Life Science Journal

Websites:
http://www.lifesciencesite.com
http://www.sciencepub.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

The animal model with warm compression and propranolol to treat SD rats with central serous chorioretinopathy

Wei-Da Chio [1], Chi-Ting Horng [2,3*]

[1] Departmet of Physical of Rehabilitation, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan, ROC.
[2] Department of Pharmacy, Tajen University, Pingtung, Taiwan, ROC.
[3] Departmet of Opthalmology, Fooying University, Pingtung, Taiwan, ROC.
* Corresponding Author Chi-Ting Horng, M.D. Ph.D., Department of Ophthalmology, Fooying University Hospital, No.5, Zhong-Shan Rd, Donggang, Pingtung, Taiwan, ROC. h56041@gamil.com

Abstract: Aim: This animal study aims to evaluate the prognosis of central serous chorioretinopathy (CSCR) treatment with oral propranolol combined with warm compression every day for 2 months. **Methods**: The treatment peroid tested 2 months with 16 males SD rats with CSCR, conducted in July 2019. All 16 right eye of cases were randomly divided into 2 groups which underwent a series of examinations including indirect ophthalmoscopy, and OCT scanning every week. Group 1 included 8 SD rats fed with propranolol (10 mg in each day), and warm compressure. The other 8 SD rats in group 2 received placebo treatment. All SD rats were inducted into the CSCR model first, and we recorded the time of total complete remission of sub-retinal fluid. If CSCR disappeared under OCT imaging, the rat was considered as a "successful" case and it stopped taking the drug at once. The other CSCR rats continued to be fed with until the end of the 2nd month. The percentages of "successful" and "un-successful" cases were recorded and all 16 cases received a further 3–month follow-up to evalute the rate of recurrence and the time of success. Moreover, the mean time of complete remission was also calculated at the same time. **Results**: All 16 male rats were enrolled in our study. Furthermore, the mean time of complete remission in group 1 and group 2 was 0.8, and 1.8 weeks, respectively. The percentages of "successful" cases in group 1 and group 2 after 2-month therapy was 87.5% (7/8) and 62.5% (5/8), respectively ($P < 0.05$). Besides, the rate of recurrence in group 1 and group 2 was 12.5% (1/8) and 37.5% (3/8) after 3 months, respectively ($P < 0.05$). **Conclusion**: We suggest that the SD rats fed with propranolol and combined with warm compression may constitute an alternative choice to treat CSCR. This new method may show the safe, cheap, effective, well tolerated and convenient benefit. Furthermore, it may even shorten the remission time of the course of treatment and decrease the rate of recurrence.
[Wei-Da Chio, Chi-Ting Horng. **The animal model with warm compression and propranolol to treat SD rats with central serous chorioretinopathy.** *Life Sci J* 2019;16(12):115-126]. ISSN: 1097-8135 (Print) / ISSN: 2372-613X (Online). http://www.lifesciencesite.com. 16. doi:10.7537/marslsj161219.16.

Keywords: Central serous chorioretinopathy (CSCR), Propranolol, ophthalmoscopy

Introduction

Central serous chorioretinopathy (CSCR) is one type of the macular diseases characterized by serious retinal detachment, the retinal pigment epithelial (RPE) detachment or dysfunction, and choroidal hyperpermeability which shows the accumulation of subretinal fluid (SRF) in the posterior pole [1]. Most of CSCR patients primarily regress spontaneously within 3 to 4 months. Besides, the older victims are more likely to present diffuse RPE loss, cystoid macular degeneration (CME) and secondary choroidal neovascularization (CNV). It may last longer in a minority of patients, potentially leading to a long-term worsening of vision with persistent or recurrent serous macular detachment. Moreover, chronic CSCR could include the irregular RPE detachments and long-standing intra-retinal cystoid cavities [2]. Macular atrophy persistence should induce poor vision after spontaneous resolution of retinal edema. In acute presentation, these subjects with CSCR may complain about various symptoms, including: decreased visual acuity, metamorphopsia, dyschromatopsia, micropsia, hypermetropization, color deficiency, and relative central scotoma due to SRF in the macula. Besides, the well-demarcated round- or oval-shaped area and loss of foveal reflex have been observed at the posterior pole because of increasing the central macular thickness with or without pigment epithelial detachments (PEDs) which provided a good hint toward diagnosis [3]. Moreover, the pathophysiology of CSCR is involved in multiple etiologies and mechanisms that lead to the widespread choroidal circulatory abnormalities and RPE disturbance which result in accumulation of SRF leaking from the impaired tight junction of the choroid. The hyper-permeability of choroid can be due to various

conditions such as stasis, ischemia, or inflammation [4]. Furthermore, there are many risk factors for developing CSCR, including male gender, mental stress, type A personality, steroids or psychotropic medication, and pre-eclampsia in pregnancy. Although rare, Cushing's syndrome or steroid-producing tumors can also occur [5]. The incidence of CSCR has been approximately 6 times higher in men than in women. It suggested that male labor is always the major global source of family incidence; they would also suffer from more psychological stress and endurance of physiologic fatigue [6]. Moreover, a multifactorial concept has evolved, involving several risk factors such as age, race, gender, blood pressure, certain systemic disorders and a behavioral pattern [7].

Although CSCR has been described as benign and self-limiting disease, it has a tendency to spontaneously reoccur and absorb. However, it develops approximately in one third of patients and sometimes cause significant impairment of visual acuity [8]. Most of acute CSCR patients show spontaneous visual recovery within 3 to 4 months. However, the remission of rats has remained unknown. Moreover, 40-50% of patients with CSCR may suffer recurrence and develop into the chronic stage, which could lead to RPE atrophy and pigmentations in macula with disruption in visual function [9]. The result even doctors could not explain; up to 50% of patients with CSCR should experience recurrence within the first year of presentation. Moreover, a small proportion of patients would suffer the irreversible visual loss due to gross RPE atrophy, subretinal fibrosis, CNV or CMD [10]. Even if the CSCR victims sometimes exhibits good vision (e.g.:20/20), the lower density of retinal cone cells were found, especially in chronic CSCR, which was consistent with residual symptoms such as the relative scotoma, metamorphopsia, decreased contrast sensitivity and even color deficiency [11,12]. However, the signs of RPE atrophy, CMD, and CNV could become worse without aggressive treatment in CSCR patients. Hence, the early prevention, diagnosis and treatment are necessary for exhibiting complete remission of SRF and its impairment of vision [13]. Some cases of severe CSCR even resulted in the death of different photoreceptors, and retinal detachment in chronic stage which decreased visual acuity [14]. How to block CSCR and enhance absorption of SRF has becomes the key problem in the treatment schedule. Until now, the treatments of CSCR have varied in clinics.

One of the characteristics of warm compress is that heat should be transferred to the adjacent structure by the methods of conduction and convention. During the warm compression, heat is transferred directly from the palpebral conjunctiva (the closed eyelids) to the pre-corneal tear layer, cornea, the aqueous humor, the limbal vasculature, bulbar conjunctiva and even sclera [15]. In addition, the closed eyelids may generate heat energy and maintain an elevated temperature [16]. The heat from warm compression could result in the vasodilation (e.g.: the retina and sclera) and increased the blood flow and volume, which may benefit the therapy of CSCR. For example, Yu and his co-workers revealed that the superficial total vascular density and superficial microvascular ring decreased in CSCR subjects [17]. Therefore, the decreased blood volume from the retina should carry a few immune factors and the antioxidants to the macula compared to the healthy ones.

In this study, we designed a new method to treat CSCR rats with propranolol and warm compression as reported successfully several years ago [17]. It is our proposal that the safe, low price, good complicance and convenience may become popular for CSCR patients in the future.

Methods

Between July 2019 and December 2016, we conducted a prospective study of 16 SD rats; subjects recruited were aged between 7 and 8 week. Hence, we selected all with right eyes for our study. Firstly, we injected the 3% saline to the subretinal space to create CSCR under microscopy; the signs could be detected easily by OCT (Optic Coherence Tomography; OPKO. E-Vision Instrument Company, Taiwan) scan (Fig. 1). Moreover, we recorded the time of total SRF remission (by OCT), age, and body weight. By the imaging, we measured the changes of dome shape height which means the amount of SRF and if the vision became better or worse, via the OCT scan. Elevated dome shape was the predominant sign of CSCR at the sub-RPE space around the macula. In the past, we could discover the mean radius of squared from CSCR by color photography (e.g.: well-defined margin in the posterior pole). In this study, we checked the inverted U-shape from elevated SRF by OCT imaging in the morning (10:00AM) every day. If SRF showed complete remission and the images from OCT became flat, the time (so called “complete remission time”) was recorded. Meanwhile, the responding CSCR rats (so called “successful” cases) had stopped continuous feeding with propranolol. The rats were divided to 2 groups who randomly received series of examinations including indierct ophthalmology and OCT imaging scanning. Group 1 included 8 rats taking propranolol (40 mg every day) in the daytime. The other 8 SD rats in group 2 received placebo treatment. If the SRF persistence would be evaluated as “failure of the treatment (unsuccessful); all 16 rats received therapy until the end of the 2nd month. Unless CSCR improved early, the SD rats in group 1 would take propranolol at least

2 months. Moreover, we checked the signs of CSCR disappeared or at the end of 2nd month to verify if CSCR had persisted or persisted. Moreover, we still continued to follow the "successful" and "unsuccessful" cases for a further 3 months to verify the rate of recurrence. The 16 SD rats received follow-up at weekly intervals during the whole study (total of 5 months). Meanwhile, we recorded the condition when RPE layer attached and SRF absorbed completely, via OCT image scan.

All results are expressed as the mean ± SD. The pair-t test was used to analyze the changes of BCVA. Analysis of data was done by using the SPSS version13.0. The *P* values less than 0.05 were considered as statistically significant.

Fortunately, there were no significant complications during the whole course of study. There were 18 subjects with CSCR that took part in our treatment protocol. In the past, we treated CSCR patients with stubborn and troubling problems several years ago [16]. In the previous article, we reported that 2 patients with stubborn CSCR had been treated with intravitreal avastin many times, but still failed and went hospital shopping. Lately, the 2 victims were rescued from vision loss by our new treatment protocol. Therefore, we arranged to perform the standard of procedures (SOP) for the 18 CSCR SD rats by the newly designed treatment (propranolol combined with warm compression over the closed eyeballs).

Results

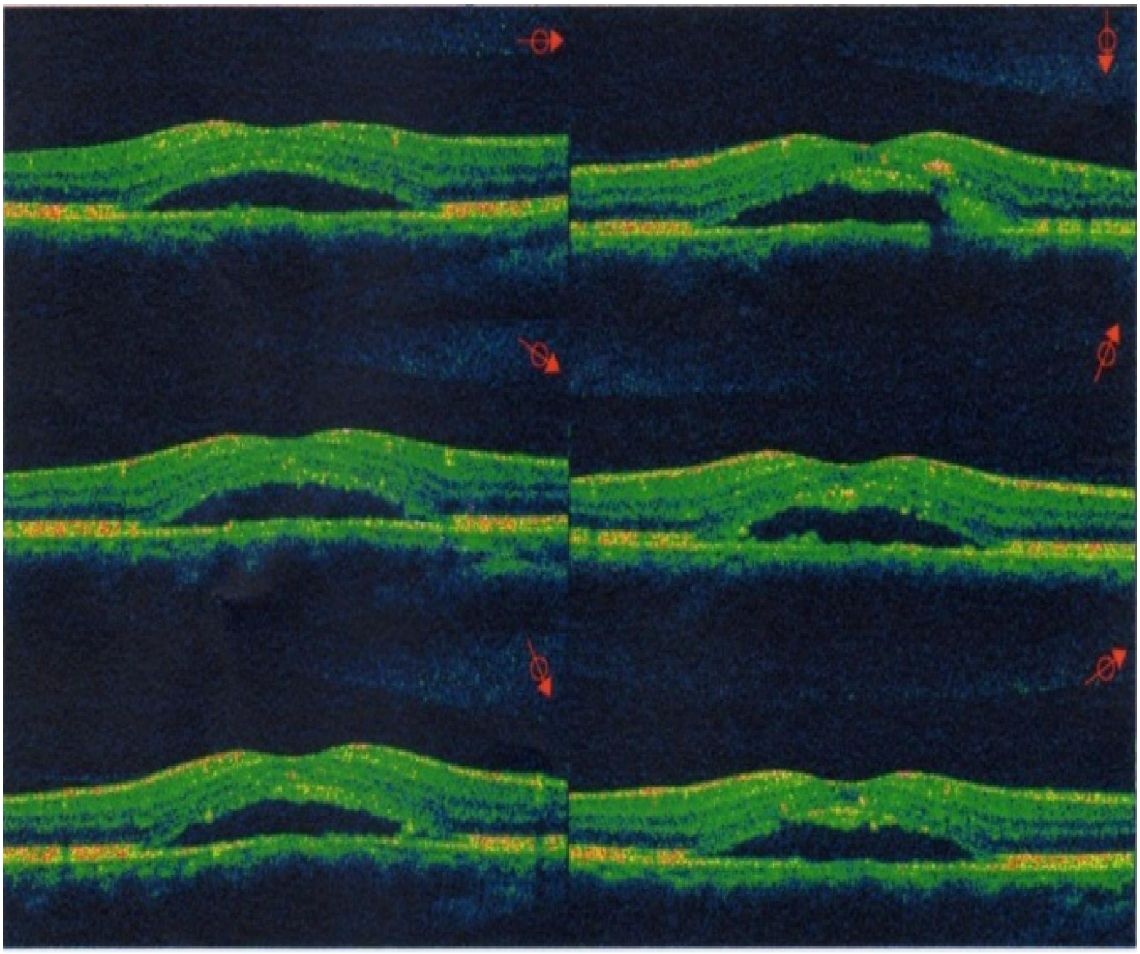

Fig. 1-1. Serial ocular coherence tonography (OCT) in one CSCR patient showed retinal pigment epithelium detachment at day 1.

The mean ages of total of the SD rats were 7.5±0.9 week. All 16 rats with CSCR were enrolled in the regimen. Furthermore, there were 75% (12/16) successful cases after the 2-months treatment, while 4 (12.5%) subjects did "not respond" to the standard treatment protocol (so called "unsuccessful" cases) in group 1. However, we also found that their dome shape in the OCT scans disappeared completely.

Moreover, we focused on the efficacy and it was exciting for us to demonstrate that the mean remission time was only 0.8 months and the "successful" rats was up to 87.5% when treated with propranolol and warm compression. The placebo group showed the mean remission time was 1.8 months and only 62.5% succeeded without propranolol with warm compression (see Table 1) ($P< 0.05$). Moreover, the signs in 7 SD rats which were fed with propranolol improved significantly in shorter time in group 1. In other words, the method using oral propranolol with warm compression four time in one day may enhance the SRF resolution completely and quickly, and modify the cell function after the RPE layer re-attached, when compared with the placebo group 2 ($P< 0.05$). Furthermore, mean complete remission time was 0.8 months in group 1, which means that the pharmacological mechanism of propranolol should accelerate the remission of SRF when compared with group 2 ($P<0.05$). From the above results, we concluded that taking propranolol with warm compression is a good strategy for CSCR, as it is a rapid and safe procedure. Moreover, no remarkable side effects were found during the study, and we found that the rate of recurrence in group 1 was 12.5 % which was significantly different compared with the placebo group 2 (37.5%) ($P< 0.05$). We believe that oral propranolol should decrease the recurrence of CSCR and shorten the remission time of residual SRF. However, the exact mechanisms need further intervention. Moreover, all the 16 SD rats were sacrificed and it showed that no renal or hepatic deformities were found in the biopsies after taking propranolol for 2 months and a further 3-months follow-up (Fig. 2). Therefore, it was suggested that oral propranolol was safe for the subjects for a longer time.

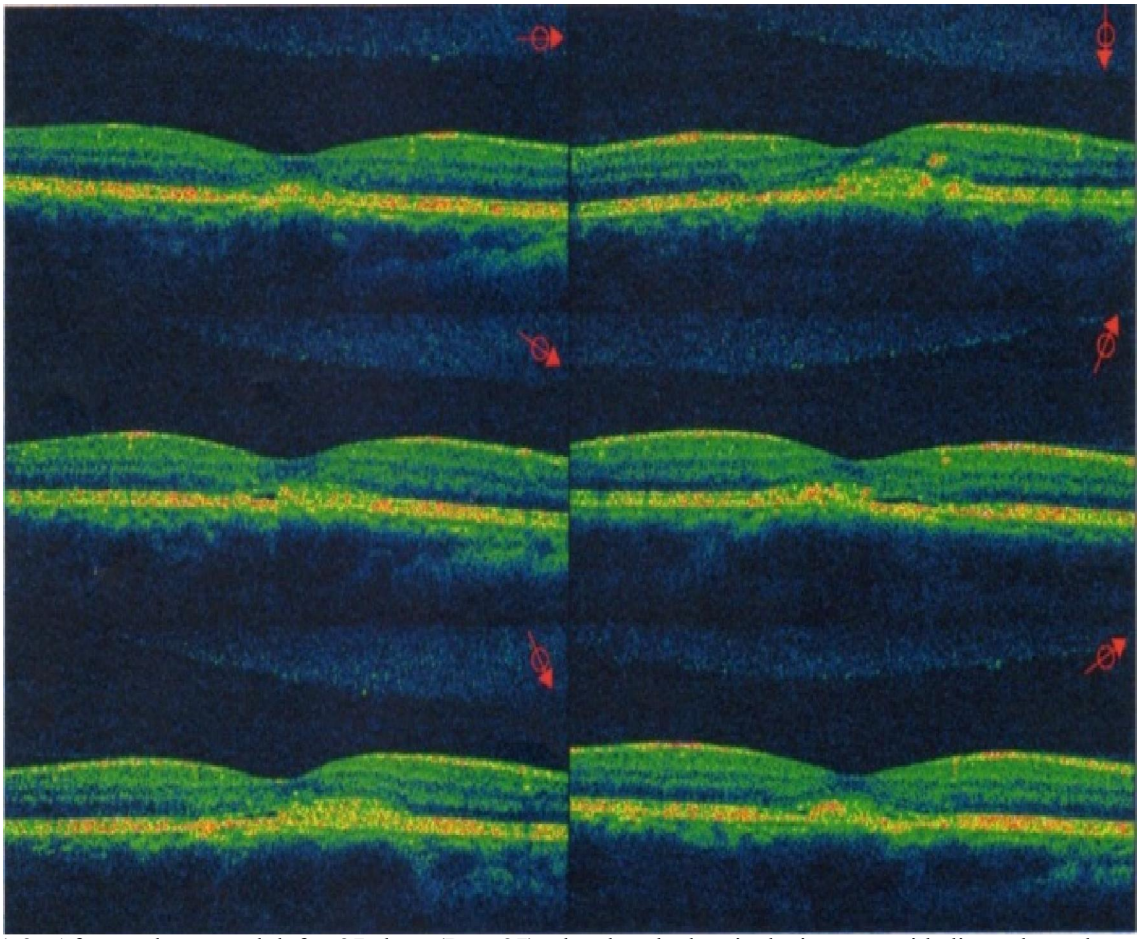

Fig. 1-2. After oral propranlol for 27 days (Day 27), the detached retinal pigment epithelium showed attached completely by the view of OCT imaging scan.

Table 1. The changes after oral propranolol in treating CSCR in all groups.

Parameter \ Group	Group 1 (N= 8)	Group 2 (N= 8)	*P* value
Mean complete remission time	1.1 months	1.9 months	< 0.05
Successful rate	87.5%	62.5%	< 0.05
Rate of recurrence	12.5 %	37.5 %	< 0.05

1. We compared the results between group 1 and 2 by pair-t test
2. When $P < 0.05$, the data was statistically significant difference
3. Group 2 belongs to placebo treatment and did not receive oral propranolol with warm compression (10 minutes per day).

Disscusion

Central serous chorioretinopathy (CSCR) usually affects persons 20 to 50 years of age who exhibit acute or sub-acute central vision loss or distortion. Moreover, the other complaints include micropsia, metamorphopsia, hyperopic (most common) or myopic shift, central scotoma, and reduced contrast sensitivity and color saturation. However, even if one eye of CSCR has decreased visual loss, the patients may also lose of the static and dynamic stereopsis which may be inconvenient in life. Moreover, males are more likely to be affected than female (nearly 6 folds). Most acute CSCR patients show spontaneous visual recovery within 4 to 6 months (in 90% of subjects), but some cases may progress to chronic or recurrent disease, which lead to areas of RPE atrophy and pigmentation in the macular area with subsequent visual loss. In many articles, up to 50% of patients with CSCR should develop recurrence within the first year of presentation. A small proportion of CSCR patients result in irreversible visual loss due to gross RPE atrophy, subretinal fibrosis, and CNV which induce the residual symptoms such as metamorphopsia, scotoma, and vision loss. Furthermore, 30% of CSCR with bilateral involvement, 40% CSCR patients with recurrence and decreased vision occurred or remained poor vision in 5-10 % of chronic CSCR [19]. As the CSCR usually resolves spontaneously, observation is currently standard in care for newly presenting cases. For chronic, recurrent, or acute CSCR in functionally monocular patients, aggressive treatment should be discussed and required.

Furthermore, CSCR is characterized by the detachment of neurosensory retina in the posterior pole, caused by the serious fluid leakage from the choroidal vessels, coming through the RPE layer. Moreover, alternation in the exudate state of the choroid may lead to serous detachment of RPE and disruption of the tissue. Therefore, the use of warm compression may also alter the choroid vasculature and enhance integrity of both of the choroidal and retinal blood vessels. To our experience, sleeplessness, being too tired and restless could result in CSCR. Moreover, there are many disorders which may lead to the CSCR formation, such as Type A personality, pre-eclasmpsia, hypercoagulability, the patients undergoing hemodialysis, bone marrow and solid organ transplantations, various vasculitis, tuberculosis, lupus, smoking, emotional stress (e.g.: shift work, scolding by boss, family device, and personal divorce), steroid overuse, inflammatory bowel disease, Cushing syndrome, and peptic ulcer [20-29]. Recently, it is reported that some habits may be associated with CSCR including smartphone use and playing video computer games for a long time, especially overnight. During this time, overexposure under higher energy (blue light) may induce oxidative stress. Moreover, free radicals should begin to attack the cells, organelles, and human DNA. Finally, the associated cells becomes damaged, induced cataract, various retinopathies and CSCR formation which would impact the users' vision. Recently, researchers proof this condition. For example, Nakamura et al. indicated that oxidative stress was partially involved in light-induced retinal damage [30]. Besides, Lin and his co-workers demonstrated that the blue light from smartphones could induce severe photo-toxicity which plays an important role in retinal degeneration. When exposed to LED blue light, the RPE cells were subjected to high energy on activation of key aptotic pathways which may cause fundus damage and atrophy of photo-receptors, and decrease the retinal thickness. Therefore, blue light from 3 C productions may be a risk factor of CSCR [31].

To our knowledge, CSCR may be present in various clinical forms with different prognosis now. Therefore, management of CSCR necessitates an individualized and selective treatment approach case by case. From various therapies, mineralocorticoid receptor antagonists appear to have the greatest potential. Some mechanisms of the steroid action on the choroid and RPE include potentiation of adrenergic hormone, and altered ion transport in RPE cells. Because the corticosteroids would strengthen the tight junctions of choroid, a few ophthalmologists strongly favored their use to treat patients with CSCR in the past; however, the treatment is contraindicated [30].

It is important to stress that in contrast to the current opinion; steroids can evoke or deteriorate CSCR and enhance the symptoms and signs. Therefore, any type of the steroid is all a factor in the

pathogenesis of the order is contraindicated in the therapy of CSCR. Recently, in several literatures, the use of steroids would reduce RPE fluid absorption, and prolong the disease duration if not used carefully. The mechanism of complication is the increased permeability of choriocapillaries, which may allow entry of large proteins (such as fibrinogen) into the sub-RPE and sub-retinal space [33]. The use of local and systemic methylprednisolone would also induce the significant CSCR [34]. Multiple routes of administration for steroids have been implicated in the advent of acute exudative changes of CSCR in previous publications. Until now, Grixtri et al. concluded that steroids possess the inflammatory abilities, however, it also disrupts the RPE tight junctions which constitute the outer blood retinal barrier, resulting in accumulation of subretinal fluid. Moreover, increased fragility choriocapillaries, and hyper-permeability were also noted [35,36]. Besides, the larger doses and systemic steroids for CSCR become contra-indicated and should be avoided in clinics carefully [37]. Recently, overload of mineralocorticoid receptor pathway in choroidal vessels has been implicated in the pathophysiology of CSCR. Furthermore, glucocorticoids also have affinity for MRs, further suggesting of a targeted role for the MR pathways. To date, the prevalence of administration of glucocorticoid via to the CSCR patients was approximate to 3.3 - 9.1%. Besides, the mechanism of steroid-induced CSRC is that the steroid may affect the choroidal vasculature, which increases capillary fragility, hyper-permeability and leak of fluid in the subretinal space. Moreover, it would affect the production of nitrixic oxide, prostaglandins, and free radicals which present risk factors for CSCR [38,39,40]. It may be prudent for all CSCR patients to avoid the use of corticosteroid by any routine of administration, unless there is a compelling medical indication [42].

Ketoconazole (one type of anti-fungal agents) should inhibit the steps of steroid synthesis and decrease the level of cortisol. Besides, it has direct anti-glucorticoids effects as an antagonist. The effects seem to present at the minimum dosage of 40g /day; however, the effectiveness were limited by its severe complications, including flush face, yellow skin, liver damage, shortness of breath (SOB), G-I upset, giddiness, nausea, vomiting, tachycardia and CNS or respiratory depression [42]. Mefepristone (RU-486) is another agent to treat CSCR cases; the pharmacological effects how that mifepristone is an antagonist of glucocorticoids and progesterone. Besides, it may inhibit cortisol-induced peripheral vasoconstriction. Unfortunately, the serious side effects such as sepsis, carcinogenic, genotoxic, potency and teratology were found [43,44].

Low-dose aspirin is another medication to treat CSCR because it has the ability to the reduce various stresses, and respond to the HPA axis. In addition, low-dose aspirin may limit the elevation of cortisol and catecholamine in serum [45]. Besides, its effectiveness in vascular diseases and combination of the lower ocular and general toxicity deserve to be used. According to new medical text, the dose of 75-100 mg of aspirin appears to be safe for humans; however, the side effects: bleeding tendency, hepatic toxicity, stress ulcer, allergy, skin rash, and bronchospasm (4 -19%) should be demanded careful use. Besides, Carbonic anhydrase inhibitors (CAIs) are a type of diuretic that act on the RPE cells, taking part in the resorption of the sub-retinal fluid. In general, the physiological function of diuretics is used to excrete the excessive extracellular fluid [46]. In recent studies, several documents show that the systemic acetazolamide (Diamox) and dorzolamide (Trusopt or Azopt) for topical use could also increase the choroidal blood flow [48,49]. Besides, diamox could effectively reduce the sub-retinal fluid and enhance the RPE layer attached in treating CSCR [49]. However, the side effects included electrolytes imbalance, metabolic acidosis, renal stone and pulmonary edema [50,51]. We must pay attention to various side effects when it is used. Besides the medical treatment, the aggressive methods are another choice which should seal the leakage, reduce the neuro-epithelial detachment and choroidal hyper-permeability. For example, intravitreal injection (IVI) of bevacizumab (®Avastin), laser photocoagulation, transpupillary thermotherapy and photodynamic therapy with verteporfin have been demonstrated to result in the reduction of the sub-retinal fluid height on OCT images, decreased the neurosensory detachment and improved the visual acuity after 2 to 8 months [52-54]. Besides, the pharmacological interventions and various laser procedures may induce the anti-vascular endothelial growth factor (anti-VEGF), seal the leakage and emerge as to the potentially effective treatment for CSCR. However, such invasive techniques may carry inherent risks or complications, show poor outcome or offer questionable long- term benefits [55].

Choroidal hyper-permeability has been assumed to be the cause of CSCR based on the basis of treatment. VEGF is one of the major cytokines that could induce the vascular hyper-permeability. An intra-ocular injection of anti-VEGF bevacizumab may improve the symptoms and signs of CSCR by blocking the activity of VEGF and even complete resolution of the sub-retinal fluid. However, it was reported that 8 months following this procedure, a complete resolution of the sub-retinal fluid was noted. Besides, the above techniques would carry inherent risks or complications (e.g.: endophthalmitis, and

relative symptomatic scotomas) and show poor outcome or offer questionable long-term benefit. It also takes higher price, and complicated procedures which bother the doctors and patients [56,57]. In our study, we found that warm compression may decrease the choroidal hyperpermeability and enhance the associated immune and repair factors from the choroidal blood vessels.

Recently, we searched for an easier, safer and cheaper method for CSCR. Thus, various types of β-blockers are used to treat CSCR by some doctors now. In our new treatment protocol, propranolol is a competitive antagonist that blocks the receptor sites for the endogenous catecholamine epinephrine and norepinephrine on the adrenergic β - receptors of sympathetic nervous system. In general, β-blockers would interfere with the binding to the receptors of epinephrine and other stress hormones, and weaken the effects of stress hormones. In our study, the propranolol (30-40 mg per day) could dramatically make 95 % patients with CSCR complete absorption within 3 months, while no other complications were found.

A possible explanation may relate to the modification of the choroidal circulation of the choroid flow. For example, choroidal blood flow is known to be regulated by both sympathetic and parasympathetic systems and steroids seem to act synergistically with sympathetic symptoms and as an antagonist of the parasympathetic system, inhibiting the production of vascular modulator nitric oxidase synthase [58]. Indeed, propranolol belongs to non-selective β-adrenergic receptor antagonists. Now, these β- receptors are found on the cells of many tissues and organs and lead to stress response. In clinics, propranolol may induce human vasodilation, decreased heart rate, blood pressure, cardiac output, and heart work, and prevent hypoxia and arrhythmia. Besides, propranolol could also decrease the incidence of angina pectoris, stress, general anxiety, tension, headache, tremor and panic disorder, especially for people with prominent somatic or autonomic symptoms [51]. Therefore, patients with asthma and severe cardiovascular disorders were excluded for safety concern. Moreover, propranolol as β-receptor has been proposed as potential means of treating CSCR because of choroidal circulation.

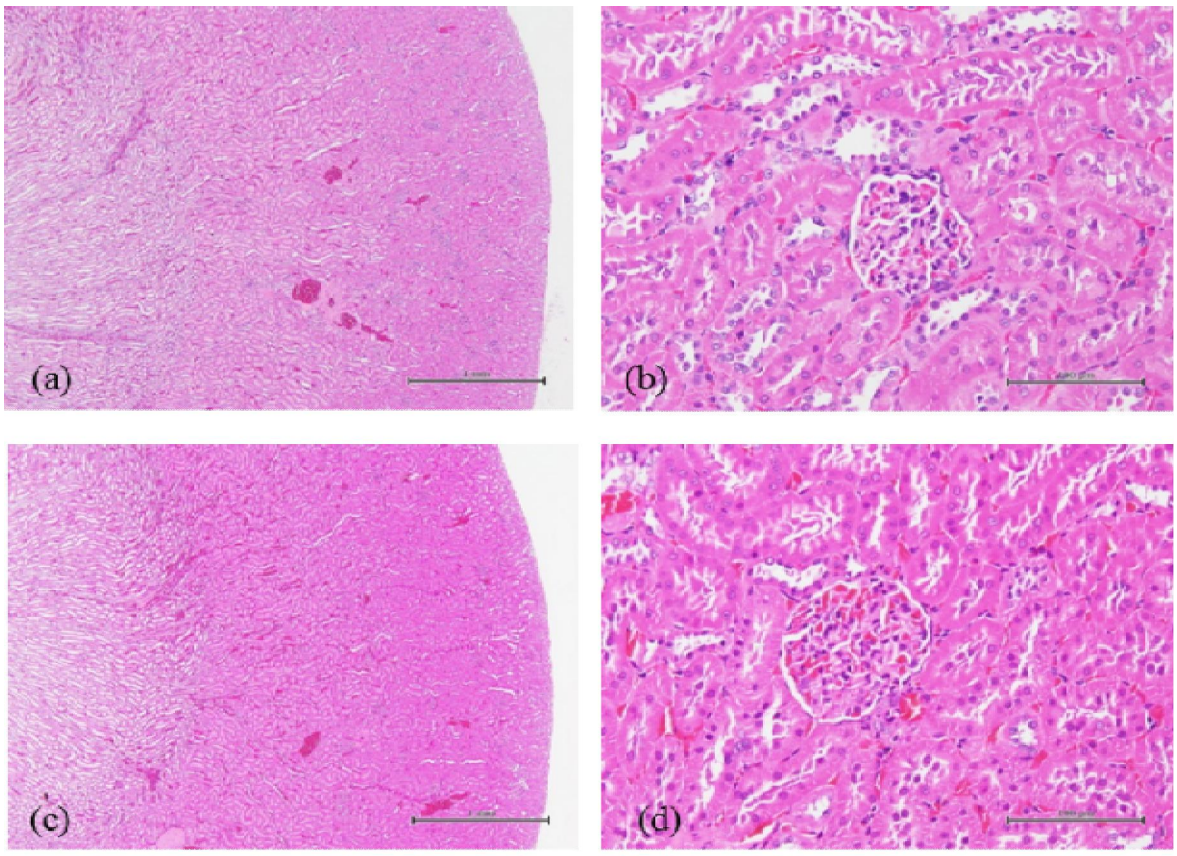

Fig. 2-1. Histopathological findings of the kidneys in SD rats. No significant change of the kidneys was noted in biopsies. (H & E stain, 40x and 400x.)

Various β-blockers may prevent the changes in RPE activity and epinephrine induced apoptosis that compromise the integrity of all RPE cells and contribute to treating CSCR. Recently, some types of the β-blockers (e.g.: propranolol, andolol, and metoprolol) were used to decrease the associated adrenergic activities. In clinics, β-adrenergic antagonist are currently popular for ophthalmologists to treat CSCR in the UK, USA, Germany and Czech Republic and Slovakia [60,61,62,63]. However, 60 patients with CSCR took part in our large population study. In Tatham's report, only 2 patients with CSCR were enrolled in the research that taking 40 mg propranolol every day. Unfortunately, while patient 1 mildly improved vision, the patient did not return to initial vision; besides in patient 2, no improvement occurred [62]. Moreover, Browing et al. used nadolol (40 mg in each day) for 8 patients with CSCR, but all failed and the agent or the dose may be ineffective [61]. Besides, other studies have shown that both metipranolol (non-selective β blocker) and metoprolol (selective β1 blocker) revealed no significant difference in the β selective and non- β selective blockers [58,59]. Besides, Charpek' reports that only 13 eyes were enrolled and 84.6% of CSCR cases showed adherence of the ablated neuroepithelium of the macula occurring at the latest within 4 months of treatment. However, in our larger evidence-based study, the successful rate was higher (87.5 %) within 2 treatment months, and the attached time was faster (the mean time: 0.8 weeks) [63]. As the option, we had prescribed propranolol which differs from other researchers. A higher successful rate (87.5%) by oral propranolol was found in our designed protocol.

Hyperthermia has been used to treat many diseases, especially malignancies. In efficacy is based on the differential absorption of heat by normal and cancer cells and the greater sensitivity to chemotherapy and radiation of heated malignancies cells [64] Moreover, hyperthermia has been used for rehabilitation by improving the peripheral blood flow, tissue metabolism, and elasticity of fibrous tissues which may benefit for the mechanism for treating CSCR. Moreover, it could also reduce the pain and spasm. In clinics and activities, appropriate modalities are used to delay muscle fatigue and enhance the exercise volume load, to improve the effectiveness of upper extremities rehabilitation in athletes and performing artists, increase skeletal muscle regeneration in elderly subjects by hot balneotherapy, reduce the static and dynamic symptoms in middle-aged women fibromyalgia under the aquatic training, and promote the microcirculation of lower extremities in patients with diabetes [65].

Warm compression applied in the ophthalmic field has a long history. Heating devices have been used to treat ocular pathologies (e.g.: retinoblastoma, posterior uveal melanoma, decrease then recurrence of intraocular tumor after chemotherapy, proliferative vitreoretinopathy, scleromalacia [66]. To date, it is most prescribed for the patients with varying presentation of mild to severe Meibomian gland dysfunction and obstruction, improvement for tear evaporation, and subsequent symptoms of dry eye[67,68]. Besides, the effect of periocular warming on accommodation has been highly valued. It is found that 50% of the eyes showed an increase in the accommodation amplitude of at least 0.5 diopters immediately after application of warm compression. The mean near visual acuity immediately after application of warm compression and at 90 minutes significantly improved relative to the near acuity values after whole eyelid closure [69]. Moreover, warm compression showed the apparent improvement in high and low contrast sensitivity [70]. Besides, it should also cure many benign conditions, such as meibomian gland obstruction, and acute conjunctivitis [71]. The function from heat brings about vasodilation and increases blood circulation of naturally occurring immune compounds and prescribed antibiotics to the affected area. Therefore, this procedure may result in the enhanced integrity of blood vessels [72]. However, when used for several indications such as posterior blepharitis, internal hordeolum, and ocular rosacea, eye warming requires enough heat to liquefy the hardened or abnormal viscous meibomian secretion in the deeper regions. However; the actual data on warm compression-induced decrease in IOP have never been reported.

The central lid margin temperature was 33.4±0.1℃ at a room temperature of 24℃. In addition, central corneal temperature is approximately to 33.3℃ [73]. However, the limbus is 0.45℃ warmer than the central corneal temperature. Moreover, the corneal surface temperature is 0.45℃ warmer nasally than centrally and temporally until 6 and 8-10 seconds after blinking [74]. For example, Matsumoto et al. affirmed that the average increase of eyelid temperature and corneal temperature after a 10-minute application of eye-steamer is 1.0-1.2 and 1.7-2.0℃, respectively [75]. Besides, it is reported that the temperature increased to 37.4℃ with the eyelid closed. Kenrick et al. revealed that the best way to optimize warm compression efficiency is to heat to approximate 45℃ [76]. In addition, the clinicians could maintain the contact between warm compression and outer eyelid surfaces for at least 4 minutes to achieve inner lower eyelid temperature ≧ 40℃. The reports revealed that mean maximum outer upper eyelid temperature of 42.2 ± 1.3℃ was reached for 6 minutes. However, the maximum tolerance of the eyelid and the cornea are approximately 45-50℃ and 37-40℃, respectively,

according to the past studies. For instance, it is suggested that, during contact heating, the time-temperature threshold at which the first sign of human skin thermal damage, tissue edema, occurs when the temperature is 45℃ after 35.5 minutes of uninterrupted exposure [77]. Nagaoka et al. found that the ocular surface temperature significantly increased and returned to baseline 10 minutes later. They also found that the retinal blood flow may decrease and choroidal blood flow increased in the foveal region after ocular warming at the same time in the healthy volunteers. Therefore, we suggest that warming compression should be good for treating CSCR.

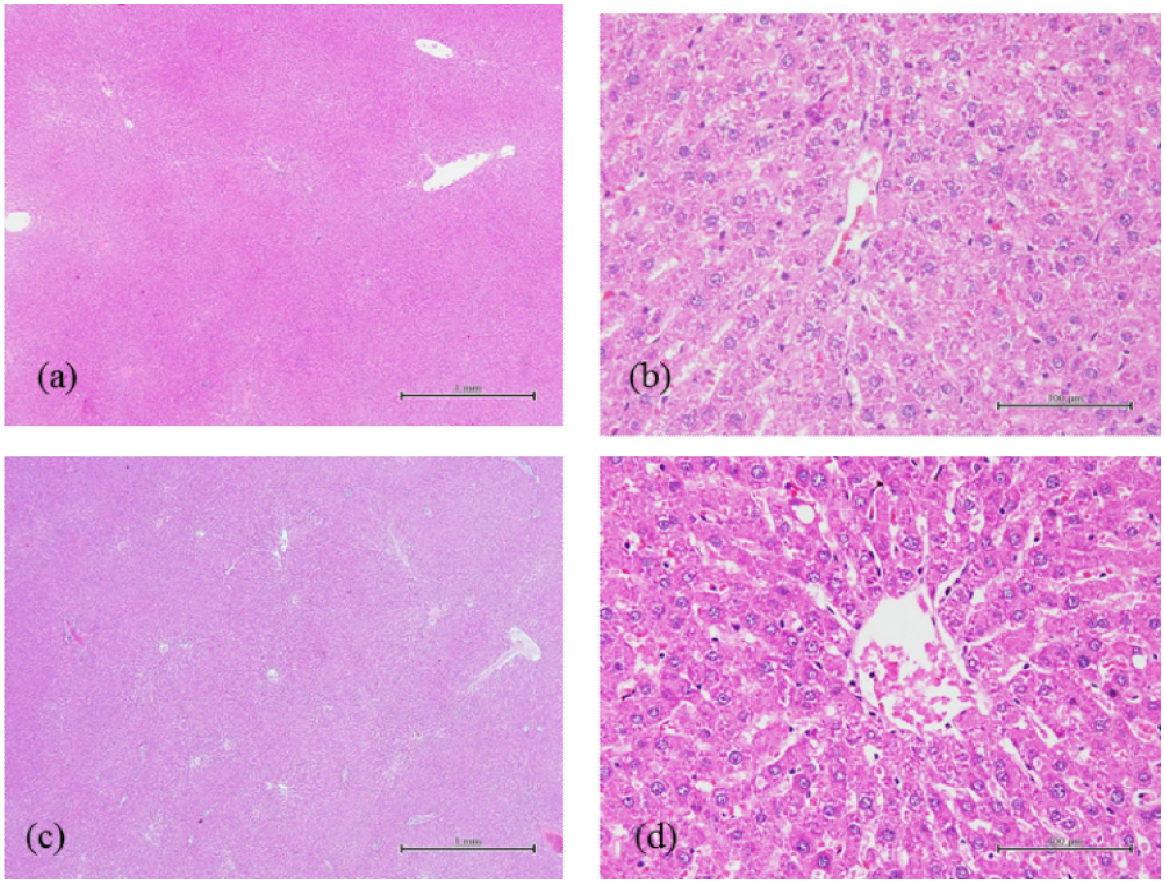

Fig. 2-2. Histopathological findings of the livers in SD rats. No significant change of the livers was noted in biopsies. (H & E stain, 40x and 400x.)

Conclusion

Central serous chroriretinopathy is a potential slight-threatening condition with a complicated pathogenesis. In general, most of the CSCR patients should resolve spontaneously within 4 months; however, the patients are naturally worried if their recovery will be as speedy and complete as possible. However, there were higher rates of recurrence and even a very few cases that did not return to their initial vision unfortunately. In an animal study, we found that SD rats fed with propranolol (10 mg per day) which had better treatment in CSCR within rapid remission time and high successful rate. Although there may be spontaneous improvement without treatment in CSCR subjects, propranolol with warm compression could be necessary in real life.

Corresponding author:
Chi-Ting Horng, M.D. Ph.D.
Department of Ophthalmology, Fooying University Hospital, No.5, Zhong-Shan Rd, Donggang, Pingtung, Taiwan (ROC).
E-mail: h56041@gmail.com

References

1. Matet A, Daruich A, Zola M, et al. Risk factors for recurrences of central serious chorioretinoipathy. Retina 2018;38(7):1403-14.
2. Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: Recent findings and new physiopathology hypothesis. Prog Retin Eye Res 2015; 48: 82-118.
3. Baran NV, Guriu VP, Esgin H. Long-term

macular function in eyes with central serous chorioretinopathy. Clin Experiment Ophthalmol 2005; 33(4): 369-72.
4. Hamimovici R, Koh S, Gagnon DR, et al. Risk factors for central serous chrioretinopathy: A case-control stidy. Ophthalmology 111(2); 244-9.
5. Ross A, Ross AH, Mohamed Q, et al. Review and update of central serous choriotretinopathy. Curr Opin Opthalmol 2011; 22(3):166-73.
6. Goldhagen BE, Goldhardt R. Diagnosed a patient with central serous chorioretinopathy? Now what?: Management of central serous chorioretinopathy. Curr Ophthalmol Rep 2017; 5 (2):141-8.
7. Türkcü FM, Yüksel H, Yüksel H. Serum dehydroepiandrosterone sulphate, total antioxidant capacity, and total oxidant status in central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol 2014; 252(1): 17-21.
8. Levin R, Brucker A, Robinson F. Long-term follow-up of idiopathic central serous chorioretinopathy by fluorescein angiopathy. Ophthalmology 1989;. 96(6): 854-9.
9. Hanumunthadu D, Tan ACS, Singh SR, et al. Management of chronic central serous chorioretinopathy. Indian J Ophthlmol 2018; 66(12): 1704-14.
10. Virgili G, Acosta R, Grover LL, et al. Reading aids for adults with low vision. Cohrance Database Syst Rev 2013; 23: (10): CD003303. doi:10.1002/14651858.CD003303.pub3.CD003303.
11. Loo RH, Scott IU, Flynn HW Jr, et al. Factors associated with reduced viusal acuity during long-term follow-up patients with idopathic central serous chorioretinopathy. Retina 2002; 22(1):19-24.
12. Wang MS, Sander B, Larsen M. Retinal atrophy idiopathic central serous chorioretinopathy. Am J Ophthalmol 2002; 133(6) 787-93.
13. Hussain D, Gass JD. Idiopathic central serous chorioretinopathy. Indian J Ophthalmol 1998; 46(3): 131-7.
14. Gramajo AL, Marquez GE, Torres VE, et al. Therapeutic benefit of melatonin in refractory central serous chorioretinopathy. Eye (Lond) 2015; 29(8):1036-45.
15. Gokul C, Gurung D.B., Adhikary PR. Thermal effects of eyelid in human temperature model. J. Appl. Math. Informatics 2014; 32(5-6): 649- 63.
16. Liu HT, Chi-Ting Horng. The role warm in lowerng the ocular pressure in various conmdition-pilot study. J Am Sci 2018; 14(9): 6-13.
17. Yu L, Shao Y, Chai Y, et al. Retinal microvasculature alteration in central serous chorioretinopathy. Mol Med Rep 2018; 17(2): 2336-40.
18. Horng CT, Yaun I, Haung YT, et al. Therapeutic use of oral propranolol to treat stubborn central serous chorioretinopathy. Life Sci J 2014;11(5): 499-505.
19. Schartz H, Maderia D, Johson RN, et al. Central serous chorioretinopathy occuring in patientss 60 years of agents and older. Ophthalmology 1992; 99(1): 63-7.
20. Yannuzzi LA. Type A behavior and center serous chrioretinopathy. Retina 1987 7(2):111-31.
21. Yamada R, Yamada S, Ishii A, et al. Evaluation of tissue plasimogen activator inhibitor-I in blood obtained from patients of idiopathic central serous chorioretinopathy. Nippon Ganka Gakki Zasshi 1993;97(8): 955-60.
22. Dada T. Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol 2000;130(3):379.
23. Schultz KL, Birnbaum AD, Goldstein DA. Ocular disease in pregnancy. Curr Opin Ophthalmol 2005; 16(5): 308-4.
24. Moon SJ, Meiler WF. Retinal complication of bone marrow and solid organ translation. Curr Opion Ophthalmol 2003; 14(6): 433-42.
25. Shah VA, Randhawa S, Boldt HC, et al. Central serous chorioretinopathy in giant arterities. Semin Ophthalmol 2006; 21(1): 45-8.
26. Chhablani J, Anantharaman G, Behar-Cohen F, et al. Management of central serous chorioretinopathy: Expert panel discussion. Indian J Ophthalmol 2018;66(12):1700-3.
27. Sohreiber JB, Nawano M, Marshallah. SM. Crrohn's disease disease complicated by idiopathic central serous chorioretinopathy with bullous retinal detachment. Dig Dis Sci 1989; 34(1): 118-22.
28. Chaine G, Haouat M, Menard-Molcard C, et al. Central serous chorioretinoipathy and systemic steroid therapy. J Fr Ophthalmol 2001; 24(2): 217- 22.
29. Carvalho-Recchia CA, Yamuzzi LA, Negrado S, et al. Corticosteroid and central serous chorioretinopathy. Ophthalmology 2002; 109(10):1834-7.
30. Nakamura M, Kuse Y, Tsuruma K, et al. The involvement of the oxidative stress in murine blue LED Light-Induced retinal damage model. Biol Pharm Bull 2017; 40(8):1219-25.
31. Lin CH, Wu MR, Li CH, et al. Editor's Highlight: Periodic exposure to smartphone -mimic low-luminance blue light induces retina damage through Bcl-2/BAX-dependent apoptosis. Toxicol Sci 2017;157(1):196-210.
32. Bouzas EA, Scott MH, Mastorakos G, et al.

Central chorioretinopathy in endogeneous hypercortisim. Arch Ophthalmol 1993; 111(9): 1229-33.
33. Nyklieck I, Bosch JA, Amerongen AN. A generalized physiological hyper-reactivity to acute stressors in hypertensives. Biol Psychol 2005;70(1): 44-51.
34. Tewai HK, Gardia R, Kumar D, et al. Sympathetic- parasympathetic activity and reactivity in central serous chorioretinopathy: a case-control study. Invest Ophthalmol Vis Sci 2006;47(8):3474-8.
35. Grixti A, Kumar V. (2013). Steroid induced central serous chorioretinopathy in giant cell arteritis. Case Rep Ophthalmol Med 2013; 2013: 924037. doi: 10.1155/2013/924037. Epub 2013 Jun 11.
36. Koss MC, Gherezghiher T. Adrenoreceptor subtypes involoveld in neurally evoked sympathetic vasoconstriction in the anterior choroid of cat. Exe Eye Res 1993; 57(4):441-7.
37. Sibayan SA, Kobuch K, Speiegel D, et al. Epiphrine, but not dexmethasone, induces apoptosis in retinal pigment epitheliunm cells in vitro: possible im [plications on the pathegeneisis of central serous chororetinopathy. Graefes Arch Clin Exp Ophthalmol 2000; 238 (6): 515-9.
38. Caccavale A, Romanazzi F, Imparato M, Negri A, Morano A, Ferentini F. Centreal serous chorioretinopathy---a pathegentic model. Clin Ophthalmol; 2011; 5: 239- 43.
39. Kleinberger AJ, Patel C, Lieberman RM, et al. Bilateral central serous chorioretinopathy caused by intranasal corticosteroids: a case report and review of the literature. Laryngoscope 2011; 121(9):2034-7.
40. Vogiatzis I, Koulouris E, Sidiropollos A, et al. Acute pulmonary edema after a single oral dose of acetazolamide. Hippokratia 2003; 17(2): 177-9.
41. Karadium P, Bouzas EA. Glucocortioid use reprenents a risk factor for central serous chorioretinopathy: a prospective, case-control study. Graef's Arch Clin Exp Ophthalmol 2004; 242(9): 800-2.
42. Golshahi A, Klingmüller D, Holz FG, et al. Ketoconazole in the treatment of central serous chorioretimnopathy: a pilot study. Acta Ophthalmol 2010; 88(5): 576-81.
43. Nielsen JS, Weinreg RN, Yannuzzi L, Jampol LM. Mifepristone traetment of chronic central serous chrioretinopathy. Retina 2007; 27(1): 119-22.
44. Lawton BA, Rose SB, Sphepherd J. Atypical presentation of serous pelvic inflammation disease following mifepristone induced medical abortion. Contraception 2006; 73(4): 431-2.
45. Nye EJ, Hockings GI, Grice JE, et al. Aspirin inhibit vassopression-induced hypothalmic-pituritaty-adrenal activity in normal humans. J Clin Endocrinol Metab 1997; 82(3): 812-7.
46. Di Luigi L, Guidetti L, Romanelli F, et al. Acetasalicylic acid inhibits the pituitary response to exercise-related stressin humans. Med Sci Sports Exerc 2001; 33(12): 2029-35.
47. Pikkel J, Beiran I, Ophir A, et al. Acetazolamide for central serous retinopathy. Ophthalmology 2002; 109(9); 1723-5.
48. Kiss B, Dallinger S, Findl O, et al. Acetazolamide-induced cerebral and ocular vasodilation in humans is independent of nitric oxide. Am J Physiol 1999; 276(6):R1661- 7.
49. Fuchsjäger-Mayrl G, Wally B, Rainer G, et al. Effect of dorzolamide and timolol on angle glaucoma and ocular hypertension. Br J Ophthalmol 2005. 89 (10); 1293-7.
50. Gonalez C (1992). Serous detachment-value of acetazolamide. J F Ophthalomlogy; 15(10); 529-36.
51. Pikkel J, Beiran I, Ophir A, et al. Acetazolamide for central serous retinopathy Ophthalmology 2002;109(9):1723- 5.
52. Jamil AZ, Rahman FU, Iqbal K, et al. Intravitreal bevacizumab in central serous chorioretinopathy. J Coll Physicians Surg Pak 2012.; 22(6):363-6.
53. Mathur V, Parihar J, Maggon R, et al. Role of transpupillary thermotherapy in central serous chorioretinopathy. Med J Armed Forces India. 2009; 65(4): 323-7.
54. Yadav NK, Jayadev C, Mohan A, et al. Subthreshold micropulse yellow laser (577 nm) in chronic central serous chorioretinopathy: safety profile and treatment outcome. Eye (Lond) 2015; 29(2):258-64.
55. Jonas, JB, Kamppeter BA. Intravitreal triamcinolone acetonide and central serous chorioretinopathy. Br J Ophthamol 2005; 89(3): 386-7.
56. Erikitola OC, Crosby-Nwaobi R, Lotery AJ, et al. Photodynamic therapy for central serous chorioretinopathy. Eye (Lond) 2014;28(8):944-57.
57. Simader C, Lung S, Weigert G, et al. Role of NO in the control of choroidal blood flow during a decrease in ocular perfusion pressure. Invest Ophthalmol Vis Sci 2009;50(1):372-7.
58. Tyrer P. Current status of beta-blocking drugs in the treatment of anxiety disorders. Drugs 1988; 36(6): 773-83.
59. Fabianova J, Porubska M, Reha K L. Central serous chorioretinopathy treatment with beta-blockers. Cesk Slov Oftamol 1998; 54(6): 401-4.
60. Charpek O, Spackova K, Rehak J. Treatment of

central serous chorioretinopathy with beta-blockers. Cesk Slov Oftamol 2002; 58(6): 382-6.
61. Browing DJ. Nadolol in the treatment of central serous retinopathy. Am J ophthalmol 1993; 116(6): 770-1.
62. Tatham A, Macfarlane A. The use of propranolol to treat central serous choriretinopathy: An evaluation by serial OCT. J Ocul Pharmacol Therapeut 2006; 22(2): 145-9.
63. Chrapek O, Jirkova B, Kandmal V, et al. Treatment of central serous chorioretinopathy with beta-blocker metipranolol. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015;159 (1):120-3.
64. Alicia AJ, Petryk AA, Cassim SM, et al. Magnetic nanoparticle hyperthermia in cancer treatment. Nano Life. 2010; 1(01n02): 10.1142/S1793984410000067.
65. Naumann J, Sadaghiani C. Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. Arthritis Res Ther 2014;16: R141. doi:10.1186/ar4603.
66. Liu HT, Horng CT. The role of warm compression in lowering the intraocular pressure in various conditions-a pilot study. J Am Sci 2018;14(9):6-13.
67. Thulasi A Djalilian A. Update in current diagnostics and therapeutics of dry eye disease. Ophthalmology. 2007; 124(11 Suppl): S27–33.
68. Chhadva P, Goldhardt R, Galor A. Meibomian gland disease: the role of gland dysfunction in dry eye disease. Ophthalmology. 2017; 124(11 Suppl): S20–6.
69. Takahashi Y, Igaki M, Suzuki A, et al. The effect of periocular warming on accommodation. Ophthalmology 2005; 112(6): 1113-8.
70. Chan CY, Chow SW, Wan HN, et al. Update on the association between dry eye disease and meibomian gland dysfunction. Hong Kong Med L 2019 25(1): 38-47.
71. Martin NF, Rubinfeld RS, Malley JD, et al. Giant papillary conjunctivitis and meibomian gland dysfunction blepharitis. CLAO J 1992; 18(3): 165-9.
72. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: Hierarchy of Competing Physiological Needs. Physiol Rev. 2015; 95(2): 549–601.
73. Efron N, Young G, Brennan NA. Ocular surface temperature. Curr Eye Res 1989; 8(9):901-6.
74. Moussa S, Eppig T, Pattmöller J, et al. Diurnal and zonal analysis of corneal surface temperature in young healthy adults. Eur J Ophthalmol 2013; 23(5):641-5.
75. Matsumoto Y, Dogru M, Goto E, et al. Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction. Cornea 2006;25(6):644-50.
76. Kenrick CJ, Alloo SS. The Limitation of Applying Heat to the External Lid Surface: A case of recalcitrant meibomian gland dysfunction. Case Rep Ophthalmol. 2017; 8(1):7–12.
77. Pavel S. Yarmolenko PS, Moon EJ, Landon C. et al. Thresholds for thermal damage to normal tissues: An update. Int J Hyperthermia. 2011; 27(4): 320–43.
78. Nagakka T, Yoshida A. The effect of ocular warming on ocluar circulation in healthy humans. Arch Ophthalmol 2004; 122(10): 1477-81.

12/13/2019