Retinal Laser Photocoagulation

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SUMMARY

Since its discovery in the 1940s, retinal photocoagulation has evolved immensely. Although the first photocoagulators utilised incandescent light, it was the invention of laser that instigated the widespread use of photocoagulation for treatment of retinal diseases. Laser permits choice of electromagnetic wavelength in addition to temporal delivery methods such as continuous and micropulse modes. These variables are crucial for accurate targeting of retinal tissue and prevention of detrimental side effects such as central blind spots. Laser photocoagulation is the mainstay of treatment for proliferative diabetic retinopathy amongst many other retinal conditions. Considering the escalating prevalence of diabetes mellitus, it is important for physicians to grasp the basic principles and be aware of new developments in retinal laser therapy.

KEY WORDS:
Laser coagulation, Light coagulation, Laser therapy, Retinal pigments, Retinal diseases.

INTRODUCTION

Laser photocoagulation is a crucial therapy for numerous retinal diseases. Photocoagulation involves protein denaturation and is the result of tissue absorption of radiant energy with conversion to heat[1]. It should not to be confused with photodisruption and photoablation, which entail distinct molecular reactions and are utilised more commonly in the anterior segment and for refractive eye surgery. While photocoagulation is possible using visible light, the invention of laser revolutionised retinal therapy by facilitating more precise, reliable and less painful application of photocoagulation. By virtue of single wavelength selection, laser also reduces the amount of damage to adjacent tissues. Its effectiveness and non-invasive methods of application have made laser photocoagulation the standard of care for many retinal conditions.

The most notable laser amenable disease is proliferative diabetic retinopathy (PDR). Over a decade, the prevalence of diabetes mellitus (DM) in Malaysia has escalated from 8.3% to 14.9% (1996-2006) and by 2030 it is predicted that 2.48million Malaysians will be affected by DM[2]. Of this diabetic population, 36.8% have diabetic retinopathy (DR) of any form and 15.0% have vision threatening DR requiring laser or surgery[3]. Despite our best efforts with risk factor management, the number of DR cases is soaring. It is therefore essential for all medical practitioners to be familiar with laser photocoagulation.

Other retinal conditions treatable with laser photocoagulation include diabetic macular oedema (DMO), retinal vein occlusions, leaking arterial macroaneurysms, age-related macular degeneration (AMD), retinopathy of prematurity (ROP) and retinal tears. For each condition, laser is targeted at different tissue types in distinct areas of the retina (Table I). Therefore, the appropriate choice of wavelength is imperative. As technology has matured, not only are different wavelengths becoming more accessible, there is a wider variety of laser delivery methods that promise to enhance precision of laser burns or simplify the application of retinal laser.

In this article we will outline the history of retinal laser photocoagulation, discuss the nature and application of various laser wavelengths and describe exciting new laser innovations available now and in the near future.

History of Retinal Laser Photocoagulation

Knowledge of non-laser photocoagulation dates back to 400BC when Socrates first described solar retinitis or eclipse burns of the retina. During the 1940s, German ophthalmologist Meyer-Schwickerath pioneered light coagulation of the retina[4]. Inspired by the effects of unprotected viewing of the 1945 solar eclipse on a medical student's macula, he developed a sunlight photocoagulator (1947) and experimented with the Beck carbon arc photocoagulator which was used clinically on several hundred patients between 1950 and 1956. Meyer-Schwickerath and Littman in conjunction with Zeiss, assembled the first xenon-arc coagulator in 1956. This was used to treat anterior and posterior segment tumours as well as retinal vascular diseases. Although this was effective and came into widespread use, it lacked precision, required long duration of exposure, was painful and resulted in multiple complications[5].

All the above photocoagulators produced light comprised of various wavelengths within the visible and infrared spectrum. Hence, full thickness retinal burns were achieved rather than tissue specific burns that were later made possible by laser (single wavelength) photocoagulators[6]. The first ophthalmic laser was the ruby laser, invented by Maimann in 1960. In addition to its efficacy in controlling PDR, this solid-state laser was more compact and reliable than its predecessor the xenon-arc coagulator (Figure 1). Then in 1968, L'Esperance introduced the argon laser which led to the widespread use of ophthalmic laser photocoagulation[7].

A multitude of photocoagulators have since been invented with a variety of media used to generate laser. Argon and

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krypton lasers use ionised gas as the lasing medium, while the tunable dye laser uses a liquid solution. Neodymium-doped yttrium aluminium garnet (Nd: YAG) and diode lasers are both solid-state lasers that utilise crystals and semiconductors respectively. The solid-state lasers are becoming the preferred option due to their portability and ability to deliver laser in continuous and pulse mode, to be later discussed in this article.

Laser Wavelengths

Laser is an acronym for Light Amplification by Stimulation Emission of Radiation. It differs from incandescent light in its monochromaticity that permits wavelength choice, and high collimation that facilitates more precise targeting. Radiation is delivered to the retina by laser and the subsequent photothermal reaction results in photocoagulation. A mere rise of 10°C to 20°C is sufficient to cause coagulation[6], however, the coagulation effect is dominant at 60-70°C.[1] The extent of heating is dependent on properties of both the laser and the target ocular tissue. Modifiable properties of the laser include duration, power and wavelength.

The wavelengths employed for retinal photocoagulation range from approximately 400nm to 800nm. This spans the majority of the visible electromagnetic spectrum (violet 380nm – red 750nm) and part of the infrared spectrum (750nm – 1mm). The ideal wavelength is characterised by good penetration through ocular media and maximal absorption in the target tissue. Shorter wavelengths are more easily scattered, hence, red light (620 - 750 nm) has better penetration than blue light (450-495 nm). Scatter is a result of radiation absorption by tissues other than the target. It can occur anywhere anterior to the retina, including the anterior segment, lens and vitreous. Therefore, the degree of scattering increases with maturity of a cataract and conditions such as vitreous haemorrhage. In such cases, longer wavelength, increased laser duration or higher energy levels may be required.

The extent of laser absorption is also dependent upon the pigment composition of the target tissue. The three major ocular pigments are melanin, xanthophyll and haemoglobin. Their absorption of different wavelengths is depicted in Figure 2. Melanin absorbs most of the visible to near infrared portion of the light spectrum. As it is the most effective light absorber, the major site of laser absorption is in the melanin containing retinal pigment epithelium (RPE) and choroid[8]. Xanthophyll has maximal absorption of blue light and is found predominantly in the macula. Haemoglobin has poor red light absorption but excellent blue, green and yellow light absorption. Knowledge of varied absorption in different ocular tissues guides appropriate choice of laser wavelength.

The argon blue-green laser (70% blue 488 nm, 30% green 514.5 nm) was the predominant ophthalmic laser for many years[9,10]. It was utilised for extrafoveal choroidal neovascular membranes in age-related macular degeneration (AMD), panretinal photocoagulation (PRP) in DR (Figure 3) and to seal breaks in rhegmatogenous retinal detachment[10]. However, it has fallen out of favour due to several disadvantages. With its short wavelength, it scatters more so than other colours and therefore requires higher energy levels to achieve adequate coagulation. While scattered radiation may be insufficient to cause photocoagulation in adjacent tissues, the potential for photochemical damage (a low energy reaction that breaks molecular bonds) is certainly higher for short wavelengths. This is especially true in procedures requiring large volume irradiation, such as PRP. Of greatest concern is the possibility of central blind spots secondary to photochemical damage of the macula, where there are high proportions of xanthophyll. Scattering at the level of the lens can also accelerate cataract formation in patients with significant nuclear sclerosis[11].

Since the discontinuation of blue laser, the green laser has become the most popular and has adopted all the same applications. The green wavelength is superior due to minimal absorption of xanthophyll coupled with strong affinity for melanin and haemoglobin. Therefore it can be used in the macular region as well as the periphery, and can target abnormal vessels. Green laser is available in two systems: argon gas (514.5nm) and solid state frequency-doubled Nd-YAG (532nm). The latter utilises a crystal of yttrium, aluminium and garnet doped with neodymium ions (Nd). Its beam is near infrared at 1064nm, however, frequency doubling achieved by a potassium-titanium-phosphate (KTP) crystal halves the wavelength resulting in green laser.

Yellow laser has attributes similar to green laser, with a few extra advantages. This longer wavelength scatters less than green and therefore has a reduced energy requirement[12]. Also, its absorption by haemoglobin is at least twice that of green laser, making it a more effective laser for vascular structures[9]. Despite being considered the best wavelength to treat vascular lesions, its application has been limited by the costliness and bulkiness of krypton yellow lasers (568.2nm) and tunable dye lasers (variable wavelength depending on dye). In 2008 the more compact and cost effective solid-state diode yellow laser (577nm) was introduced into clinical practice (Figure 1-A). The University of Malaya is currently conducting clinical trials comparing the yellow laser with conventional green laser for PDR and DMO.

When diode lasers were first introduced, they emitted wavelengths in the infrared range (780-840nm). Compared with visible wavelengths, infrared light scatters less and therefore is particularly useful for treating patients with dense ocular media such as cataract and vitreous haemorrhage, in addition to retinal and choroidal tumours[13]. However, it is not as effectively absorbed with only 20% absorption of infrared wavelength (800nm) compared to 95% absorption of blue wavelength (514nm)[14]. Hence, higher energy levels and longer exposure are required to achieve similar photocoagulation effects[6,11]. Greater patient discomfort may therefore be a consequence[8]. Fortunately, diode lasers are now available in a variety of visible wavelengths. These portable, economical lasers are fast becoming the favoured option for ophthalmologists purchasing new platforms.

Clinical Applications of Laser Photocoagulation

As previously mentioned, DR is the most prevalent retinal disease treatable with laser photocoagulation. DR is categorised into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is

characterised by varying degrees of microaneurysms, retinal haemorrhages, hard exudates, cotton wool spots, macular oedema, venous beading and loops, intraretinal microvascular abnormalities, and capillary non-perfusion. New vessel formation is the hallmark of PDR and is usually found in conjunction with variable degrees of the above features (Figure 3-A). These vessels are fragile and associated with fibrosis and traction. If allowed to proliferate, there is an increased risk of vitreous haemorrhage and retinal detachment. The landmark Diabetic Retinopathy Study[15] found that panretinal photocoagulation (PRP) reduced the risk of severe vision loss in patients with PDR or severe NPDR by at least 50% compared with untreated eyes. PRP involves up to 2000 laser burns applied to the peripheral retina, and although the mechanism of action is yet to be fully elucidated, it causes regression of neovascularisation (Figure 3-B.) PRP is currently the mainstay of treatment for PDR.

Diabetic macular oedema (DMO) can occur at any stage of DR and is the leading cause of severe visual morbidity in diabetic patients[9]. Retinal thickening is a consequence of accumulated fluid originating from leaking microaneurysms and diffuse capillary leakage. Leaking microaneurysms can be treated with focal laser, while diffuse capillary leakage requires application of macular grid laser, which spares the foveal avascular zone. Another landmark study conducted by the Early Treatment Diabetic Retinopathy Study Research Group found that the risk of visual loss in patients with clinically significant DMO was substantially reduced by focal photocoagulation[16].

Several other randomised clinical trials have also demonstrated efficacy of laser photocoagulation for the following retinal diseases: subfoveal choroidal neovascularisation in patients with AMD[17], retinopathy of prematurity[18,19] and macular oedema secondary to branch retinal vein occlusion[20].

Laser Delivery Systems

Laser photocoagulation can be applied to the retina via several routes. The most common is transpupillary laser either performed on slit lamps through specialised contact laser lenses, or with binocular indirect ophthalmoscopy through non-contact lenses. The latter is useful for peripheral retinal lesions as this apparatus offers a wider field of view. Laser can also be transmitted via fibreoptics to an endolaser probe for intraocular delivery during vitreoretinal procedures. Contact probes are also available for trans-scleral application.

In recent years, ophthalmologists have been offered a choice of temporal modes for laser delivery. Currently the majority of retinal photocoagulation is achieved using continuous mode: Laser is emitted at a sustained energy level for a given period of time, usually between 100-200ms (Figure 4-B)[6]. The major concern with continuous laser is the damage to subadjacent retinal tissue secondary to passive thermal diffusion beyond the target site. In fact, macular grid laser using conventional continuous mode has previously been shown to cause delayed enlargement of laser scars up to 300% the size of the original laser spot, with detrimental effects if the fovea was involved[21]. A new approach called subthreshold micropulse mode is thought to limit the amount of damage to subadjacent tissue. Rather than maintaining the same degree of energy throughout the exposure time, laser is delivered in ultrashort pulses (microseconds) with adjustable on and off times (Figure 4-A). The length of these pulses needs to be shorter than the thermal relaxation time of the target tissue, that is the time required for heat to be transferred away from the irradiated tissue. Micropulse laser thereby induces a temperature rise insufficient to cause ancillary damage to surrounding retinal tissue[22-24]. This technology has been most extensively explored in the treatment of DMO, and has been shown to minimize scarring to the extent that laser spots are generally undetectable on ophthalmic and angiographic examination.

The majority of studies have tested 810nm micropulse laser as earlier diode lasers were only available in the infrared spectrum. The introduction of newer solid-state laser platforms permits micropulse application of lasers in the visible spectrum. Of particular interest will be the combination of yellow wavelength with micropulse delivery for the treatment of common conditions like DMO. This is also currently under investigation at the University of Malaya.

New and Future Innovations

Novel approaches of laser photocoagulation are always being considered. Another subthreshold laser system, Retina Regeneration Therapy (Ellex 2RT, Ellex Medical Lasers, Atlanta) is currently being evaluated. It is a 532 nm laser that produces 3 nanosecond pulses. The energy level of pulses delivered by Ellex 2RT are lower than those of micropulse laser and therefore is purported to stimulate renewal of RPE rather than destroy it. Its proposed utility is in the treatment of early AMD and diabetic maculopathy.

Introduced in 2005, the Pascal (Pattern scan laser, OptiMedica, Santa Clara, California) photocoagulator is a 532 nm frequency-doubled Nd:YAG solid-state laser. It is a semiautomated system that delivers laser pulses in a rapid, predetermined sequence with a variety of laser spot patterns and sizes (Figure 5). The main benefits are thought to be greater accuracy and faster treatment with a time reduction from 100-200 ms per burn in conventional photocoagulation compared with 10-20ms per burn with Pascal[25]. So far, it has been assessed as a mode of delivering PRP, macular grid laser and retinopexy in patients with DR, macular oedema and retinal detachments, respectively.

Another laser platform, Navilas (Navigated laser, OD-OS, Inc., Teltow, Germany) integrates live fundus imaging and fluorescein angiography with photocoagulation. It allows the clinician to take and view retinal images on a computer screen then plan the area and pattern with which to deliver 532 nm laser pulses (Figure 6). Areas that should not be treated, such as the optic nerve and macula are also demarcated. The use of a slit lamp is obviated as the computer carries out laser treatment to marked areas of the retina. OD-OS has recently been given clearance to commence marketing of their new invention.

Table I: Common retinal conditions treated with lasers

Retinal condition	Laser therapy
Proliferative diabetic retinopathy (PDR) - New abnormal retinal vessels with varying degrees of microaneurysms, haemorrhages, hard exudates, cotton wool spots.	Panretinal photocoagulation (PRP) involves 1000-2000 laser burns to the peripheral retina. Subsequent regression of neovascularisation reduces the chance of vitreous haemorrhage and tractional retinal detachment.
Diabetic macular oedema (DMO) - Leaking microaneurysms or diffuse capillary leakage cause retinal thickening.	Focal laser targets leaking microaneurysms. Macular grid laser targets diffuse capillary leakage. The foveal avascular zone is not lasered.
Macular oedema in branch retinal vein occlusion (BRVO) - Oedema develops due to increased capillary permeability and release of angiogenic growth factors after BRVO	Macular grid laser as for DMO
Central retinal vein occlusion (CRVO) - Obstruction of venous outflow can result in retinal haemorrhages, oedema and ischaemia.	Chorioretinal venous anastamosis is achieved through targeted laser photocoagulation that allows venous blood to bypass the site of obstruction and enter the choroid[26]. PRP can be done if neovascularisation occurs
Retinal tears - The site of fluid egress that results in rhegmatogenous retinal detachment.	Retinopexy is performed by laser application around the break to seal retina to RPE and choroid.
Retinopathy of prematurity (ROP) - Proliferative retinopathy affecting premature infants exposed to high oxygen concentrations. Abnormal vessel growth is present at the junction between immature avascular peripheral retina and vascularised posterior retina.	Laser is applied to avascular retina to retard further growth of abnormal vessel into this region. This prevents traction and subsequent retinal detachment.
Leaking arterial macroaneurysms - Dilatation of the retinal arteries that can lead to fluid leakage or haemorrhages.	Laser photocoagulation applied to or surrounding the macroaneurysm causes it to thrombose or sclerose thus reducing exudation and risk of haemorrhage.
Retinal ischaemia due to vasculitis, retinal vein or arterial occlusion - Retinal hypoxia can result in increased angiogenic growth factor expression, which stimulates neovascularisation of the retina, disc and iris. These can progress to vitreous haemorrhage or neovascular glaucoma.	Laser ablation of hypoxic retinal tissue reduces the release of angiogenic growth factors that stimulates neovascularisation.

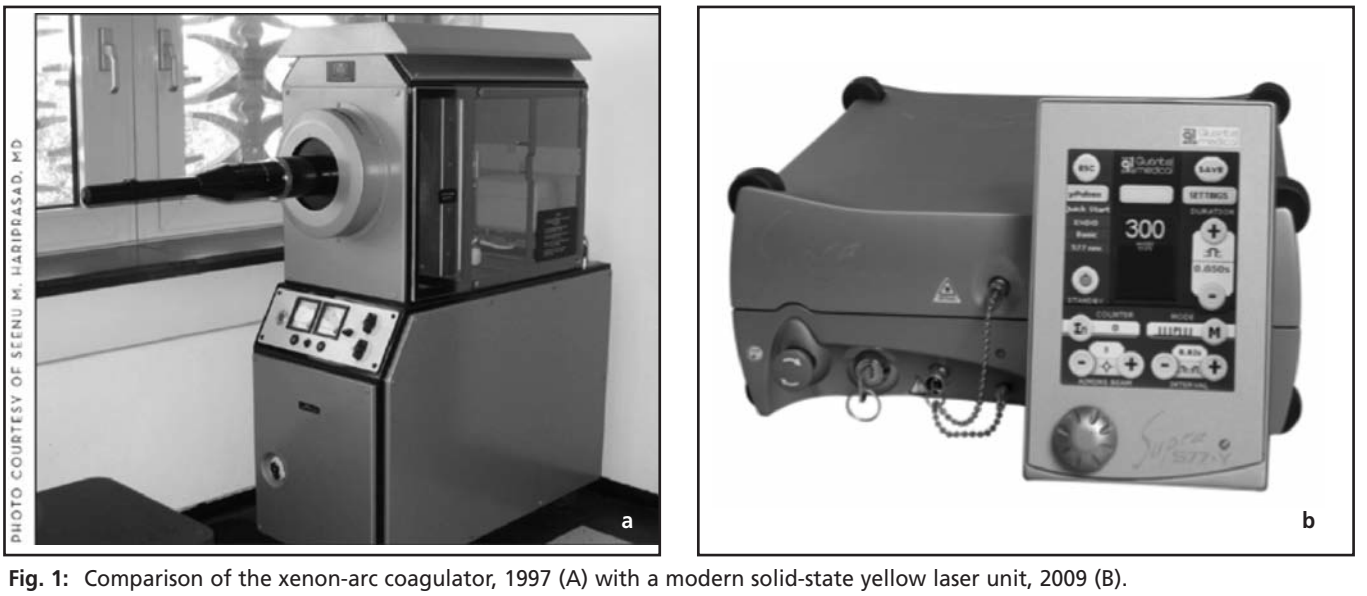

Fig. 1: Comparison of the xenon-arc coagulator, 1997 (A) with a modern solid-state yellow laser unit, 2009 (B).
[Note. From "Retinal Lasers: Past, Present, and Future" by M.D. Ober and S. M. Hariprasad, Jan 2009, Retinal Physician, p. 37.][5]

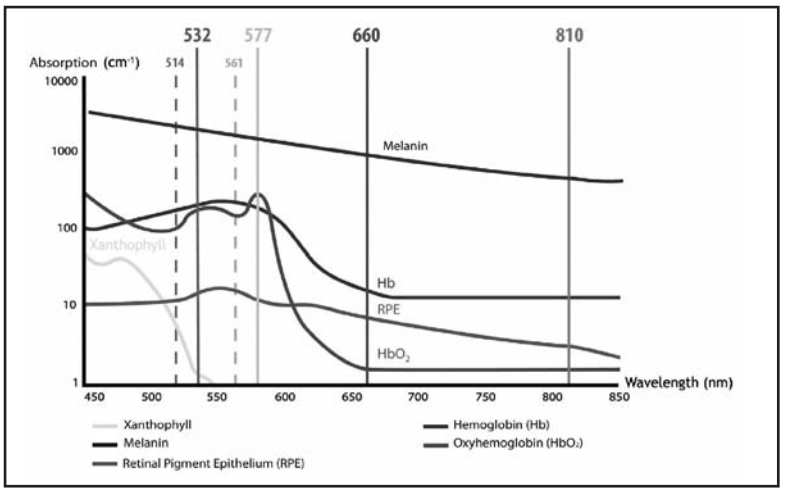

Fig. 2: Absorption of different laser wavelengths by various ocular pigments. Macular xanthophyll has greater absorption of blue light than any other wavelength. Haemoglobin has good absorption of most visible wavelengths except red light. Deoxygenated hemoglobin absorbs red more strongly than oxyhaemoglobin. Melanin and RPE have excellent absorption of all wavelengths and absorption diminishes with increasing wavelength.

[Note. Based on "Wavelength selection in macular photocoagulation. Tissue optics, thermal effects, and laser systems" by M.A. Mainster, 1986, Ophthalmology, 93, pp. 952-8.][27]

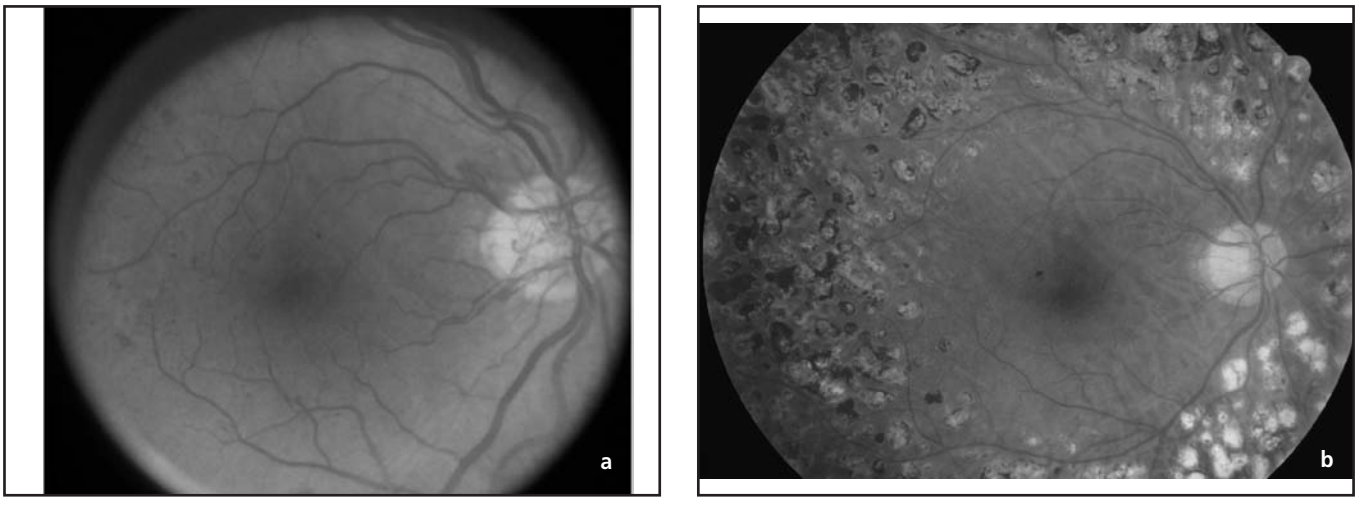

Fig. 3: New vessel growth on the optic nerve seen in PDR (A) regresses after treatment with PRP (B). The patient retains good vision, as the macula is untouched by laser. PRP prevents severe visual loss due to vitreous haemorrhage and retinal detachment.

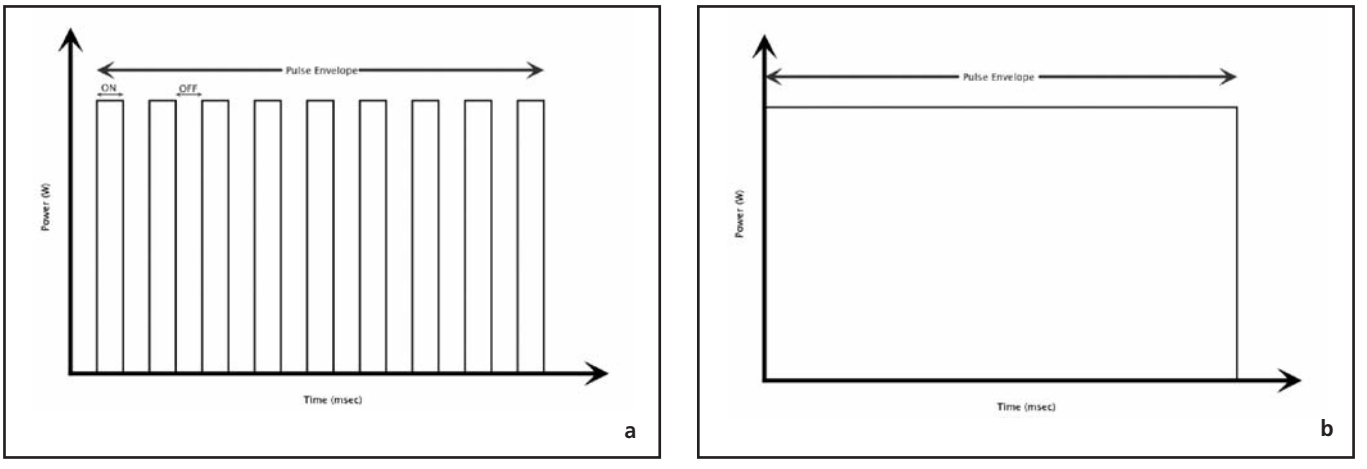

Fig. 4: Scheme of micropulse mode (A). Laser is delivered in microsecond pulses contained within millisecond envelopes. Thermal isolation is achieved through short duration of "ON" time causing selective destruction of RPE cells and dissipation of heat during the "OFF" phase. On and off times are adjustable. This is in contrast with conventional continuous laser, which delivers energy in a single pulse of predetermined duration (B). There is greater thermal diffusion to surrounding retinal tissue (B).

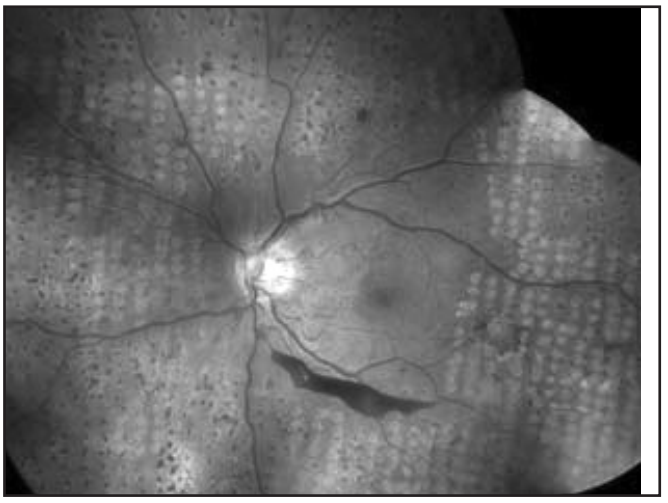

Fig. 5: Complete panretinal photocoagulation for diabetic retinopathy using the Pascal platform. Note the even distribution of laser scars compared with conventional laser scars in Figure 3.

[Treatment and photograph by Harry W. Flynn, JR., MD, Bascom Palmer Eye Institute Miami, Florida]

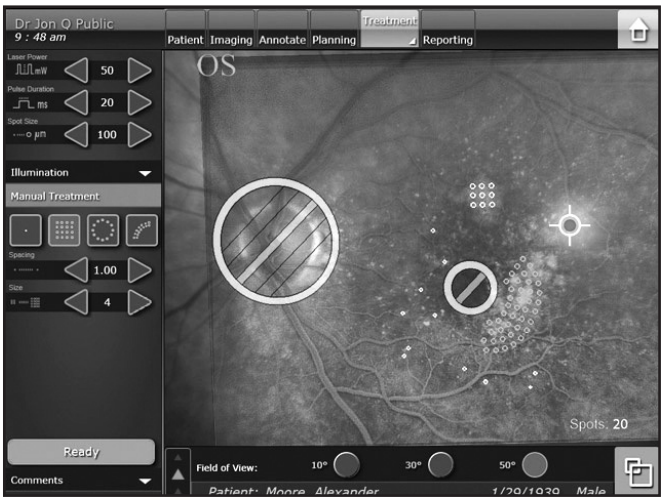

Fig. 6: Screen shot of Navilas treatment stage. A fluorescein angiogram is overlaid on a live colour fundus image. Yellow dots designate planned treatment and white dots designate completed treatment. Treatment is pre-planned by the ophthalmologist then laser treatment is performed by the computer.

[Courtesy of OD-OS, Inc., Teltow, Germany]

CONCLUSION

The ever-evolving realm of laser technology has propelled the refinement of retinal laser therapy. Whereas, availability, size of units and cost effectiveness have previously limited clinical application of certain wavelengths and delivery methods, these are now more accessible. Laser wavelengths are an important variable and our understanding of their attributes and pitfalls continues to grow. Green laser has superseded blue-green laser, and now yellow laser threatens to overshadow the green laser with its superior safety profile and wider clinical application. We even have new delivery methods that promise greater efficiency, increased accuracy, minimised collateral damage and even detailed pre-planning of laser spot application.

For many decades now, laser photocoagulation has remained the mainstay of treatment for various retinal diseases. It offers ophthalmologists a safe, non-invasive method of treating common retinal conditions such as PDR, DMO and AMD, with proven efficacy in multiple clinical trials. The desire to achieve improved visual outcomes with fewer side effects, drives continuing research in the field of retinal laser photocoagulation.

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Retinal Laser Photocoagulation - Multiple Choice Questions

1. Retinal laser photocoagulation . . .

a) is a photothermal reaction. (True/False)
b) was discovered in the 1940s. (True/False)
c) utilises wavelengths between 400-800nm. (True/False)
d) can cause damage to subadjacent tissue. (True/False)
e) can only be applied during a vitrectomy. (True/False)

2. Blue laser . . .

a) scatters less than red laser. (True/False)
b) is well absorbed by macular xanthophyll. (True/False)
c) is the best wavelength for treating vascular lesions. (True/False)
d) is better absorbed by melanin than any of the other ocular pigments. (True/False)
e) is currently the laser of choice. (True/False)

3. Panretinal photocoagulation . . .

a) is targeted at leaking microaneurysms. (True/False)
b) is the treatment of choice for mild non-proliferative diabetic retinopathy. (True/False)
c) can be delivered using the Pascal photocoagulator. (True/False)
d) causes proliferation of new abnormal vessels. (True/False)
e) can prevent retinal detachments. (True/False)

4. Micropulse laser mode . . .

a) reduces subadjacent tissue damage. (True/False)
b) is the equivalent of Ellex Retina Regeneration Therapy. (True/False)
c) delivers laser at a sustained energy level for 100-200ms. (True/False)
d) has been extensively investigated for lasers in the visible spectrum. (True/False)
e) is useful for treating diabetic macular oedema. (True/False)

5. Laser photocoagulation can be used to treat . . .

a) retinal tears. (True/False)
b) retinopathy of prematurity. (True/False)
c) refractive errors. (True/False)
e) acute angle closure glaucoma. (True/False)
f) choroidal neovascularisation. (True/False)