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The use of laser therapy in retinal diseases. Part III

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HIGHLIGHTS

Despite introduction of other potentially innovative, beneficial and successful therapeutic methods, lasers are still considered the gold standard.

ABSTRACT

Retinal diseases account for the vast majority of ophthalmologic disorders. Over the past years, laser-based approach has been successfully used. Despite introduction of other potentially innovative, beneficial and successful therapeutic methods, lasers are still considered the gold standard. In this review, we discuss the spectrum of currently prevailing laser methods and new insights into novel perspectives and techniques regarding laser management of retinal disorders. This paper is divided into three sections. Two parts, already published in previous issues, have presented methodology with the spectrum of laser-based techniques and literature review investigating the existing knowledge in laser management of diabetic retinopathy, diabetic macular edema and vascular retinal disorders. Finally, the current one, consists of the principles guiding laser treatment of retinal tears, retinal degeneration, retinopathy of prematurity, age-related macular degeneration and other retinal diseases.

Key words: laser therapy, retinal diseases, laser photocoagulation

LASER THERAPY IN RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a retinopathy leading to blindness in premature infants [1, 2]. According to the World Health Organization (WHO) the most common cause of blindness in children (defined as vision below 3/60 according to Snellen Charts) is retinopathy of prematurity, followed by cataracts (28%) and eyeball anomalies (11%) [1, 3].

The main risk factors for the development of ROP (according to a study by Seiberth et al.) include birth weight, gestational age, necrotizing enterocolitis, multiple blood transfusions in the child, oxygen therapy lasting > 7 days, and pre-eclampsia in the mother [1, 4].

The classification of ROPs is based on the location of lesions (zones I–III), its severity (stages 1–5) and the presence of plus disease [1, 5, 6]. Location of lesions may be as follows:

- zone I – concentrically around the optic nerve disc, from its center to the double distance between the disc and the center of the fovea
- zone II – concentric 360 degrees from the edge of zone I, reaches ora serrata from the nasal side
- zone III – the remaining temporal part of the retina in the crescentic shape of a crescent [1, 5, 6].

Stages ROP severity:

- stage I – demarcation line – flat, whitish structure, parallel to the orra seratta, dividing vascular and avascular retina
- stage II – ridge that extends above the plane of the retina, comprising small proliferating blood vessels
- stage III – comprising stage II with additional extraretinal fibrovascular proliferations
- stage IV – partial retinal detachment, usually concave, foveal (4A) and extrafoveal (4B)
- stage V – total retinal detachment [1, 5, 6].

Other symptoms are: plus disease, pre-plus disease, threshold disease and aggressive posterior form of ROP (APROP). The plus disease includes vessels dilatation and arterial tortuosity of the in the two quadrants of the posterior pole; there may also be pupil dysfunction (iris vasculature dilatation), vitreous body haze, preretinal and vitreous body hemorrhages. The occurrence of these symptoms indicates the progression of ROP. Pre-plus disease is an abnormal dilation and curvature of vessels of lesser intensity than in plus disease. Threshold disease means the occurrence of extraretinal proliferations (stage III) in zone I or II in an area of 5 adjacent or 8 clock hours in total. Its diagnosis is an indication for treatment. APROP includes symptoms of the plus disease with neovascularization occurring in zone I. Untreated APROP quickly leads to complete retinal detachment [1, 5, 6].

As many as 92–96% of ROP cases undergoes spontaneous regression without any therapeutic intervention, and only 10% of preterm infants tested prophylactically will develop severe stages of ROP requiring treatment [1, 7].

Currently, the greatest importance in the treatment of ROP is diode laser therapy of the avascular retina or much less frequent cryotherapy [1, 5].

According to the 2019 PTO guidelines, the indications for retinal laser therapy (up to 72 h from diagnosis) are: any stage of ROP in zone I with plus disease, stage III in zone I without plus disease, stage II or III in zone II with plus disease. Treatment should be considered when type 1 ROP has developed in one eye and the accompanying eye does not meet the criteria for a diagnosis of same ROP type. Sometimes in such cases it is more advantageous to qualify both eyes for treatment [8].

Depending on the ophthalmologist's experience, the anatomical success of laser due to ROP is estimated at 93.8–100% [1, 9]. Literature data indicate that in a 10-year follow-up after laser therapy there is a higher final visual acuity compared to cryo-application [1, 10]. Diode laser therapy – unlike cryotherapy – does not require long general anesthesia, allows manovers closer to the posterior pole and has fewer general complications (bradycardia and apnea). After cryotherapy, conjunctival damage and swelling, bleeding to the vitreous body and increased myopia are more frequent [1, 11, 12].

Alternative for ROP treatment are intravitreal injections of anti-VEGF (bevacizumab, ranibizumab, aflibercept). It might be used as monotherapy or with conjunction with laser ablation. Nowadays, this procedure is off labeled and required ethics committee approval and parents informed consent. It is simple procedure, with shorter duration, higher probability of physiological retinal vasculature development and smaller myopia, while comparing to lasers.

There are no strict guidelines for the use of anti-VEGF therapy in the current global recommendations, the available observations suggest effectiveness in the treatment of posterior ROP. It might be considered as optional therapy in patients with cornea, lens or vitreous body haze and in which achievement of mydriasis is severely hampered. Laser therapy with diode or argon laser remains the treatment of choice for ROP worldwide. In some clinically advanced cases, pars plana vitrectomy (PPV) is necessary, which involves the excision of the vitreous body and fibrous membranes pulling the retina. Often, lensectomy procedure is a necessity [8].

LASER THERAPY IN AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is a term used to describe changes associated with the aging of the central part of the retina (the macula) without other accompanying

causes in patients over 55 years of age [13]. It is considered the most common cause of vision loss in an aging population [14].

There are two main types of AMD:

- geographic atrophy (GA) is a sharply limited area of depigmentation associated with partial or complete atrophy of the retinal pigmented epithelium with large visible choroidal vessels [13]
- the exudative form of AMD is also called subretinal neovascularization (CNV). In most cases, this form is characterized by the proliferation of new vessels originating from the choroid and penetrating under the retinal pigmented epithelium (type 1) and into the subretinal space (type 2) [5, 13]. Recently RAP and PVC [5] have also been included in the exudative form:
  - retinal-vascular proliferation (RAP) is an exudative form of AMD in which neovascularization begins in deeper vascular plexuses with subsequent formation of retinal-vascular connections [5]
  - polypoidal choroidal vasculopathy (PCV) – is an exudative form in which abnormalities begin in the inner layer of the vascular vessels with the formation of numerous distal aneurysms which may be the source of bleeding and exudates. A hemorrhage is clinically visible at the fundus of the eye, without the presence of drusens [5].

Over the years, attempts have been made to treat the exudate form of AMD in various ways. Photodynamic therapy has been used in the exudative form together with steroid injections, subfoveal procedures, macular translocation, or radiotherapy [13].

In clinical practice, exudative AMD therapy comes down to the use of anti-VEGF preparations, and in the case of PCV photodynamic therapy in monotherapy or in combination with anti VEGF. The treatment options for the non-exudative form of AMD are limited and primarily include counseling, smoking cessation, visual rehabilitation and vitamin supplementation according to the AREDS study in order to reduce the risk of progression in patients who can be expected to benefit from such treatment. Clinical trials of new therapies are currently ongoing [13].

A number of papers have recently been published on the use of a subliminal nanosecond laser for the treatment of non-exudative form of AMD [15–18].

Guymer et al. published a 36-month, multi-centre, randomized study of laser intervention in early stages of age-related macular degeneration. Patients were treated with a 2RT laser or with placebo and observed every 6 months. In the late stages of AMD, the study did not show a significant slowdown in the rate of retinal progression during nanosecond laser treatment compared to simulated treatment. However, a slowdown in the progression of lesions after laser application was observed in persons without reticular pseudodrusen (RPD). The study gives hope for further trials with a 2RT laser [15].

Photocoagulation of drusens is believed to reduce their size, but it does not seem to reduce the risk of AMD progression. The nanosecond laser may have a rejuvenating effect on RPE (retinal pigmented epithelium) and Bruch's membrane [5].

LASER IN RETINAL TEARS AND DEGENERATION OF THE RETINA

Retinal detachment is one of the most serious vision-threatening condition. Despite the improved results of surgical treatment, the quality of patients' vision is often unsatisfactory, especially when the detachment covers the macula, so the prevention of detachment is very important [19]. Retinal detachment (RD) may be rhegmatogenous (called primary, most common), tractional or of an exudative nature [5].

The tears and holes in the retina are full-walled defects in its sensory layer. Their prognostic significance is related to the risk of the liquefied fraction of the vitreous body penetrating under the retina. They may arise either as a result of the disappearance of the internal layers of the retina (e.g. in the central part of the lattice degeneration) or as a result of the pulling and tearing of parts of the retina by the vitreous body at the vitreo-retinal junctions [20]. The predisposing changes to retinal detachment are: lattice degeneration, cochlear-type degeneration, degenerative retinal dissection, cystic retinal degenerations, myopic retinal-choroidal atrophy [5].

Treatment (in the form of urgent laser therapy or, less commonly, cryopexy) is required in all symptomatic horseshoe holes [5, 19, 20]. It reduces the risk of retinal detachment from 90% to about 5% [5]. In other cases, there is insufficiently reliable clinical data to recommend laser therapy [20].

In recent years, the trend towards less aggressive prophylactic treatment of asymptomatic holes and flaps is observed with emphasis on patients observation and education. A patient with a change predisposing to retinal detachment or with another risk factor for retinal detachment should be informed about the nature of vitreous and retinal detachment symptoms and the importance to seek urgent professional help, if these symptoms occur [5]. The risk of prophylactic treatment is usually very low, but can lead to new tears, very serious complications are extremely rare [5].

The decision to undertake treatment should be considered on a case-by-case basis, taking into account the existence or absence of such risk factors as: presence of vitreo--retinal traction, symptoms of PVD (posterior vitreous

detachment), axial myopia, pseudophakia, previous retinal detachment in the other eye, family predisposition. Prophylactic treatment of peripheral degenerative lesions is considered, especially with the additional risk factors mentioned above for retinal detachment development [20]. Different sources give different indications for the prophylactic treatment of degenerative lesions/symptomatic holes. Prophylactic treatment should be considered with asymptomatic tears, including round holes with flaps and atrophic holes before planned cataract surgery [5, 19, 21], laser capsulotomy, trabeculectomy, intravitreal injection [5], in case of retinal detachment in the second eye [19, 21], in myopia – especially high [19, 21].

In addition, photocoagulation due to lattice degeneration, can be performed before the planned cataract surgery, child delivery, and in case when the detachment occurred in the second eye [19].

Prophylactic treatment with photocoagulation of the retina in the eye without any degenerative changes is recommended in patients with a giant tear in the second eye [19, 22]. The risk of detachment in the second eye is very high, reaching 65% [19, 23].

In retinoschisis, no prophylactic treatment is usually required [19, 24].

The purpose of retinal detachment laser therapy is to create a strong retino-vascular connection around its edge. Laser therapy compared to cryotherapy is characterized by a faster formation of retino-vascular junction and results in the release of a much smaller number of pigmented epithelial cells, which play a major role in the subsequent formation of vitreoretinal proliferative changes [20].

Typically, the spot is 200–300 μm in size, with a duration of 0.1 s and a power to achieve moderate retinal pallor [5]. It is important to surround the lesion with 2–4 rows (depending on the source) of almost blending burns [5, 19, 20]. If the lesion to be treated is adjacent to ora serrata, the laser therapy area should cover its posterior edge and reach ora serrata at both ends, forming an U-shape [20].

After application of the laser treatment, the patient should avoid excessive exercise for about 7 days until a suitable scar is formed. The patient should be controlled after 1 or 2 weeks [5].

LASER THERAPY IN OTHER RETINAL DISEASES

Peripheral proliferative changes of the retina

Some retinal diseases cause ischemia of the peripheral part of the retina and the following neovascular changes, often as a result of inflammatory changes in retinal vessels. There are many reports of regression of peripheral neovascular lesions as a result of laser treatment [20].

These diseases can be divided into non-inflammatory and retinal vasculitis-related. The first group includes: sickle cell retinopathy, Bloch-Sulzberger syndrome (incontinentia pigmenti), Norrie disease, familial exudative vitreoretinopathy and others. The second group includes inflammatory and infectious diseases that embolize the vascular lumen as a result of the inflammation of the vascular wall. Proliferative retinopathy is a common complication of retinal vasculitis in such inflammatory diseases of the retina as inflammation of the intermediate part of the ciliary body, Behçet disease, Eales disease, viral retinitis (adenovirus and cytomegalovirus), sarcoidosis, toxoplasmosis, borreliosis, syphilis, systemic connective tissue diseases and systemic vasculitis (e.g. systemic lupus, giant cell arteritis etc.).

The inflammatory process leads to numerous venous thrombi, obstructions and closure of the peripheral vessels, and as a result to retinal ischemia, which is a stimulus for activation of vascular growth factors. After fluorescein angiography reveals the zones of ischemia, scattering laser therapy is performed, in case of anterior segment ischemia (NVI) – full PRP should be performed [20].

It is recommended that a mandatory deep peripheral fundus examination in both eyes should be performed in patients with inflammatory retinal vasculitis to detect and treat early lesions and reduce their complications [20].

Coats disease

Coast disease, perifoveal telangiectasias and Leber's miliary aneurysms are treated by some authors as different manifestations of the same disease [20].

It is idiopathic and is associated with intra-retinal and subretinal exudates, often with exudative retinal detachment, without vitreo-retinal traction.

It most often manifests in boys in their first decade of life (5 years of age on average) with unilateral loss of vision, strabismus or leukocoria [5].

In patients with mild non-visual symptoms or complete retinal detachment – which do not promise to improve vision – observation is recommended [5].

In patients in the early stages of the disease with a small amount of retinal fluid, laser therapy appears to be the best therapeutic method. The goal of treatment is to close dilated incomplete vessels, aneurisms and non-perfused areas, which should result in the withdrawal of retinal edema in both the posterior pole and the periphery [20].

There are also reports in the literature on the use of anti-VEGF preparations (also in combined therapy with laser therapy), cryotherapy, vitreo-retinal surgery (with complete retinal detachment) or enucleation (in patients with neovascular glaucoma and painful eyeballs) [5].

Perifoveal telangiectasis

Perifoveal telangiectasis can be associated with a benign form of Coats disease [5] – they are characterized by clusters of microaneurisms or saccular vascular network dilatations. There are three groups of patients. The first group includes cases of unilateral dilatation of the perifoveal vascular network with or without leakage. In the second group there are cases of bilateral involvement of the perifoveal area, especially in the temporal part. The symptoms are usually less visible compared to the first group, but may be complicated by vascular neovascularization (CNV). The third group includes cases of bilateral disease with characteristic progressive capillary vessel occlusion [5, 20].
Laser therapy is recommended especially in cases with unilateral symptomatic leakage. The treatment should cover the leakage area and should be directed to microaneurisms (fluorescein angiography might be helpful) [20]. Laser therapy may be technically difficult due to the distance of the lesions from the central fovea [5].

Retinal artery macroaneurysm

Occurs mainly in older individuals with hypertension and/or generalised atherosclerosis. Most lesions are asymptomatic, but serous fluid leakage, causing retina edema, sometimes with serous detachment, or bleeding involving both the retina and vitreous body [20].
Laser therapy should be used if the edema or exudates endanger or cover the macula, especially if the visual acuity is compromised. Burns may be applied to the macroaneurysm, around the aneurysm (to reduce the risk of arterial closure) or in both. It may take many months before swelling and hard exudates are absorbed [5].
Maltsev has published the results of a study in which he recognizes direct laser photocoagulation as an option for the treatment of symptomatic retinal macroaneurysm of retinal artery, without any laser-related side effects. At the same time, this study suggests that, compared to conventional laser photocoagulation, direct lesion laser therapy offers a lower potential risk of retinal damage as a side effect, as it requires less impact and less total laser energy during surgery [25].
Ramel is also positive about laser therapy in this disease entity [26].
The treatment of macroaneurysm of the retina and its complications in the form of hemorrhages has also been described by use of intravitreal injections of bevacizumab, hyaloidotomy with a YAG laser, intravitreal gas injections, rtPA (recombinant tissue plasminogen activator), and vitrectomy [5].

Retinal capillary hemangioma

Retinal capillary hemangioma is a rare, vision-threatening tumor, sometimes in an isolated form. About 50% of patients with single lesion and almost all patients with multiple lesions have von Hippel-Lindau syndrome [5].
Complications may include leakage with exudates formation and/or bleeding, retinal detachment, haemorrhage into the vitreous body, secondary glaucoma, phthisis bulbi [5].
The treatment uses direct photocoagulation of small lesions. After closure of the nutritional vessels, the tumor is treated with burns of low energy and long duration, sometimes several times. In case of large lesions, changes excluding laser therapy due to location or complications, other methods of treatment are described: cryotherapy, brachytherapy, vitreo-retinal surgery, PDT (photodynamic therapy) or anti-VEGF [5].

Preretinal hemorrhage

Preretinal hemorrhage is the extravasation of blood between the inner limiting membrane and the posterior surface of the vitreous body, sometimes also under the inner membrane [20]. Occasionally, in the case of prefoveal localization, especially in monocular patients, an incision of the posterior surface of the vitreous body should be considered. This allows for potential evacuation of the hemorrhage into the vitreous body [5, 20]. Both Nd : YAG and argon lasers can be used. An incision is made in the lower part of the lesion. The lack of the expected effect is usually caused by the organization of the hemorrhage or the use of too little pulse energy [20].

An optic nerve pit

An optic nerve pit is a congenital lesion. The exudative macular detachment develops in about half of the eyes with paracentral localisation of the pit (mean age 30). The pathomechanism of this process is not fully explained. The subretinal fluid is believed to come from the vitreous body, less likely to come from the subarachnoid space and from the exudation of abnormal vessels within the base of the pit. The macular image may suggest CRS, so it is important to assess the n II disc in all patients with CRS [5]. The laser retina barrier around the edges of the pit is controversial [20]. It is used when visual acuity deteriorates, with an effectiveness of 25–35% [5].

CONCLUSION

Lasers have been successfully used to treat retinal diseases for many years. Despite attempts to introduce other therapeutic methods, the role of laser therapy is still very important. Ophthalmologists are constantly improving their diagnostic and therapeutic capabilities, hence multiple attempts to test new types of lasers in recent years. The current trends are moving in the direction of shortening the time of contact of impulses with the retina and breaks

between them, as well as the use of several impulses at the same time (which shortens the total time of laser therapy, increases the comfort of both the patient and the doctor, causes permanent damage to the retina to a smaller extent – and thus smaller losses in the field of vision). A lot of hope is in the micropulse laser, which does not cause permanent damage to the retina. If the navigated laser therapy systems pass the clinical trials, the computer will soon be able to plan and perform the laser therapy itself in a very short time.

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