinal fluid, adequate pupil dilation, clear media, ability to perform Humphrey visual field test	Poor glycemic control (HbA1c > 10 mg/dL), uncontrolled hypertension (BP ≥ 180/110), history of chronic renal failure or renal transplant for diabetic nephropathy, lens opacity or cataract that could influence vision or results, any previous surgical or laser treatment to study or fellow eye, history of DME in study or fellow eye, previous ocular condition that may be associated with risk of macular edema, active lid or adnexal infection, previous retinal treatment (laser, drug or surgery), planned intra-ocular surgery within 1 year
Nagpal 2010[7]	Bilaterally symmetrical PDR or NPDR severe	History of previous laser treatments and/or intravitreal injections in either eye, pre-treatment BCVA of <6/24, media opacities obscuring the fundus in either eye, diabetic maculopathy, glaucoma, uveitis, retinitis pigmentosa, myopia greater than −6 diopters, retinal degenerations and dystrophies, optic disc pathologies
Yang 2010[20]	NPDR severe	Previous PRP, media opacity (cataract, vitreous bleeding), age-related macular degeneration, epiretinal membrane, macular diseases, glaucoma, retinal vessel obstruction, ophthalmic surgery within the last 6 months, intravitreal anti-VEGF injection, severe macular edema, macular traction
Muraly 2011[39]	Early and high-risk PDR of both eyes, PDR with 2–4 high risk characteristics, age ≥ 18 years old, BCVA 6/60 or better	Vitreous hemorrhage obscuring view, vision in only one eye or those in whom only one eye had PDR/PDR HR, maculopathy, tractional retinal detachment, media clarity inadequate, previous laser, poor follow-up, uncontrolled systemic parameters (high blood pressure, blood sugar, nephropathy)
Salman 2011[41]	PDR, NPDR with need for laser, Type 2 DM with need for laser, able to sign consent	Ischemic maculopathy, previous laser or intravitreal injection, vitrectomy or associated retinal diseases such as retinal vein occlusion
Chhablani 2015[34]	PDR HR, Type 1 or 2 DM, ≥ 18 years old	Low-risk PDR, monocular status, poor compliance, pregnant, history of prior PRP or vitrectomy, history of anti-angiogenic injections within the previous 2 months, evidence of center-involved DME, intravitreal dexamethasone implant, media opacities obscuring fundus details, coagulation abnormalities, use of anticoagulants other than aspirin
Zhang 2017[38]	Newly diagnosed PDR HR	No information
Inan 2018[11]	Bilateral PDR HR, Type 1 or 2 DM	Previous focal/grid photocoagulation, history of orbital trauma, orbital infection or surgery, corneal or lens opacities, vitreous hemorrhage, non-compliance
Nemcansky 2019[40]	NPDR severe, PDR	Previous retinal laser photocoagulation, vitrectomy, associated vascular retinal diseases
Passos 2019[37]	Treatment-naïve severe NPDR or PDR, Type 1 or 2 DM, ≥ 18 years old, ability to understand and sign a written consent form	History of intravitreal injections during the previous 6 months, vitrectomy, or any ocular comorbidity
Ahmed 2020[18]	Newly diagnosed PDR, Type 1 or Type 2 DM, >18 years old, Snellen BCVA of 6/60 or better, adequate pupil dilation, clear media	Previous laser photocoagulation or macular laser treatment on the study eye, recent intraocular surgery (within 3 months), media opacities that interfere with evaluation of the posterior segment, mean central macular thickness > 300 microns by OCT, contraindication to fluorescein angiography, poor glycemic control (HbA1c > 10 mg/dL), uncontrolled hypertension, BP ≥ 180/110 mm/Hg, vitreoretinal traction, indication/plan for intraocular surgery within 6 months
Seymenoğlu 2013[21]	PRP-naïve PDR, > 18 years	No information

(*Continued*)

Table 2 (Continued).

Study ID	Inclusion Criteria	Exclusion Criteria
Yilmaz 2016[43]	PDR	Ocular disease other than diabetic retinopathy, systemic disorders other than diabetes, diabetic macular edema, advance proliferative diabetic retinopathy (NVI, NVG, RD), history of intraocular surgery, active lid or adnexal infection, history of previous retinal laser therapy or intravitreal injection, history of systemic medications in the last 3 months, history of ocular medications during the last year, history of ocular or head trauma, smokers and heavy alcoholic drinkers
Comparison 2: Novel Navigated Laser versus Conventional Multi-Spot Laser		
Chhablani 2015[34]	See above.	See above.
Inan 2016[19]	PDR HR, Type 1 or 2 DM, > 18 years	PDR low risk, poor compliance, pregnant, history of focal/grid photocoagulation or PRP, orbital trauma or surgery, inflammatory signs, significantly increased corneal or lens thickness, vitreous hemorrhage
Amoroso 2019[8]	Bilateral pre-PDR or PDR eligible for PRP, treatment-naïve, ≥ 18 years old	Intravitreal hemorrhage, media opacities inhibiting laser treatment
Comparison 3: Novel Navigated Laser versus Conventional Single-Spot Laser		
Chhablani 2015[34]	See above.	See above.
Polat 2019[36]	PDR, Type 1 or 2 DM, > 18 years old	History of vitrectomy or ocular trauma, active or history of intraocular inflammation, media opacities obscuring fundus details or affecting power parameters, mental or visual deficiency and inability to express pain on pain scales
Kim 2014[22]	PDR	Previous retinal photocoagulation, corneal opacity, cataract, vitreous hemorrhage, media opacity

Abbreviations: PDR, proliferative diabetic retinopathy; DM, diabetes mellitus; VA, visual acuity; CRT, central retinal thickness; μm, micrometers; OCT, optical coherence tomography; BP, blood pressure; DME, diabetic macular edema; NPDR, non-proliferative diabetic retinopathy; BCVA, best-corrected visual acuity; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor; HR, high risk; NVI, neovascularization of the iris; NVG, neovascular glaucoma; RD, retinal detachment.

Risk of Bias of Included RCTs

Figure 2 displays the assessment of the risk of bias of the included RCTs. Only 4 of the 13 included RCTs specified the method of random sequence generation in the methodology. Only 1 study specified the method of allocation concealment and was classified as having low risk of bias arising from the randomization process (Domain 1); the rest were classified as having some concerns of bias in this domain. In the evaluation of bias due to deviations from the intended protocol (Domain 2), the reviewers decided that knowledge of the intervention by the care providers should not result to deviations from the intended protocol, hence all studies were judged as having low risk for bias in this domain. However, we judged the protocol Ahmed et al[18] as having some concerns of bias since the SSL and MSL procedures were conducted in different settings. In the assessment of bias due to missing outcome data (Domain 3), majority of the studies were assessed to be at low risk for attrition bias due to the short follow-up period. Complete data was reported in all studies except for the study of Polat et al,[36] where pain scores of 8 of 29 patients who underwent PRP using 100-millisecond shots were not reported. In the evaluation of bias in measurement of the outcome (Domain 4), we found serious concerns in the study of Muraly et al,[39] where pain outcomes were defined by unmasked physicians who were also performing the laser procedure. The studies of Polat et al,[36] Inan et al,[11] and Inan et al[19] were assessed as having high risk of bias in selection of the reported result (Domain 5) given that the number of laser shots were standardized for the two procedures and were not reflective of usual clinical practice. The reviewers also found high risk of bias in the report of Ahmed et al[18] since two different pain scales were averaged. Overall, the reviewers found that only one study had low risk for bias, 4 were at high risk for bias, and the rest had some concerns for bias.

Table 3 Laser Parameters in Included Studies

Study ID	Machine	Spot Size	Duration	Power (mW)	# of Burns	# of Sessions
Comparison 1: Conventional Multi-Spot versus Conventional Single-Spot Laser						
Muqit 2010[34]	MSL: PASCAL® 532 nm SSL: PASCAL® 532 nm	MSL: 400 μm SSL: 400 μm	MSL: 20 ms SSL: 100 ms	MSL: 287 ± 71 SSL: 142 ± 22 Fluence (J/cm^2): MSL: 4.8 SSL: 11.8	MSL: 1500 SSL: 1500	MSL: 1 SSL: 3
Nagpal 2010[7]	MSL: PASCAL® 532 nm SSL: Solid state green laser (GLX) 532 nm	MSL: 200 μm SSL: 200 μm	MSL: 20 ms SSL: 200 ms	MSL: 630 (40–1000) SSL: 288 (200–400) Fluence (J/cm^2): MSL: 40.33 SSL: 191	MSL: 1093 (950–1100) SSL: 575 (500–700)	MSL: 2 SSL: 2
Yang 2010[20]	MSL: PASCAL® 532 nm SSL: PASCAL® 532 nm	MSL: 200 μm SSL: 200 μm	MSL: 20 ms SSL: 200 ms	MSL: 468.83 ± 106.08 SSL: 307.10 ± 12.18 p = 0.01 Fluence (J/cm^2): MS: 26.21 ± 7.29 SS: 189.4 ± 45.33	MSL: 1728.90 ± 324.39 SSL: 1624.92 ± 511.92	MSL: 1 SSL: 3
Muraly 2011[39]	MSL: PASCAL® SSL: Nd:YAG laser 532 nm	MSL: 400 μm SSL: 400 μm	MSL: 20–30 ms SSL: 200 ms	MSL: 439 (275–950) SSL: 192.8 (125-300)	MSL: 2795 (2100–3892) SSL: 1414 (1200-1672)	MSL: 1 SSL: 2–3
Salman 2011[41]	MSL: PASCAL® 532 nm SSL: Novus Spectra Green-light Diode Pumped Solid State Photocoagulator (Lumenis) 532 nm	MSL: 400 μm SSL: Not stated	MSL: 20 ms SSL: 100 ms	MSL: 410 ± 115.2 SSL: 215 ± 51.3	MSL: 1090 ± 410.4 SSL: 700 ± 201.1	MSL: 1–2 SSL: 1–3
Chhablani 2015[34]	MSL: PASCAL® 532 nm SSL: PASCAL® 532 nm	MSL: 200 μm SSL: 200 μm	MSL: 20–30 ms SSL: 100–200 ms	MSL and SSL: 200–400 mW (No significant difference)	MSL: 2334 ± 656 SSL: 1433 ± 513	More than one (35–47% of all groups needed retreatment)
Zhang 2017[38]	MSL: SupraScan® 577 nm SSL: SupraScan® 577 nm	MSL: 200–300 μm SSL: 200–300 μm	MSL: 35–50 ms SSL: 250–300 ms	MSL: 450–800 mW SSL: 250–450 mW	No information	MSL: 3 SSL: 4
Inan 2018[11]	MSL: PASCAL 532 nm SSL: ELLEX 532 nm	MSL: 200–400 μm SSL: 200–400 μm	MSL: 30 ms SSL: 100 ms	Not reported	MS: 435.36 ± 77.46 SS: 436.18 ± 74. 63 (per session)	MSL: 4 SSL: 4
Nemcansky 2019[40]	MSL: PASCAL® SSL: PASCAL®	MSL: 400 μm SSL: 400 μm	MSL: 20 ms SSL: 200 ms	MSL: 473 ± 128 SSL: 295 ± 96	MSL: 2113 ± 328 SSL: 1685 ± 179	MSL: 1–2 SSL: >1–3

(*Continued*)

Table 3 (Continued).

Study ID	Machine	Spot Size	Duration	Power (mW)	# of Burns	# of Sessions
Passos 2019[37]	MSL: SupraScan® 577 nm SSL: PASCAL® 532 nm	MSL: 400 μm SSL: 400 μm	MSL: 20 ms SSL: 100 ms	MSL: 451.4 ± 138.0 SSL: 356 ± 136.5	MSL: 2504 ± 377.3 SSL: 1287.6 ± 187.6	MSL: 2.7 ± 0.6 SSL: 3.9 ± 0.7
Ahmed 2020[18]	MSL: PASCAL® 532 nm SSL: ELLEX 532 nm	MSL: 200 μm SSL: 200 μm	MSL: 20 ms SSL: 100 ms	MSL: 525 ± 125.4 SSL: 260 ± 130.7	MS: 2820.63 + 394.18 SS: 2611.42 + 285.61	MS: 2.0 ± 0 SS: 2.1 ± 0.3
Seymenoğlu 2013[21]	MSL: PASCAL® 532 nm *SSL*: GYC 1500 532 nm	MSL: 200 μm SSL: 200 μm	MSL: 20–30 ms SSL: 200 ms	MSL: 650 (250–1500) SSL: 330 (200–600)	MS: 2885 (2100–3951) SS: 1642 (1364–1948)	MSL: 1 SSL: 2
Yilmaz 2016[42]	MS: PASCAL SSL: VISULAS 532 nm	MSL: 400 μm SSL: 400 μm	MSL: 20–30 ms SSL: 200–400 ms	MSL: 528 ± 68 SSL: 242 ± 42	MSL: 2018 ± 132 SSL: 1812 ± 142	MSL: 1 SSL: 3–4
Comparison 2: Novel Navigated Laser versus Conventional Multi-Spot Laser						
Chhablani 2015[34]	NNL: NAVILAS® 532 nm MSL: PASCAL® 532 nm	NNL: 300 μm MSL: 200 μm	NNL_S: 20–30 ms NNL_L: 100–200 ms MSL: 20–30 ms	NNL and MSL: 200–400 mW	NNL_S: 1810 ± 369 NNL_L: 1120 ± 446 MSL: 2334 ± 656	More than one (35–47% of all groups needed retreatment)
Inan 2016[19]	NNL: NAVILAS® MSL: PASCAL®	NNL: 200–400 μm MSL: 200–400 μm	NNL: 30 ms MSL: 30 ms	No information.	NNL: 389.47 ± 71.52 *MSL*: 392.7 ± 54.33	NNL: 1 MSL: 1
Amoroso 2019[8]	NNL: NAVILAS® 577 nm MSL: SupraScan 577 nm	NNL: 390 μm MSL: 390 μm	NNL: 20 ms MSL: 20 ms	NNL: 304.6 (300–350) MSL: 306.8 (300–350)	NNL: 1774 (964–2504) MSL: 1778 (1049–2549)	NNL: 1 MSL: 1
Comparison 3: Novel Navigated Laser versus Conventional Single-Spot Laser						
Chhablani 2015[34]	NNL: NAVILAS® 532 nm MSL: PASCAL® 532 nm	NNL: 300 μm SSL: 200 μm	NNL_S: 20–30 ms NNL_L: 100–200 ms SSL: 100–200 ms	NNL *and* MSL: 200–400 mW	NNL_S: 1810 ± 369 NNL_L: 1120 ± 446 SSL: 1433 ± 513	More than one (35–47% of all groups needed retreatment)
Polat 2019[36]	NNL: NAVILAS® 532 nm SSL: ELLEX 532 nm	NNL: 200–400 μm SSL: 200–400 μm	NNL_S: 30 ms NNL_L: 100 ms SSL: 100 ms	NNL: 291.9 + 85.3 SSL: 368.4 ± 72.0	NNL: 375.4 ± 108.4 MSL: 374.2 ± 105	NNL: 4 MSL: 4
Kim 2014[22]	MSL: NAVILAS® SSL: OcuLight® GL	No information	NNL: 30 ms SSL: 100 ms	NNL: 373.3 ± 38.1 SSL: 209.3 ± 20.5	NNL: 2055.2 ± 288.7 SSL: 658.8 ± 65.3	NNL: 1 SSL: No information

Abbreviations: mW, milliwatts; MSL, multi-spot; SSL, single-spot; nm, nanometers; μm, micrometer; ms, millisecond; J, joules; cm^2, square centimeters; NNL_S, short-pulse novel navigated laser; NNL_L, long-pulse novel navigated laser.

Figure 2 Risk of bias assessment of included RCTs.

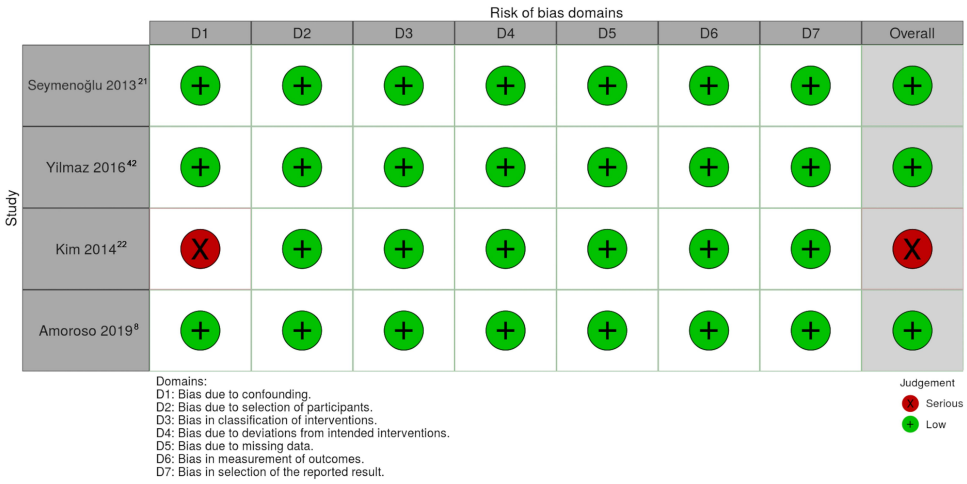

Figure 3 Risk of bias assessment of included CCTs.

Risk of Bias of Included CCTs

Figure 3 shows the assessment of the risk of bias of the included RCTs. In the evaluation of bias due to confounding (Domain 1), the reviewers found serious concerns in the methodology of Kim et al[22] where both interventions were performed on the same eye. NNL was used for the superior, nasal, and inferior quadrants during the first session, then conventional SSL was done in the temporal retina a week later. The coverage of a larger area may have resulted to greater ciliary nerve stimulation, thereby causing greater pain. Thus, reported pain scores with NNL may have been falsely higher while scores with conventional laser were falsely lower in this study design. No confounding factors were noted for the other studies. The reviewers did not find significant concerns in the selection of participants (Domain 2), classification of interventions (Domain 3), deviations from intended interventions (Domain 4), missing data (Domain 5), measurement of outcomes (Domain 6), and selection of the reported result (Domain 7). Overall, three CCTs appeared to have low risk of bias, and only the study of Kim et al[22] was assessed to have serious risk of bias.

Results of the Intervention

Comparison 1: Conventional MSL versus Conventional SSL

Eleven RCTs (Figure 4) and 2 CCTs were included in this comparison. Two groups investigating the effect of laser on macular edema in the study of Salman et al[41] were excluded from this review. The reviewers decided not to conduct a meta-analysis since no two studies were sufficiently similar, and this was supported by a large I^2 statistic (>96%) when the 11 RCTs are included. As illustrated in the Forest plot for Comparison 1 (Figure 4), all included RCTs favored conventional MSL over conventional SSL in terms of pain. The studies published by Nemcansky et al[40] and Passos et al[37] crossed the line of no effect. The calculated mean difference of pain scores between the two groups reported across the included studies ranged from 0.5 to 6 VAS points favoring conventional MSL over conventional SSL. No significant changes in the results are found when the results of studies with high risk of bias are removed from the analysis.

Two CCTs likewise favored conventional MSL. Seymenoğlu et al[21] conducted a CCT where 35 eyes of 35 patients underwent conventional MSL in 1 session and the same number of eyes underwent conventional SSL in 2 sessions. VAS scores were 2.17 ± 1.18 and 5.54 ± 3.28 for conventional SSL and conventional MSL, respectively. In another CCT by Yilmaz et al[42] which studied 40 eyes of 40 patients with diabetic retinopathy, VAS pain scores were 1.7 ± 1.4 versus 5.2 ± 3.0 for conventional MSL and conventional SSL (p = 0.001), respectively.

Comparison 2: NNL versus Conventional MSL

Only two RCTs (Figure 5) and 1 CCT were included for this comparison. For both RCTs shown in Figure 5, pattern NNL appears to be more beneficial compared to conventional MSL in terms of pain, using a pulse duration of 30-ms for both groups. The calculated mean difference of pain scores is equivalent to 0.7 to 2 VAS points favoring NNL over conventional MSL.

The CCT conducted by Amoroso et al[8] also found significantly higher VAS scores among patients who underwent 577-nm pre-planned NNL versus 577-nm conventional MSL, with pulse durations set at 20-ms (2.4 ± 1.6 versus 7.1 ± 2).

Chhablani et al[34] also presented data that allows comparison of pain scores among individuals who underwent long-pulse pattern NNL (100-ms) compared to those who underwent conventional MSL (30-ms). The mean VAS score was lower for those who received NNL compared to

Study or Subgroup	Conventional MSL Mean	SD	Total	Conventional SSL Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Muqit 2010[35]	2.4	2.3	20	4.9	3.3	20	-0.86 [-1.51, 0.21]
Nagpal 2010[7]	0.33	0.216	60	4.6	1.296	60	-4.57 [-5.25, -3.88]
Yang 2010[20]	2.18	0.97	78	5.88	1.06	77	-3.62 [-4.14, -3.11]
Muraly 2011[39]	1.2	0.404	50	3.06	0.712	50	-3.19 [-3.79, -2.59]
Salman 2011[41]	0.61	2.15	30	2.72	2.15	30	-0.97 [-1.51, -0.43]
Chhablani 2015[34]	2	0.65	22	3.8	2.1	14	-1.26 [-2.00, -0.52]
Zhang 2017[38]	1.15	0.812	20	1.95	0.759	20	-1.00 [-1.66, -0.34]
Inan 2018[11]	2.86	1.21	12	5.75	1.35	16	-2.17 [-3.14, -1.20]
Nemcansky 2019[40]	3.28	1.9	30	3.93	1.88	30	-0.34 [-0.85, 0.17]
Passos 2019[37]	4.9	2.4	21	5.9	2.2	20	-0.43 [-1.05, 0.19]
Ahmed 2020[18]	0.515	0.834	40	1.28	1.16	40	-0.75 [-1.20, -0.30]

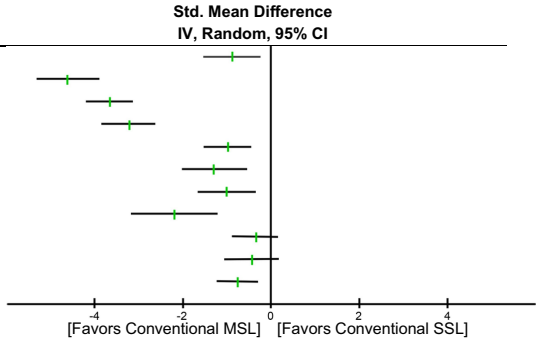

Figure 4 Forest plot comparing conventional MSL and conventional SSL.

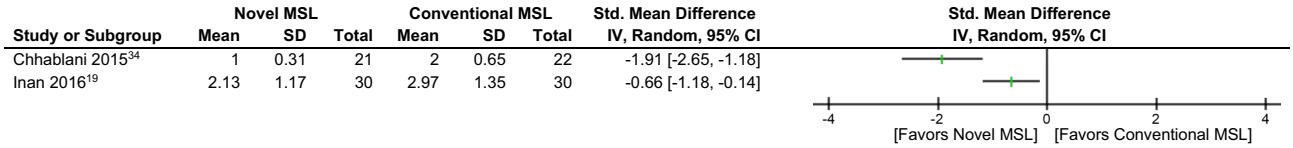

Figure 5 Forest plot comparing NNL and conventional MSL (Pulse duration: 30-ms).

those who underwent conventional MSL, although the confidence intervals had an overlap (1.5 ± 0.56 versus 2.0 ± 0.65).

Comparison 3: NNL versus Conventional SSL

Two RCTs (Figure 6) and 1 CCT were included for this analysis. All studies in this comparison used the pattern mode of NAVILAS®. The study of Chhablani et al[34] found that pain scores were significantly lower for patients who underwent 30-ms NNL compared to scores reported by the 100-ms conventional SSL group (1.00 ± 0.31 versus 3.8 ± 2.10). Furthermore, VAS scores were still lower for the NNL group compared to the conventional SSL group when the NNL pulse duration was set at 100-ms (1.50 ± 0.56 versus 3.8 ± 2.10). The study of Polat et al[36] where patients underwent NNL on one eye and conventional SSL on the other eye also found lower pain scores with NNL even when the pulse duration was set at 100-ms for both treatment arms, although this study reported incomplete data. Figure 6 shows the Forest Plot comparing pain scores using long-pulse (100-ms) NNL versus conventional SSL. The computed mean difference of pain scores is equivalent to 1 to 2 VAS points favoring long-pulse NNL over conventional SSL.

The CCT of Kim et al[22] also showed a significantly higher mean VAS score among patients undergoing conventional SSL versus short-pulse NNL (6.9 ± 1.1 versus 3.3 ± 1.2). Although the study design has a serious risk of bias, the reviewers believe that this bias effectively lowers VAS scores in the conventional SSL group given that a smaller area is treated with this laser, further supporting that NNL is less painful compared to conventional SSL.

Discussion

Pain during panretinal photocoagulation is attributed to thermal effects on the choroid, stimulation and direct photocoagulation of long and short ciliary nerves, and diffusion of heat into the retinal nerve fiber layer.[35,36,43,44] Pain with PRP has been described with terms such as "ache", "pin-prick-like" and "sharp" among others; other side effects such as photophobia, anxiety, and nausea were also reported.[45] Pain responses are thought to be influenced by different factors such as culture, individual pain threshold, degree of fundus pigmentation, sex, duration of diabetes, experience of prior laser therapy, retinal location of laser administration, and wavelength used.[11,21,36,43,44,46] There is conflicting evidence on the role of sex in pain scores; initial studies have claimed that females report higher pain scores after PRP, but the observation was not consistent across different studies.[11,35] Lower pain scores among patients with longer duration of diabetes are attributed to chronic damage in retinal pain neurons, following a mechanism similar to that of diabetic neuropathy.[11,36] Polat et al[36] identified previous laser experience as an important factor in the expression of pain during laser therapy. In their study, stratification between "experienced" and "inexperienced" group revealed lower reported pain scores among experienced patients treated with conventional SSL.[36] A similar observation was reported in the study of Inan et al.[11] However, both of these studies demonstrated overall high risk of bias; hence, further studies may be needed to support this theory. Another important factor that affects pain responses is the area of photocoagulation. It is known that administration of laser shots at the horizontal periphery causes more pain due to the direct stimulation of the ciliary nerves.[21]

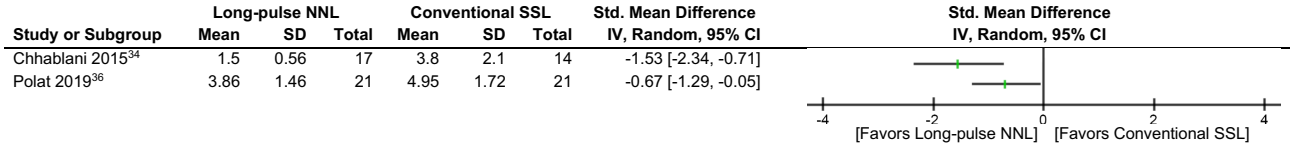

Figure 6 Forest plot comparing long-pulse NNL and conventional SSL (pulse duration: 100-ms).

A good understanding of pain in relation to laser platforms can allow treatment optimization.[8] Majority of the studies in this review employed a 532-nm green laser. The use of longer wavelengths, specifically those in the red to infrared range, allows deeper penetration into the sensory-rich choroid and greater pain sensation.[11,46] Theoretically, use of light with shorter wavelengths may improve patient comfort during the procedure.[11] In the report of Passos et al,[37] pain tolerance and photophobia levels were not statistically different for patients who underwent 577-nm MSL and 532-nm SSL. In this study, it is possible that additional pain brought about by the use of the longer wavelength was compensated by the shorter pulses of the MSL. In the report of Muraly et al,[39] where pain scores were based on the physician's observations of the patient's responses to treatment, a greater proportion of patients who underwent conventional SSL experienced moderate to very severe pain compared to those treated with conventional MSL. However, it is difficult to give weight to the findings of this study as it is subject to detection bias.

Multi-spot pattern lasers have gained popularity due to ease of its use. A single depression of the foot pedal delivers multiple laser shots in shorter pulses, thus shortening treatment time. Although the shorter pulse duration deviates from the treatment protocol specified in the ETDRS, several studies report that it does not decrease the effectiveness of PRP for diabetic retinopathy.[7,10,34,44] Inan et al[11] reported lower pain scores using conventional MSL on one eye versus SSL on the other eye when the number of spots are equalized per eye. This method, however, does not replicate usual practice as more laser spots are required to complete PRP by MSL. The effect of this bias may favor conventional MSL versus conventional SSL. Results of studies with low to some risk of bias show that MSL is more tolerable for patients in comparison to conventional SSL despite the higher number of spots administered. Shorter pulses lead to shorter time for thermal and inflammatory changes to take place thereby diminishing choroidal and retinal damage.[14,20,35,44,45] The 20 to 30-millisecond pulse duration used in MSL balances adequate administration of therapeutic laser and reduction of collateral damage.[7,14,41,47] Muqit et al attributed the lower pain scores in conventional MSL to the pattern application, which may have resulted to pain habituation (i.e. decreasing pain responses throughout duration of PRP) and improved comfort. In this study, pain during the entire duration of the laser procedure was reported by 55% of eyes that underwent conventional SSL versus 15% for those who underwent conventional MSL.[35] Another advantage of using short-pulse over long-pulse settings is the preservation of the patient's visual fields, as the burns expand less over time.[7,8] Nagpal et al[7] found that 200-µm spots expanded to 430-µm and 310-µm for conventional SSL and conventional MSL, respectively, after 3 months of therapy. In addition, treatment time is significantly reduced, which may also improve compliance.[8,11,45] Nagpal et al[7] reported reduced total time of 1.43 minutes using conventional MSL compared to 4.53 minutes using conventional SSL.

Findings of this review are consistent with an earlier report of Al-Hussainy et al,[44] where lower pain scores were recorded with shorter pulse settings despite a higher total power administered compared to long-pulse, low power settings. Short-pulse laser therapy causes less tissue photocoagulation when compared to long-pulse laser, thereby requiring significantly more spots and a higher total power than long-pulse conventional SSL to complete therapy.[35,40,41] This suggests that laser fluence, the product of power and time over a given area, rather than total power alone, determines pain perception. Studies have demonstrated that a reduction in laser fluence results into a corresponding decrease in pain scores and vice versa.[7,10,11,41] Nagpal et al reported lower fluence with conventional MSL compared to conventional SSL when both treatments are administered in 2 sessions (40.33 J/cm^2 vs 191 J/cm^2).[7]

The NAVILAS® NNL platform makes use of a frequency doubled, Neodymium-doped Yttrium orthovanadate ($Nd:YVO_4$) solid-state laser photocoagulation system. It is capable of infrared and color retinal imaging and fundus fluorescein angiography. The laser applications are pre-planned on the retinal image display, allowing precise and efficient administration of laser spots and uniform energy distribution. It also has a "eye tracking" feature that improves safety and accuracy.[36,48,49] In a comparison of pain scores of patients undergoing laser with NNL and conventional MSL (PASCAL®), Inan et al[19] found that 13.3% of patients had no pain using the NNL while those in the conventional MSL all had some degree of pain. Amoroso et al[8] conducted a CCT on bilateral eyes of 16 patients using 577-nm NNL on one eye and conventional MSL on the other eye. It was found that mean pain scores using conventional MSL were thrice the mean scores obtained using NNL (7.1 + 2.1 versus 2.4 + 1.6, $p < 0.001$). This was the highest VAS score reported associated with PRP in all the studies included in this review, but the results may have been influenced by the non-randomized study design. This is also the only study that

compared pain scores using the pre-planned mode of NAVILAS®, in contrast to other studies by Kim,[22] Chhablani,[34] Polat,[36] and Inan[19] where the pattern mode was employed. Amoroso et al[8] attributed lower pain scores using NNL to the short breaks in between the application of each spot, allowing retinal tissue restoration and decreased pain stimulation. Spatial summation of pain is also minimized using the pre-planned mode of the NNL wherein the linear delivery yields a greater separation of the first and last laser spots. In contrast, conventional MSL automatically applies the spots in clusters which can cause greater spatial summation of pain.[8]

Novel navigated laser systems may be set to deliver both short and long pulse durations, allowing adherence to the ETDRS guidelines. Chhablani et al[34] and Polat et al[11] investigated the difference in pain scores among patients undergoing NNL versus conventional SSL using 100-ms pulse duration for both groups. As seen in the results of Comparison 3, both studies reported significantly lower VAS scores using the NNL system compared to conventional SSL systems.[34,36] Chhablani et al[34] stated that the use of infrared imaging in NNL instead of the white light used in conventional laser lessens the pain experienced by patients. The delivery of pattern laser in sudden pulses with NNL also avoids repeated pain stimulation in comparison to single-spot laser therapy.[34] This review shows that the newer NNL technology effectively lessens the pain experience of patients, even when pulse durations are the same. At a set pulse duration of 100-ms, the improved patient experience with the newer laser was attributed to differences in the method of laser beam positioning, heat radiation, and choroidal heating.[36] Refractive properties of the contact lens used with NNL under topical anesthesia allowed less tilting for peripheral laser administration thereby improving patient comfort.[19,34–36]

Only the study by Chhablani et al[34] uniquely studied all comparison groups of interest. Four groups were included in the study: short-pulse NNL (30-ms), conventional MSL (30-ms), long-pulse NNL (100-ms), and conventional SSL (100-ms). Average VAS scores were 1.0 ± 0.31, 2.0 ± 0.65, 1.5 ± 0.56, and 3.8 ± 2.10, respectively, indicating the benefit of using navigated pattern laser when looking at pain as the primary outcome. This study also shows that conventional SSL with long pulse durations (100 to 200-ms) yields the highest pain scores.[34]

This is the first systematic review that aimed to compare pain scores as a primary outcome among patients with diabetic retinopathy undergoing conventional SSL, conventional MSL, and NNL. Qualitative analysis from moderate-quality evidence showed a trend favoring NNL over conventional MSL, and conventional MSL over conventional SSL when looking at pain as the primary outcome. Ophthalmologists should take this into account when choosing the method for laser therapy for their patients, especially those with low pain tolerance. Administrators of ophthalmic treatment facilities can also take this into consideration when acquiring laser machines.

The review did not analyze the differences in the effectiveness of the different types of laser in the management of advanced diabetic retinopathy. The current review yielded 17 studies with a total of 783 patients and 1961 eyes. Majority of the RCTs included in this review had some concerns for bias; included CCTs demonstrated low risk of bias. A limitation of this study is the incomplete data available for some of the included studies and possible reporting bias. The magnitudes of the differences in pain scores should be interpreted with caution, given that there were significant variations in the laser settings used. A meta-analysis was deemed impractical due to marked heterogeneity in methodology among included studies.

Conclusions

Pain is an undesirable adverse effect of panretinal photocoagulation that may affect compliance to therapy. It is important for ophthalmologists to seek ways to minimize discomfort of the patients during any ocular procedure. With available evidence from largely heterogenous, moderate-quality studies in this systematic review, there is a benefit in using MSL over SSL for PRP among patients with diabetic retinopathy, focusing on pain as an important adverse outcome. Furthermore, NNL systems yield even lower pain scores in comparison to the conventional SSL and MSL systems.

Disclosure

The authors report no conflicts of interest for this work.

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