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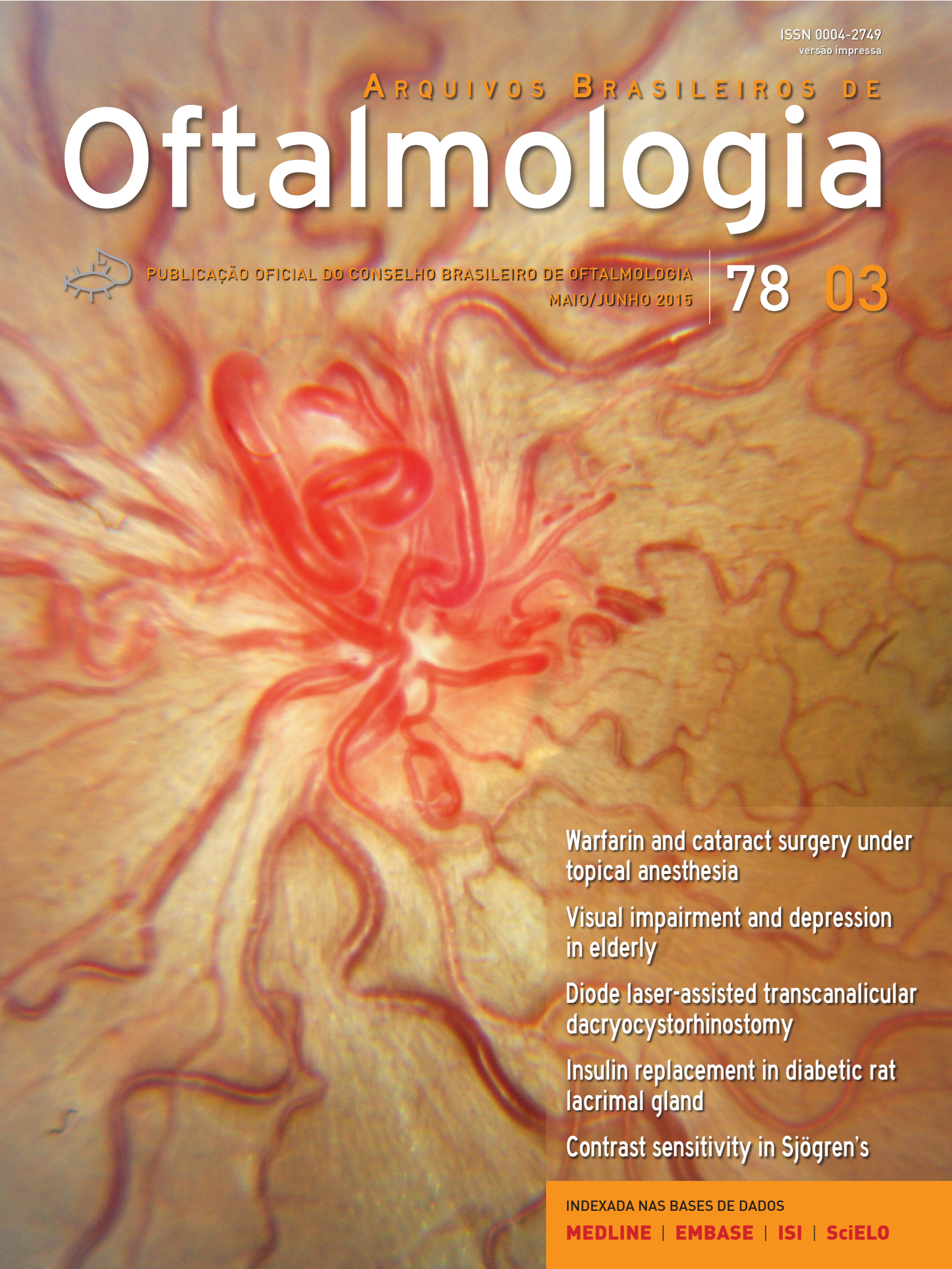

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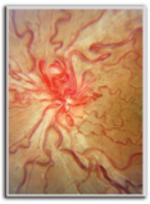

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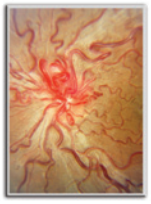

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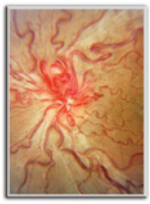

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Can glaucoma affect sleep quality?

O glaucoma pode afetar a qualidade do sono?

Carolina Pelegrini Barbosa Gracitelli[1], Augusto Paranhos Jr.[1]

Glaucoma is an optic neuropathy characterized by the progressive loss of retinal ganglion cells (RGCs) and associated morphological changes to the optic nerve and retinal nerve fiber layer (RNFL)[1]. Although most RGCs are related with cortical image processing, a small proportion of RGCs, called intrinsically photosensitive RGCs (ipRGCs), are not involved in the thalamo-cortical pathway of image processing and mediate non-image-forming visual functions such as circadian photoentrainment and pupillary light reflex (PLR)[2,3].

In 2000, ipRGCs were described in mammalian inner retina as a new photoreceptor that expresses the photopigment melanopsin[3]. These cells account for approximately 3% of the entire RGC population in the human retina[3]. The ipRGC is most sensitive to short wavelength, i.e., blue light, and directly contributes to the post-illumination pupil response of sustained constriction (>6 s) after the offset of high luminance (250 cd/m^2)[4]. The loss of the ganglion cell population that happens in glaucomatous disease potentially leads to damaged function and/or a decreased number of ipRGCs[2].

The pupillary light reflex test is used as an indicator of the afferent input from the retina and optic nerve. Recently, studies using pupillography with different stimuli tested conditions to target specific retinal ganglion cell subtypes, such as ipRGCs. Evaluating this specific class of RGCs, our group demonstrated a significant correlation between structural damage, as measured based on RNFL thickness, and the sustained response to blue flashes with high luminance during the pupillary light reflex in glaucomatous patients[5]. In addition, we found a significant correlation between the severity of glaucoma, as measured by functional damage and the sustained pupillary response[5]. The main clinical finding in this study was the correlation between the RNFL thickness and pupillary response[5]. Probably, in the future, with further investigations clinical examination of the pupillary response could be used for monitoring glaucoma progression and assessing prognosis.

The true impact of ipRGC damage caused by glaucoma on sleep quality or circadian rhythm has only recently been elucidated. In the human brain, the primary circadian pacemaker is the suprachiasmatic nucleus (SCN), and light plays an important role in synchronizing the circadian system[6]. The light intensity seems to influence melatonin secretion, which in turn modulates sleep and the circadian rhythm. The responses driven by photic input from the eyes are transmitted through the retinohypothalamic tract to the SCN[7] and from there to the upper part of the thoracic spinal cord, the superior cervical ganglia, and the pineal gland[8]. The SCN receives photic input from ipRGCs. Their input synchronizes the SCN to the solar day, which keeps the human circadian rhythm close to a 24-hour cycle by driving the nocturnal synthesis of the pineal hormone melatonin and inducing the circadian phase and sleep[9]. Using polysomnography, we showed that compared with healthy subjects, glaucoma patients had worse sleep quality, and the polysomnographic parameters of sleep disorders were associated with a poorer sustained response to the pupillary reflex in glaucoma patients[10]. Therefore, the damage to the ipRGCs caused by glaucoma decreases their input synchronization, thereby leading to sleep disorders.

Moreover, some evidence has shown that the damage to ipRGCs caused by glaucoma is also correlated with increased daytime sleepiness as measured by a self-report questionnaire (Epworth sleepiness scale), and this symptom is also correlated with polysomnographic parameters and a decreased sustained pupillary response[11]. It is well known that excessive daytime sleepiness affects the quality of life, daytime function, and mortality. Therefore, these two major non-image-forming functions of ipRGCs should be considered in certain glaucoma evaluations.

In fact, certain specific drawbacks of this issue should be mentioned. Until recently, we investigated these non-image-forming visual functions in glaucomatous population using small sample sizes and cross-sectional designs that did not allow the longitudinal association of the pupillometry with the progression of glaucoma. There is a relatively weak association between the RNFL thickness and sustained pupillary response, and the strength of this association varies depending on the severity of the disease. Therefore, the pupillary reflex should be considered a good tool for progression detection but not for glaucoma diagnosis. Using this pupillary test as a surrogate measure for glaucoma instead of existing techniques is thus not recommended. However, a complete evaluation would also need to include a more thorough assessment of test-retest variability. Although we certainly believe that there is a relationship between glaucoma damage (measured by RNFL thinning) and

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ipRGC functions (i.e., polysomnography parameters), different issues could influence these complex systems, which comprise the circadian rhythm. Further studies with larger cohorts of patients should be performed to evaluate this hypothesis.

In conclusion, previous studies and our results provide ample evidence to suggest that glaucoma leads to RGC death, including ipRGC death. These cells are connected to several non-image-forming functions, including circadian photoentrainment and pupillary reflexes. Therefore, not only the image-forming but also non-image-forming visual systems are associated with glaucomatous disease. The circadian function has not been well investigated in clinical daily practice, but it can interfere with the quality of life of these patients. Concerns about sleep disturbances in glaucoma patients should be incorporated into clinical evaluations. In addition, abnormal PLR in glaucomatous patients is potentially associated with other consequences, such as sleep disorders.

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Expressions of matrix metalloproteinases-1 and -9 and opioid growth factor in rabbit cornea after lamellar keratectomy and treatment with 1% nalbuphine

Metaloproteinases de matriz 1, 9, e fator de crescimento opióide, em córneas de coelhos depois de ceratotomia e tratamento com nalbufina a 1%

Miguel Ladino Silva[1,2], Alexandre Pinto Ribeiro[3], Germana Alegro Silva[1], Irma Ximena Barbosa Sanchez[4], Roberta Renzo[1], Ricardo Uscategui[1], Tiago Barbalho Lima[1], Marcela Aldrovani[1], José Luiz Laus[1]

ABSTRACT

Purposes: To evaluate the effects of nalbuphine 1% on the expression of metalloproteinase 1 (MMP-1), metalloproteinase 9 (MMP-9), and opioid growth factor (OGF) in rabbit corneas after lamellar keratectomy.

Methods: The rabbits were assigned to two groups: group nalbuphine (GN, n=30), which received 30 µL of nalbuphine 1% in 4 daily applications at regular intervals until corneal epithelialization, and group control (GC, n=30), which received physiological saline solution under the same conditions adopted in GN. The corneas were collected for immunohistochemistry on days 1, 3, 5, 7, and 9 after lamellar keratectomy, and the expressions of MMP-1, MMP-9, and OGF were analyzed.

Results: The expressions of MMP-1 and MMP-9 increased until day 5 of the evaluation, with no differences observed between GN and GC (p>0.05). On days 7 and 9, significant reductions were observed in the expression of MMP-1 (p<0.01), with no differences observed between GN and GC (p>0.05). The expression of OGF was constant in all periods (p>0.05), restricted to the corneal epithelium, and there was no difference between the groups (p>0.05).

Conclusions: The study results showed that nalbuphine 1% did not alter the expression patterns of MMP-1, MMP-9, and OGF in rabbit corneas after lamellar keratectomy.

Keywords: Cornea; Photorefractive keratectomy; Nalbuphine/therapeutic use; Matrix metalloproteinases; Receptors, opioid; Immunohistochemistry; Animals; Rabbits

RESUMO

Objetivos: *Avaliar os efeitos da nalbufina 1% sobre a expressão da metaloproteinase 1 (MMP-1), da metaloproteinase 9 (MMP-9) e do fator de crescimento opióide (OGF), em córneas de coelhos submetidas à ceratectomia lamelar.*

Métodos: *Constituíram-se dois grupos: grupo nalbufina (GN, n=30), que recebeu 30 µL de nalbufina 1% em 4 aplicações diárias, a intervalos regulares, até a epitelização corneal; controle (GC, n=30), que recebeu solução salina nas mesmas condições adotadas no GN. As córneas foram colhidas para imuno-histoquímica decorridos 1, 3, 5, 7 e 9 dias das ceratectomias lamelares, visando a se avaliarem as MMP-1, MMP-9 e OGF.*

Resultados: *A expressão das MMP-1 e de MMP-9 se elevou até o quinto dia de avaliação, sem diferença entre GN e GC (p>0,05). Nos dias 7 e 9, observou-se redução significativa na expressão das enzimas (p<0,01), sendo que diferenças não foram observadas entre os grupos (p>0,05). O OGF exibiu imunomarcação constante em todos os períodos (p>0,05), restrita ao epitélio corneal. Não foram encontradas diferenças entre os grupos (p>0,05).*

Conclusões: *Com base dos resultados obtidos, há como admitir que a nalbufina 1% não alterou o padrão de expressão da MMP-1, da MMP-9 e do OGF em córneas de coelhos submetidas à ceratectomia lamelar.*

Descritores: *Córnea; Ceratectomia fotorrefrativa; Nalbufina/uso terapêutico; Metaloproteinases da matriz; Receptores opióides; Imuno-histoquímica; Animais; Coelhos*

INTRODUCTION

Humans and animals often develop ulcerative keratitis[1], which leads to discomfort and pain due to the activation of nociceptors predominantly located in the superficial layer of the cornea[2]. Nalbuphine is an opioid kappa agonist/mu antagonist that produces moderate to severe analgesia[3] and has been used in premedication, surgery, and the postoperative period of obstetric and pediatric practices focused on controlling pain associated with burns[4]. Nalbuphine activity depends on the dose, application site, and sex of the patient[5,6]. Studies on the analgesic effects of nalbuphine on the cornea have shown that instillation reduces the corneal sensitivity to touch in dogs[5]. In contrast, nalbuphine has been demonstrated to sometimes cause damage to the corneal epithelium and stromal fibroblasts[7]. It is unclear if nalbuphine can impair the expression of enzymes and growth factors involved in corneal wound healing.

Owing to their importance in maintaining and repairing the epithelium and corneal stroma, matrix metalloproteinases (MMPs) have been widely studied[8,9]. MMPs are calcium-dependent zinc-containing endopeptidases involved in inflammation, wound healing, tissue remodeling, and pathological processes[9]. These enzymes have been detected in tears and corneal tissue during wound healing and in ocular surface disease[8-10]. In corneal ulcers, the combination of the overexpression of MMP-1 and MMP-9 can lead to rapid degradation of corneal extracellular matrix[9]. MMP-1 has long been associated with corneal destruction after injury and alkali-induced burns[11]. MMP-9 digests denatured collagen, gelatin, and native type IV, V, and VII collagens as well as other extracellular components[12]. Higher levels of MMP-9 have been found in the corneal epithelium of patients with cornea edema[13]. Matsubara et al.[13] observed that the basement membrane can be dissolved by MMP-9, which facilitates corneal

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ulceration. Knockout mice without MMP-9 have been found to be resistant to corneal epithelial barrier disruption[14]. MMP-9 has been shown to be active during remodeling of the corneal stroma after lamellar keratectomy[8].

Opioid growth factor (OGF) is an endogenous peptide found in different tissues[15]. It serves as a growth factor in developing and renewing neoplastic cells and tissues[16]. In vitro and in vivo studies have shown that OGF is constitutively expressed in the process of wound healing of rat and rabbit corneal epithelium[17]. Regarding domestic species, OGF and its receptor have been identified in dogs, cats, and horses in large concentrations in the corneal epithelium[18]. OGF downregulates epithelial cell division and migration in the closing of corneal epithelial abrasions and has a pivotal role in ocular surface repair[17].

The goal of this study was to evaluate the effects of 1% nalbuphine instillation on the expression of MMP-1, MMP-9, and OGF on rabbit corneas after lamellar keratectomy.

METHODS

Experiments were performed in accordance with the guidelines set forth by the Association for Research in Vision and Ophthalmology (ARVO) for the use of animals in ophthalmic and vision research and was approved by the Ethics Committee on Animal Use of the Faculty of Agrarian and Veterinary Sciences, UNESP Jaboticabal (nº 028793-08). Sixty healthy, adult, male, New Zealand White rabbits with an average weight of 3 kg were used. The animals were individually kept in proper, clean, and sanitized cages in well-ventilated areas, with a diet of commercial ration and "ad libitum" potable water.

For general anesthesia, an intramuscular injection of 15 mg/kg of ketamine (Cetamina- S(+); Cristalia Produtos Químicos e Farmacêuticos, Campinas, SP, Brasil) with 0.5 mg/kg of midazolam (Dormire®; Cristalia, São Carlos, SP, Brasil) was used and maintained using isoflurane (Isofluorano; Cristália Produtos Químicos e Farmacêuticos) diluted in oxygen 100%. The procedures for local anesthesia involved instillation of one drop of proxymetacaine 0.5% (Proximetacaína-Anestalcon; Alcon, São Paulo, Brasil).

Lamellar axial keratectomy was performed in one of the eyes by using a trephine of 200-µm depth and 6-mm diameter (Trépano for cornea, 6 mm; Steel Inox, São Paulo, SP, Brasil). A 60°crescent scalpel (Bisturi Crescente Angulado; Ziemer Ophthalmic Systems AG, Switzerland) was used to remove the corneal layer. All interventions were performed by the same surgeon by using a microscope with a magnification of ×20 (MC-M902®; DF Vasconcelos, São Paulo, SP, Brasil).

The rabbits were assigned to two groups: group nalbuphine (GN, n=30), which received 30 µL of nalbuphine solution 1% (Cristália Produtos Químicos e Farmacêuticos) instilled 4 times a day at regular intervals for up to 9 days (time of corneal epithelialization) and were clinically monitored by using the fluorescein eye stain test (Fluoresceína em tiras®; Ophthalmos, São Paulo, SP, Brasil), and group control (GC, n=30), which received 30 µL of physiological saline solution (0.9% NaCl) at the same times and under the same criteria as used for instillation in the GN. For prophylaxis of the infection, all eyes were treated with tobramycin eye drops 0.3% (Tobrex®; Alcon, São Paulo, SP, Brasil), at intervals of 6 h. The animals were not treated orally or parenterally to prevent pain[19].

After 1, 3, 5, 7, and 9 days of lamellar keratectomy, six animals of each group were euthanized by intramuscular injection of 20 mg/kg of ketamine (Cetamina-S(+); Cristalia Produtos Químicos e Farmacêuticos) and 0.75 mg/kg of midazolam (Dormire; Cristalia, São Carlos, SP). Lidocaine hydrochloride 2% (Xylestesin®; Cristalia) was administered intrathecally without a vasoconstrictor[20]. The entire corneal buttons were harvested, fixed in 10% buffered formalin, and processed for routine inclusion in paraffin. Cross-sections (5 µm thick) of the corneal tissue were subjected to immunohistochemistry (IHC).

IHC was performed by using antibodies against MMP-1 (1:200) (Anti-MMP 1 Rabbit pAb®; Cabiochem, Darmstad, Germany), MMP-9 (1:100) (Anti-MMP 9(Ab-3) Mouse mAb (56-2A4)®; Cabiochem), and OGF (1:100) (anti-Enkephalin, Clone NOC1®; Cabiochem) according to the manufacturer's instructions for each antibody. Dilutions were optimized in our laboratory to eliminate nonspecific staining. Sections were submitted for the blocking of endogenous peroxidase achieved by using a solution of methyl alcohol (Alcohol Metílico Commercial 100%®; Synth, Diadema, SP, Brasil) and hydrogen peroxide (Peroxido de Hidrogenio 50%®; Synth) at a final concentration of 8%. Incubation of the primary antibodies was performed in a moist chamber for 18 h at a temperature of 4°C. Immediately thereafter, a secondary antibody (ADVANCE™ / HRP, Rabbit/Mouse; DAKO, Carpinteria, USA) was added. Diaminobenzidine (DAB Chromogen® Rabbit/Mouse; DAKO, Carpinteria) was used as a chromogen.

The samples were photographed (Nikon Eclipse E200® microscope; Nikon, Melville, NY, EUA) (400X) and evaluated in software (Motic Image Plus 2.0; Hong-Kong, China). The expressions of MMP-1, MMP-9, and OGF were established by using semiquantitative IHC scores proposed by Stern et al.[21] (Table 1).

Data were statistically evaluated by using the Kruskal-Wallis' test and Dunn's post-hoc test. GraphPad Prism 4.0® software (GraphPad Software, Inc., La Jolla, CA, USA) was used to perform the statistical analyses, and a p-value of <0.05 was used to indicate statistical significance.

RESULTS

The expression of MMP-1 was observed in the interstitial space of the basal epithelial cells, over the basal lamina, and in the corneal stroma occupying approximately 75% of the evaluated microscopic fields (IHC scores of 5 and 6), with no significant difference observed between the GN and GC until day 5 of the evaluation ($p>0.05$). On days 7 and 9, gradual reductions were observed (IHC scores of 3 and 2, respectively) in the expression of MMP-1 ($p<0.01$), with no difference observed between the groups ($p>0.05$). MMP-1 was restricted to the basal region of the corneal epithelium (Figure 1).

There was no significant difference in the IHC scores of MMP-9 between the groups during the evaluations ($p>0.05$). In both the GC and GN, a similar pattern of identification to the one found for MMP-1 was observed from day 1 until day 5 of the evaluation ($p>0.05$). On days 7 and 9, significant reductions in MMP-1 were observed ($p<0.001$) (IHC scores of 2 and 1, respectively), which were restricted to the basal lamina and the interstitial space of epithelial cells near the basal lamina (Figure 2).

Regarding OGF, cytoplasmic localization in the epithelial suprabasal and basal cells was observed. No differences in OGF expression were observed between the periods (IHC scores of 1 and 2 for all) or between the groups ($p>0.05$) (Figure 3).

Table 1. Classification by semi-quantitative index of immunostaining in the corneal epithelium (Stern et al. 2006)

Índex	Immunostaining
0-0.5	Absence of staining: <10%
1	10%-25% of microscopic fields
2	25%-50%
3	>50%
4	>75%
5	>95%

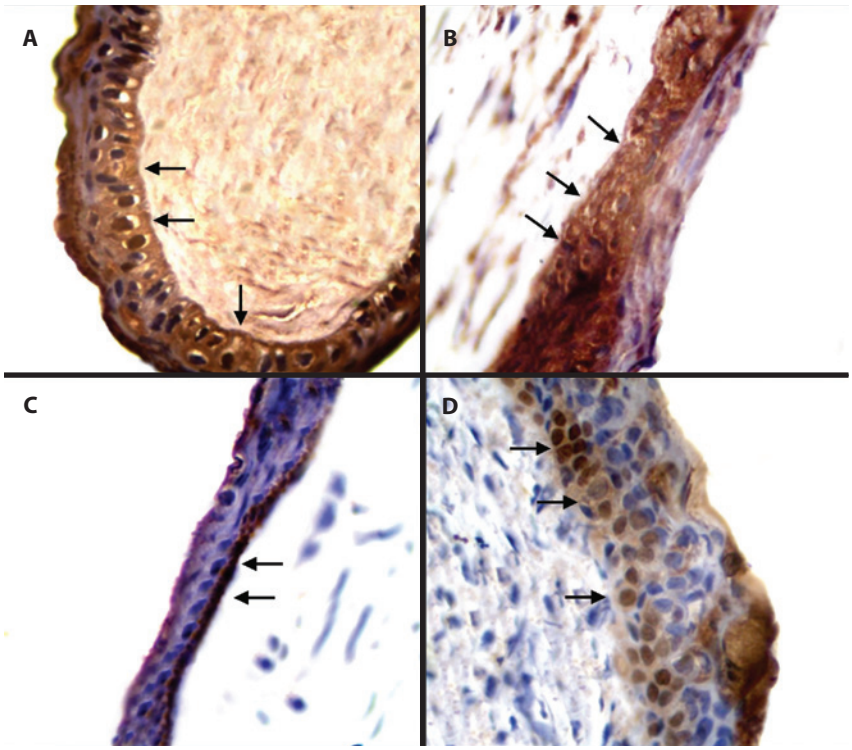

Figure 1. Photomicrographs of corneas from male adult New Zealand White rabbits in group nalbuphine (GN) (B and D) and group control (GC) (A and C) 1 (A and B) and 9 (C and D) days after lamellar keratectomy. In A and C, immunostaining of metalloproteinase-1 in the basal cells and corneal stroma (arrows) is shown. In B and D, a decrease in the immunostaining of metalloproteinase-1 is observed in the basal cells (arrows). Polymer bound with peroxidase. Magnification, ×400.

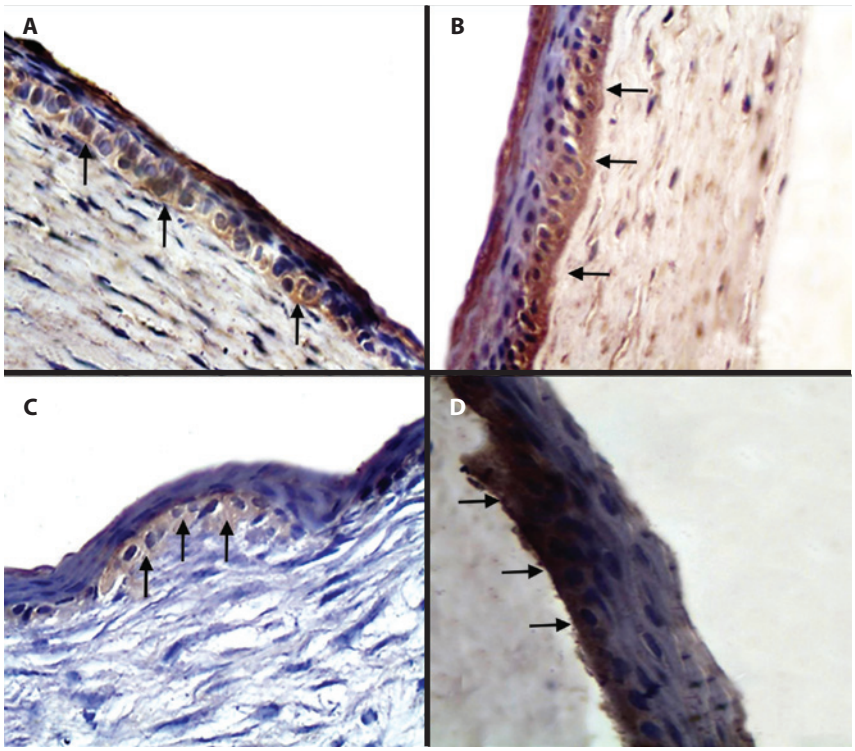

Figure 2. Photomicrographs of corneas from male, adult, New Zealand White rabbits in group nalbuphine (GN) (B and D) and group control (GC) (A and C) 1 (A and B) and 9 (C and D) days after lamellar keratectomy. In A and C, immunostaining of metalloproteinase-9 in the basal cells and corneal stroma (arrows) is observed. In B and D, a decrease in the immunostaining of metalloproteinase-9 is observed in the basal cells (arrows). Polymer bound with peroxidase. Magnification, ×400.

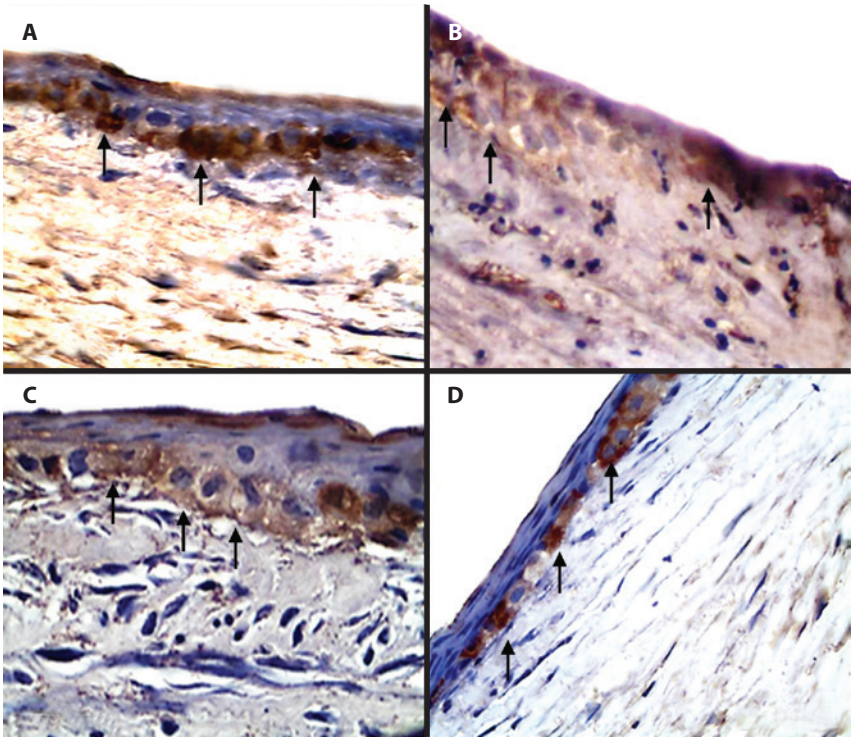

Figure 3. Photomicrographs of corneas from male, adult, New Zealand White rabbits in group nalbuphine (GN) (B and D) and group control (GC) (A and C) 1 (A and B) and 9 (C and D) days after lamellar keratectomy. In A and B, immunostaining of opioid growth factor in the basal cells and intracytoplasm (arrows) and absence of the opioid growth factor in the stroma are observed. In C and D, staining of the opioid growth factor indicates similar concentrations in the two groups. Polymer bound with peroxidase. Magnification, ×400.

DISCUSSION

MMPs are zinc-dependent endopeptidases secreted by keratocytes, epithelial cells, and other cell types[9]. In this study, greater IHC scores were observed in the corneal epithelium near the border of the lesion, in accordance with the results reported by Ribeiro et al.[22]. In the present research, MMP-1 and MMP-9 were detected in the basal membrane and superficial stroma. A similar finding was reported by Ye and Azar[23]. In contrast, Mulholland et al.[8] found MMP only in the corneal sub-epithelial region; this could be related to differences in the IHC technique used. IHC results depend on the type of detection procedure and the antibody used (monoclonal versus polyclonal).

The IHC technique used in the present study cannot discriminate between the active and inactive forms of MMPs[22]; however, it is able to detect different expression patterns of these proteases. Additional studies should be conducted in this area in the future. Several procedures are available to quantify MMPs, and all have advantages and limitations. Western blotting and zymography are used to evaluate expression at the protein level[24]. SDS-PAGE substrate zimography and reverse zymography allow only measurement of the relative activities of MMPs because pure preparations of MMP are often unavailable to permit standardization[24]. In situ zimography is a complementary procedure for IHC and reverse zimography; however, it may be difficult to discriminate between different MMPs classes[24]. With in situ zymography, only active MMPs are detected by visualizing areas where they have digested the substrate, which also occurs with serine, cysteine, or aspartic proteinases[24].

There are no previous reports about the effects of opioid agonists/antagonist drugs on the expression of MMPs. Here, decreases in the expressions of MMP-1 and MMP-9 in the lesion were observed on days 7 and 9, respectively, in the GC and GN. Clinical parameters and epithelization times in rabbit corneas treated under the same experimental protocols as used here have been reported in a previous study[19].

Ribeiro et al.[22] using IHC and zymography showed that morphine (pure opioid agonist) increased the expression of MMP-9 in corneas after lamellar keratectomy. Here, nalbuphine produced no alterations in MMP-1 or MMP-9. A study involving a MCF-7 breast cancer cell line showed the inhibitory effects of MMP induced by morphine[25], which is in contrast with the results obtained with nalbuphine in the present study. In MCF-7 cells, however, the attenuation of MMP secretion by opioids was not mediated by opioid receptors but was under the control of the nitric oxide system[25].

Hormonal factors must be considered when evaluating the effects of opioid analgesics. In this research, only male rabbits were used to eliminate eventual biases related to sex. Sexually dimorphic kappa-mediated antinociception has been observed in antithetical antinociceptive/nociceptive responsiveness of females versus males to kappa agonists/antagonists[26]. Apparently, selective kappa agonists produce greater antinociceptive effects in males[27]. In contrast, women have greater analgesic effects from the mixed mu/kappa ligands: pentazocine, nalbuphine, and butorphanol[28]. Interactions of opioids with estrogen are poorly understood and should be further investigated to provide insights into sex differences in analgesia.

In the present study, OGF was detected in epithelial suprabasal and basal cells. This finding is consistent with those obtained in other studies[15]. Even with kappa agonist/mu antagonist action, nalbuphine did not alter OGF expression. In the present study, it was also found that the agonist fraction of nalbuphine did not interfere with the expression of endogenous peptides. In a previous study[29], pharmacological intervention with opioid antagonist naltrexone (NTX; 30 mg/kg, twice daily) was related to the inhibition of OGF and delay in corneal repair of diabetic rats. A study conducted in inflammatory models in

the abdominal cavity demonstrated that local application of morphine increased the concentration of endogenous opioid peptides[30].

In conclusion, results of the present study showed that instillation of nalbuphine 1% did not alter the immunohistochemical expression patterns of MMP-1, MMP-9, and OGF in rabbit corneas after lamellar keratectomy.

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The relationship of birth weight, gestational age, and postmenstrual age with ocular biometry parameters in premature infants

A relação entre o peso ao nascer, idade gestacional e idade pós-menstrual com a biometria ocular em bebês prematuros

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ABSTRACT

Purpose: To analyze ocular biometry parameters and evaluate their relationship with gestational age, birth weight, and postmenstrual age in prematurely born infants.

Methods: The right eyes of 361 premature infants born before the 36th gestational week were evaluated. Birth weight, gestational week, and gender were recorded. An A-scan Biometer was used for obtaining axial measurements, including anterior chamber depth, lens thickness, vitreous length, and total axial length.

Results: Gestational age and birth weight values ranged from 23 to 36 weeks and from 560 to 2,670 g, respectively. The mean gestational age and birth weight were 30.8 ± 2.8 weeks and 1,497.9 ± 483.6 g, respectively. During the first examination (4-5 weeks of postnatal age), birth weight and gestational age of the infants correlated significantly and positively with lens thickness, vitreous length, and axial length (r>0.5, p<0.001), but not with anterior chamber depth (r<0.5). Increased vitreous and axial lengths correlated significantly with increasing postmenstrual age of the infants (r=0.669, p<0.001; r=0.845, p<0.001, respectively).

Conclusions: Lens thickness, vitreous length, and axial length, but not anterior chamber depth, were significantly correlated with birth weight and gestational age. All four parameters increased with increasing postmenstrual age, with higher correlations for vitreous and axial lengths than for anterior chamber depth and lens thickness. It was concluded that axial elongation resulted primarily from increasing posterior chamber length.

Keywords: Anterior chamber; Axial length, eye; Biometry; Gestational age; Premature; Birth weight

RESUMO

Objetivo: *Medir os comprimentos axiais dos componentes oculares e avaliar a relação com a idade gestacional, peso ao nascer e idade pós-menstrual em crianças nascidas prematuramente.*

Método: *O olho direito de 361 crianças prematuras, que nasceram com menos de 36 semanas de gestação, foram avaliados. O peso ao nascer, semanas de gestação e gênero foram registrados. Um biômetro* A-scan *foi utilizado para a obtenção das medidas axiais da profundidade da câmara anterior, espessura do cristalino, comprimento vítreo e comprimento axial total.*

Resultados: *A idade gestacional e os valores de peso ao nascimento variaram de 23 a 36 semanas e de 560 a 2.670 g, respectivamente. A idade gestacional e o peso ao nascer foram 30,8 ± 2,8 semanas e 1.497,9 ± 483,6 g. Ao primeiro exame (4 a 5 semanas de idade pós-natal), o peso ao nascimento e a idade gestacional dos recém-nascidos apresentaram correlação positiva, estatisticamente significativa, com a espessura do cristalino, comprimento vítreo e comprimento axial total (r>0,5 p<0,001), mas não com a profundidade da câmara anterior (r<0,5). O alongamento de comprimento vítreo e do comprimento axial total se correlacionaram significativamente com o aumento da idade pós-menstrual dos lactentes (r=0,669; p<0,001 e r=0,845; p<0,001, respectivamente).*

Conclusões: *A espessura do cristalino, o comprimento vítreo e o comprimento axial total, mas não profundidade da câmara anterior, foram significativamente correlacionados com o peso ao nascimento e com a idade gestacional. Todos os quatro componentes aumentaram com a idade pós-menstrual, apresentando correlações mais elevadas do comprimento vítreo e comprimento axial total do que da profundidade da câmara anterior e espessura do cristalino. Concluiu-se que o alongamento axial resultou principalmente do aumento do comprimento da câmara posterior.*

Descritores: *Camada anterior; Comprimento axial do olho; Biometria; Idade gestacional; Infant; Premature; Peso ao nascer*

INTRODUCTION

Preterm birth is a significant public health concern, as it is associated with a high risk of infant mortality, various morbidities in both the neonatal period and later age, and significant socio-economic difficulties[1,2]. Prematurely born children are disadvantaged in terms of perinatal mortality and long-term growth[3-5], and they have low birth weight and shorter eyes as compared with full-term children[6,7].

At present, ultrasound and optical biometry (partial coherence laser interferometry) are used to measure intraocular distances. However, eye measurements in newborns are only possible using ultrasonic methods. Ultrasound biometry, commonly referred to as A-scan and B-scan, is utilized for diagnostic testing and biometric measurements[8]. A-scan ultrasonography provides a one-dimensional measurement of length in the axial plane. Additionally, it facilitates the monitoring

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eye growth during infancy[9]. The ultrasound axial length of the eye is measured using either contact or immersion techniques. The contact technique is used more frequently, while measuring the axial length of children's eyes by pediatric cataract surgeons[10].

This study is aimed to measure ocular biometric parameters in premature infants and to investigate their relationship with birth weight, gestational age, and postmenstrual age.

METHODS

Infants

Premature infants enrolled in the retinopathy of prematurity (ROP) screening and who were born between September 1, 2013 and January 1, 2014 at Zekai Tahir Burak Women's Health Education and Research Hospital were selected for this cohort study. The inclusion criterion was birth at ≤36th gestation week. Infants with all types of congenital anomalies were excluded, even mild ones, and those with congenital eye abnormalities were also excluded from the study. Infants who had received previous treatment, such as laser photocoagulation and/or intravitreal injections, were also excluded.

Examinations for ROP and biometry measurement were initiated between postnatal weeks 4 and 5. Follow-up examinations were planned at approximately 1-3-week intervals depending on ROP results and retinal findings. The measurements were performed at approximately one-month intervals. Biometry measurements were performed on both eyes, but only data from the right eye were included in the analysis.

This study was approved by the local ethics committee of Zekai Tahir Burak Women's Health Education and Research Hospital and performed in accordance with the ethical standards stipulated in the Declaration of Helsinki. Parents or guardians of all infants gave informed consent prior to the examinations.

Birth parameters

Data on birth weight (g) and gestational age (weeks) were obtained from medical records, the hospital physician, or nurse records. The birth weight of a newborn was measured using an electronic weighing machine. Newborns were weighed without clothes within the first few hours of delivery. Gestational age was determined on the basis of the first day of the last normal menstrual period and the day of delivery, or on the basis of prenatal ultrasonography[11].

Eye examinations and measurements

Topical phenylephrine hydrochloride 2.5% with topical tropicamide 1% were administered two times at an interval of 10 min, and fundoscopy was performed only after a minimum of 30 min after the latter administration[12]. The eyelids were retracted using a pediatric speculum following the administration of the topical anesthetic 0.5%-proparacaine hydrochloride. An indirect ophthalmoscope (Heine Optotechnik, Herrsching, Germany) was used for fundoscopy with scleral indentation. ROP was graded according to The International Classification of Retinopathy of Prematurity[13].

Anterior chamber depth, lens thickness, vitreous length, and axial length were measured with an A-scan biometer (Compact Touch 3-in-1 Ultrasound system, B-scan, Biometry, Pachymetry; Cedex, France). The A-scan probe was placed gently on the center of the cornea, perpendicular to its axis. Researchers were careful to avoid the indentation of the cornea. The average value of at least five measurements was recorded for each eye.

Data analysis

Statistical analysis was conducted using Statistical Package for the Social Sciences™ 16.0 (SPSS Inc. Chicago, IL). Results are reported as means ± standard deviation. The one-sample Kolmogorov-Smirnov test was used for determining normally distributed variables, and one-way analysis of variance (ANOVA) test was used for evaluating the homogeneity of variance.

For comparison of gender with biometry parameters (anterior chamber depth, lens thickness, vitreous length, and axial length), the measurements during the first examination were evaluated, and a parametric test, t-test, for independent samples, was used. The Pearson product-moment correlation coefficient was used to evaluate the relationship of biometry parameters with birth weight and gestational age during the first examination and with postmenstrual age at all examinations. Differences were considered significant at a probability (p) level <0.05, and correlation coefficients were considered to be significant at r>0.5.

RESULTS

The study population comprised 185 females and 176 males, adding up to a total of 361 infants. Gestational age and birth weight values ranged from 23 to 36 weeks and from 560 to 2,670 g, respectively. The mean gestational age and birth weight were 30.8 ± 2.8 weeks and 1,497.9 ± 483.6 g, respectively. During the follow-up period, 159 (approximately 44.0%) infants developed ROP, whereas 202 (approximately 56.0%) did not. Stage 1, stage 2 and stage 3 ROP were developed by 95 (59.7%), 48 (30.1%), and 16 (10.0%) infants, respectively. The first examination took place at the 4th or 5th postnatal week. Data from at least one examination for each infant was used in the study. The mean number of examinations was 2.6 per infant, yielding a total of 939 examinations.

Mean birth weight and gestational age demonstrated no significant difference between girls and boys at the initial examination (p>0.05) (Table 1). In male infants, the mean anterior chamber depth was 0.10 mm longer, the vitreous length was 0.06 mm longer, and axial length was 0.09 mm longer, while the mean lens thickness was 0.05 mm shorter as compare with the female infants. However, female and male preterm infants did not differ significantly in any aspect of biometric parameters (p>0.05). The postmenstrual age of the infants ranged from 28 to 56 weeks during follow-up, and the mean postmenstrual age during the first examination was 35.2 ± 5.7 weeks (Table 2).

Table 1. Comparison of mean gestational age and mean birth weight among male and female infants

	Female	Male	p	Total
Number	185	176	*0.172*[a]	361
Mean gestational age (weeks ± SD)	30.7 ± 2.9	31.0 ± 2.7	*0.124*[b]	30.8 ± 2.8
Mean birth weight (g ± SD)	1,420.1 ± 477.0	1,576.3 ± 418.9	*0.064*[b]	1,497.9 ± 483.6

[a]= one-sample Kolmogorov-Smirnov test; [b]= independent-sample t-test; SD= standard deviation; n= number; g= gram.

Table 2. Comparison of mean biometry parameters during the first examination among male and female infants by the t-test for independent samples

Mean ± SD	Female (n=185)	Male (n=176)	p	Total
Postmenstrual age (week)	34.90 ± 3.10	35.60 ± 3.40	*0.124*	35.20 ± 3.80
Anterior chamber depth (mm)	2.14 ± 0.28	2.24 ± 0.32	*0.097*	2.19 ± 0.36
Lens thickness (mm)	3.68 ± 0.64	3.61 ± 0.34	*0.095*	3.64 ± 0.53
Vitreous length (mm)	10.20 ± 1.52	10.26 ± 1.87	*0.716*	10.23 ± 1.04
Axial length (mm)	16.02 ± 1.05	16.11 ± 0.68	*0.129*	16.06 ± 0.73

SD= standard deviation; n= number; mm= millimeter.

The correlation between birth weight and gestational age with biometry parameters is shown in table 3. During the first examination, the mean postmenstrual age was 35.2 ± 3.8 weeks, and the birth weight and gestational age of the infants correlated significantly and positively with lens thickness, vitreous length, and axial length (r>0.5, p<0.001). However, no strong correlation was found between birth weight and gestational age with anterior chamber depth (r<0.5).

Increased vitreous and axial lengths correlated significantly with increasing postmenstrual age of the infants (r=0.669, p<0.001; r=0.845, p<0.001, respectively). Anterior chamber depth and lens thickness increased with increasing postmenstrual age. However, the correlation between anterior chamber depth and lens thickness with postmenstrual age was weak (r=0.432, p<0.001; r=0.412, p<0.001, respectively) (Figures 1-4).

DISCUSSION

The eye undergoes significant growth between the neonatal period and adulthood. Investigations of the globe in neonates and infants have demonstrated that the posterior segment of the globe is relatively less developed than the anterior segment. These parameters change rapidly over the first 18 months of age[14-16]. The A-mode of ultrasound (amplitude mode) is a type of ultrasound in which a single transducer scans a line through the body with echoes plotted on a screen as a function of depth. Generally, in children, A-scan biometry is used for measuring the anterior-posterior diameter of eye. Ultrasonography is commonly used for clinical examinations of infants because of its safety and non-invasive character[17].

The mean axial length of the full-term newborn eye is 16.8 mm, while in adults it is 23.6 mm[18]. However, the axial length of the eye in term infants varies according to the method of measurement. Lengths obtained by ultrasonographic biometry tend to be shorter than the lengths obtained by pathologic studies. It was reported that the newborn eye had a mean axial length between 17.1 and 17.5 mm. At term, the anterior chamber depth averages 2.05 mm, with a range of 1.8-2.4 mm[19]. Isenberg *et al.*[20] demonstrated that the mean axial length was 16.2 mm, the anterior chamber depth was 2.0 mm, lens thickness was 3.8 mm, and vitreous chamber depth was 10.5 mm for term newborns. Globe size and axial length undergo dramatic changes during infancy. Although the anterior chamber depth of a newborn eye is approximately 75%-80% of that of adult eyes, their posterior segment at birth is less than half the size of that of the adult eye[14]. Similarly, in the present study, we found that the axial length elongation is mostly due to vitreous chamber elongation during the growth of postmenstrual age of the infants, i.e., at the age of 28th-56th week.

There are few reports in the literature on ocular biometric parameters in premature infants. Axial length continues to increase from birth. High refractive errors are common in the neonatal period following full-term and preterm birth and are related with poor emmetropization. It was argued that premature birth signals increased the risk of

Table 3. Correlation between birth weight and gestational age with biometry parameters during the first examination

	Anterior chamber depth	Lens thickness	Vitreous length	Axial length
Birth weight	r=0.037, p=0.775	r=0.551, p<0.001	r=0.612, p<0.001	r=0.577, p<0.001
Gestational age	r=0.125, p=0.001	r=0.582, p<0.001	r=0.680, p<0.001	r=0.634, p<0.001

(r= Pearson correlation).

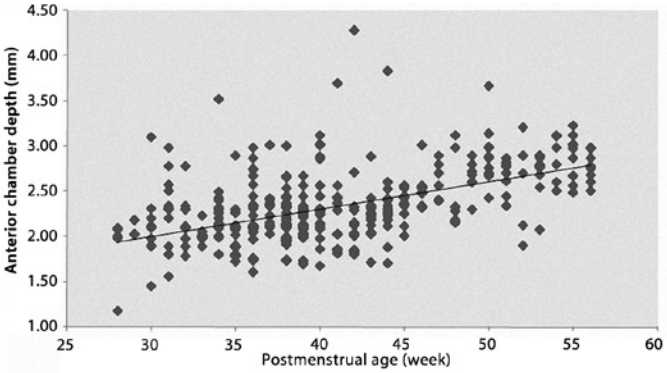

Figure 1. Relationship between anterior chamber depth and postmenstrual age (r=0.432, df=938, p<0.001). The regression line fit to the data has a slope of 0.029.

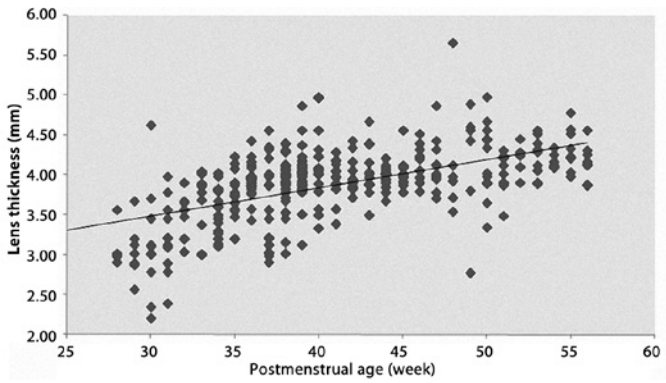

Figure 2. Relationship between lens thickness and postmenstrual age (r=0.412, df= 938, p<0.001). The regression line fit to the data has a slope of 0.039.

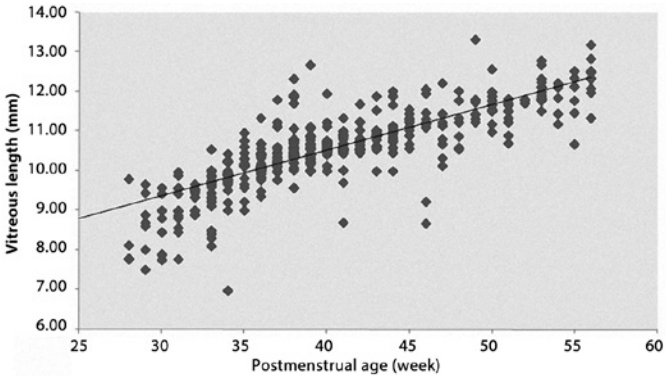

Figure 3. Relationship between vitreous length and postmenstrual age (r=0.669, df=938, p<0.001). The regression line fit to the data has a slope of 0.115.

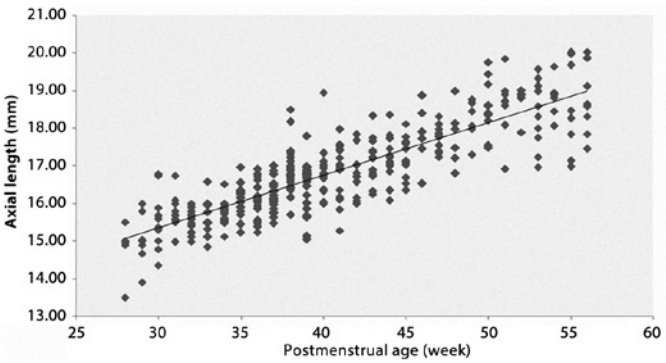

Figure 4. Relationship between axial length and postmenstrual age (r=0.845, df=938, p<0.001). The regression line fit to the data has a slope of 0.152.

abnormal refractive development[21-24]. Kobayashi *et al.*[25] measured anterior segments in 39 premature infants (at the gestational age of 25-39 weeks) using ultrasound biomicroscopy. They found that the mean anterior chamber depth was 1.3 mm at the 34.4 postconceptional week. These values appear quite low compared with our findings; we detected an anterior chamber depth of 2.10 mm at the 34th postmenstrual week (Figure 1).

We found that the mean anterior chamber depth was 2.19 mm, lens thickness was 3.64 mm, vitreous length was 10.23 mm, and axial length was 16.06 mm at the 35th postmenstrual week. Our results are in agreement with the investigation of Cook *et al.*[26] with regard to the development of biometric parameters in premature infants with or without retinopathy of prematurity (Figures 1-4). These authors obtained a mean axial length between 16.37 and 16.66 mm, anterior chamber depth between 2.14 and 2.26, posterior segment length between 10.18 and 10.47, and lens thickness between 3.93 and 4.04 mm. Similarly, we have previously reported the mean anterior chamber depth as 2.1 ± 0.4 mm, lens thickness as 4.1 ± 0.7 mm, vitreous length as 10.3 ± 1.5 mm, and axial length as 16.4 ± 1.3 mm in 138 eyes of 69 premature infants with ROP[27].

In the present study, the anterior chamber depth, vitreous length, and axial length were slightly greater in boys than girls. On the other hand, the lens was slightly thicker in girls than boys; however, these differences were insignificant. In a similar manner, the mean axial length in the male gender for term neonates was reported to be 0.2 mm longer than that for the female neonates[19]. Laws *et al.*[28] also found that male infants had longer axial lengths. This may be related to larger biparietal or occipitofrontal head diameter and to heavier weight of male infants. In another study, axial growth was measured at 3 and 9 months of age with similar findings[15].

Both birth weight and gestational age have an effect on ocular growth[26]. Saw *et al.*[29] examined the association of birth parameters with biometry in children aged 7-9 years, and suggested that children who were born heavier or who were born more mature had longer axial lengths and deeper vitreous chambers. However, they found no significant association between birth weight and lens thickness or anterior chamber depth. We documented that the birth weight and gestational age had a significant effect on lens thickness and vitreous and axial lengths. However, their impact on anterior chamber depth was minimal. As mentioned, infants with high gestational age and birth weight have larger head circumference and longer ocular biometric parameters.

The relationship between the size of the eyeball and other factors, such as birth weight, gestational age, and postmenstrual age has recently been documented[9,28-30]. Axial length grows linearly during the postnatal period in premature infants[28]. Axer-Siegel *et al.*[30] reported that in preterm infants with maturation, the anterior chamber depth and the axial length are enlarged, whereas lens thickness remains stable. In our study, both vitreous and axial lengths showed strongly positive correlation with postmenstrual age. However, anterior chamber depth and lens thickness showed little positive change in correlation with the growth in postmenstrual age.

It is important to clarify the role of birth parameters on ocular biometric measures, such as anterior chamber depth, lens thickness, vitreous length, and axial length, in premature infants. While the anterior chamber depth, vitreous length, and axial length were slightly longer in boys, the lens was slightly thicker in girls at the average 35th postmenstrual week. Birth weight and gestational age had a significant effect on lens thickness, vitreous length, and axial length but had little impact on anterior chamber depth in this study. Moreover, the vitreous length and axial length showed strongly positive correlation with postmenstrual age. However, anterior chamber depth and lens thickness showed little change in correlation with the growth in postmenstrual age.

In this study, there were several limitations, including a short study period, lack of a control group including full-term infants, and the fact that it is a single-center study. In conclusion, our study demonstrated that axial length elongation is mostly due to an increase of the posterior chamber length during the growth of premature infants in the postmenstrual 28th-56th week.

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Evaluation of possible factors affecting contrast sensitivity function in patients with primary Sjögren's syndrome

A avaliação dos possíveis fatores que afetam a função de sensibilidade ao contraste em pacientes com síndrome de Sjögren primária

Sedat Arikan[1], Ferhat Gokmen[2], Arzu Taskiran Comez[1], Baran Gencer[1], Selcuk Kara[1], Ayla Akbal[2]

ABSTRACT

Purpose: The contrast sensitivity (CS) function in patients with primary Sjögren's syndrome (pSS) may be impaired either frequently as a result of dry eye diseases or rarely as a result of optic neuropathy. In this study, we aimed to evaluate the CS function in pSS patients as well as to assess corneal aberrations and thickness of the peripapillary retinal nerve fiber layer (pRNFL).

Methods: Fourteen eyes of 14 pSS patients (pSS group) and 14 eyes of 14 healthy participants (control group) were subjected to assessment of CS at the spatial frequencies of 1.5, 3.0, 6.0, 12, and 18 cycles/degree (cpd) using a functional visual acuity contrast test (FACT); measurement of corneal high-order aberrations (HOAs) in terms of coma-like, spherical-like, and total HOAs using Scheimpflug corneal topography; and measurement of the thickness of both the macular ganglion cell-inner plexiform layer (mGCIPL) and pRNFL in all quadrants using optical coherence tomography. None of the participants were under treatment with artificial tears.

Results: The results of the CS test did not differ between the 2 groups at all spatial frequencies (p>0.05). In addition, there were no statistically significant differences between the 2 groups in terms of corneal HOAs (p>0.05) and thickness of mGCIPL (p>0.05). However, among all quadrants, only the inferior quadrant of pRNFL in pSS patients was statistically significantly thinner than that in the healthy participants (p=0.04).

Conclusions: The CS function in pSS patients can be maintained with normal thickness of both pRNFL and mGCIPL and with lack of increased corneal HOAs, which may be present even in the absence of artificial tear usage.

Keywords: Sjogren's syndrome; Corneal wavefront aberration; Dry eye diseases; Optic disk/pathology; Optical coherence tomography

RESUMO

Objetivo: *A função de sensibilidade ao contraste em pacientes com síndrome de Sjögren primário (pSS) pode ser prejudicada, quer frequentemente como resultado de doenças do olho seco, ou mais raramente como um resultado de neuropatia óptica. Neste estudo, objetivamos avaliar a função de sensibilidade ao contraste de pacientes com pSS, além da avaliação das aberrações da córnea e a espessura da camada de fibras nervosas da retina (pRNFL).*

Métodos: *Catorze olhos de 14 pacientes com pSS e 14 olhos de 14 participantes saudáveis foram submetidos, respectivamente, à avaliação do teste de sensibilidade aos contrastes (CS) nas frequências espaciais de 1,5, 3,0, 6,0, 12 e 18 ciclos/grau (cpd), utilizando teste de contraste acuidade visual funcional (FACT); a medida das aberrações de alta ordem da córnea (HOAs) em termos de coma, aberrações esféricas e aberrações totais, utilizando topografia corneana por Scheimpflug; e medida de espessura da camada de macular de células ganglionares plexiforme interna (mGCIPL) e a espessura de pRNFL em todos os quadrantes usando tomografia de coerência óptica. Nenhum dos participantes estava sob tratamento com lágrimas artificiais.*

Resultados: *O teste CS em pacientes pSS não diferiu do que o teste CS em participantes saudáveis em todas as frequências espaciais (p>0,05). Não houve também nenhuma diferença estatisticamente significativa entre os dois grupos em termos de HOAs da córnea (p>0,05), e espessura de mGCIPL (p>0,05). No entanto, entre todos os quadrantes, apenas o quadrante inferior da pRNFL em pacientes pSS foi significativamente mais fino que o quadrante inferior da pRNFL em participantes saudáveis (p=0,04).*

Conclusões: *A função de CS em doentes com pSS pode ser mantida em condições de ambas as espessuras normais de pRNFL e mGCIPL, assim como nas condições de falta de aumento HOAs da córnea, que pode ser mantida, mesmo na ausência do uso de lágrimas artificiais.*

Descritores: *Síndrome de Sjögren; Aberrações de frente de onda da córnea; Síndrome de olho seco; Disco óptico/patologia; Tomografia de coerência óptica*

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by dysfunction of the lacrimal and salivary glands, leading to keratoconjunctivitis sicca and xerostomia in the absence of other coexisting connective tissue diseases. Dysfunction of both the lacrimal and salivary glands in pSS patients arises from destructive mononuclear infiltration of the acinar and ductal epithelia of these glands. As dry eye, which is the hallmark ocular manifestation of pSS, can frequently compromise the quality of vision due to irregularities of the ocular surface, nevertheless, efforts are commonly directed toward improvement of the ocular surface structures of these patients in ophthalmic practice.

However, it has been reported that pSS patients may also suffer from visual acuity changes or visual quality disturbances as a result of optic neuropathy, which may occur before or at the same time as the diagnosis of pSS[1-3]. Thus, when evaluating the visual quality of pSS patients, both functional and morphological analyses of the optic nerve should also be performed in addition to examination of the ocular surface structures. In this context, along with optical coherence tomography (OCT), which allows assessment of the morphological features of the optic nerve to some extent, a contrast sensitivity (CS) test can be beneficial in the assessment of the functional feature of the optic nerve, because it may enable determination of visual disturbances, even in the early stages of optic nerve diseases[4,5]. In some

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clinical conditions associated with optic nerve involvement, patients can show disability with their low-contrast visual acuities, while their high-contrast visual acuities remain unaffected[6]. Therefore, patients who may be at risk of optic neuropathy, such as those with pSS, should also be examined using a CS test, although they may have completely normal visual acuity levels according to the Snellen chart.

In the present study, to evaluate the effects of these possible factors on the CS function in pSS patients, we assessed the CS of pSS patients using the functional visual acuity contrast test (FACT) and evaluated corneal high-order aberrations (HOAs) using Scheimpflug corneal topography and the thickness of the peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) using OCT.

METHODS

This prospective and comparative study was conducted at the Ophthalmology Department of Canakkale Onsekiz Mart University School of Medicine. The study protocol followed the Declaration of Helsinki for research involving human subjects and was approved by the local ethics committee. Healthy subjects and patients diagnosed with pSS who had been followed-up by the Physical Medicine and Rehabilitation Department of Canakkale Onsekiz Mart University School of Medicine were recruited for the study. Diagnosis of pSS was made on the basis of suggestions of the American-European study group on the classification criteria for Sjögren's syndrome[7]. As per the American-European study group, "the presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive"; accordingly, patients who met these criteria of pSS were included in this study.

Written informed consent was obtained from both pSS patients and healthy subjects who agreed to participate in this study as volunteers. Then, comprehensive ophthalmologic examination consisting of the measurement of best-corrected visual acuity (BCVA) and intraocular pressure, slit-lamp biomicroscopy, and funduscopic examination was performed for all participants.

The exclusion criteria for this study were established as having any history of previous ocular surgery or eye trauma, contact lens use, cataract diagnosis, corneal and conjunctival diseases, ocular inflammatory diseases, glaucoma, retinal diseases, chronic eye drop usage including artificial tears, systemic diseases except pSS, and BCVA below 20/20. The participants who met the eligibility criteria were subjected to corneal topographic assessments for measuring the root mean square (RMS) values of corneal HOAs including coma-like, spherical-like, and total HOAs using a Scheimpflug camera (Sirius version 1.2, CSO, Firenza, Italy); measurement of the thickness of pRNFL in the superior, inferior, nasal, and temporal quadrants of the optic nerve; measurement of the thickness of mGCIPL using Cirrus HD-OCT 4000 (Carl Zeiss Meditec Inc., Dublin, CA); and measurement of the level of CS at a number of different spatial frequencies such as 1.5, 3.0, 6.0, 12, and 18 cycles/degree (cpd) using FACT (OPTEC 6500 Contrast Sensitivity View-in Tester, Stereo Optical Company, Inc., Chicago, IL) in the day and without-glare mode. As described previously[8,9], the corneal transparency of the participants was assessed by measuring the percentage of light scatter density from the central cornea; for this, we used the histogram mode of the Scheimpflug camera.

With respect to statistical analysis, the Mann-Whitney U test was performed using SPSS version 13 (Statistical Package for Social Sciences Inc., Chicago, IL, USA) in order to evaluate the relationships between the pSS patients and healthy subjects in terms of the thickness of pRNFL and mGCIPL, RMS values of corneal HOAs, and level of CS. A p-value of ≤0.05 was accepted as statistically significant.

RESULTS

Fourteen right eyes of 14 female pSS patients and 14 right eyes of 14 female healthy subjects were enrolled into this study. The participants were divided into 2 groups: the pSS group comprising the pSS patients and the control group comprising the healthy subjects. The mean duration of disease was 5.7 ± 5 (1-20) years in the pSS group. All pSS patients who participated in the current study were under treatment with hydroxychloroquine (HQ); the mean duration of HQ usage was 3.8 ± 2.8 (1-10) years. The mean logMAR value of the BCVA was 0 in both groups. The mean age of the pSS group and control group was statistically similar [51.3 ± 5.7 (45-64) years and 49.2 ± 5.9 (39-58) years, respectively] (p>0.05). There were no statistically significant differences between the 2 groups in terms of the spherical equivalent value [0.47 ± 0.79 (0.00-2.50) D and 0.46 ± 0.53 (0.00-1.50) D, respectively] (p>0.05). In the pSS group, 5 and 2 patients were positive for the anti-Ro antibody and anti-La antibody, respectively, whereas 4 patients were positive for both anti-Ro and anti-La antibodies; 3 patients were negative for both anti-Ro and anti-La antibodies. In the control group, all participants were negative for both anti-Ro and anti-La antibodies. All relevant clinical data for the pSS patients is presented in table 1.When we compared the thickness of pRNFL in all quadrants, only the inferior quadrant of pRNFL in the pSS group was statistically significantly thinner than that in the control group (p<0.05) (Figure 1). There were no statistically significant differences between the 2 groups in terms of the CS function at all spatial frequencies such as 1.5, 3.0, 6.0, 12, and 18 cpd (p>0.05) and in terms of the RMS values of coma-like, spherical-like, and total HOAs (p>0.05) (Figure 2 and Figure 3, respectively). The thickness of mGCIPL in the pSS group and control group was similar [85.7 ± 3.7 (80-92) µm and 85.8 ± 4.2 (81-92) µm, respectively] (p>0.05).

Table 1. All relevant clinical data of primary Sjögren's syndrome (pSS) patients

	pSS group (N=14)	Control group (N=14)	p-value
Schirmer I test (mm, mean ± SD)	7.8 ± 4.3	16.2 ± 2.7	p<0.0001*
TBUT (seconds, mean ± SD)	9.9 ± 3.5	14.5 ± 2.4	p=0.001*
Salivary gland focus score (mean ± SD)	1.07 ± 0.99	- - -	
BCVA (logMAR)	0	0	
Subjects anti-Ro ab + (n)	4	0	
Subjects anti-La ab + (n)	2	0	
Subjects anti-Ro + and anti-La ab + (n)	4	0	
Subjects with neuropathy (n)	0	0	
Cornea light scatter (%, mean ± SD)	21.1 ± 2.5	20.9 ± 2.5	p=0.9

TBUT= tear film break-up time; BCVA= best-corrected visual acuity.

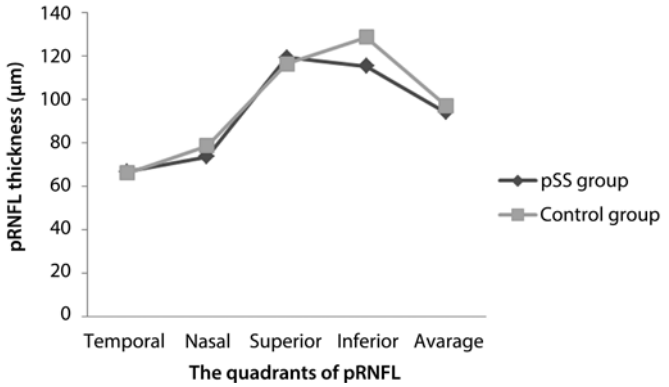

Figure 1. Mean thickness of the peripapillary retinal nerve fiber layer (pRNFL) in all quadrants in both groups. Note that among all quadrants of pRNFL, a significant difference between the 2 groups was observed only in the inferior quadrant.

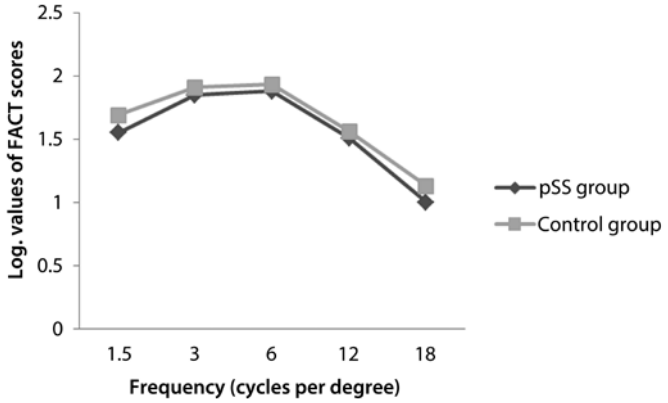

Figure 2. The mean functional visual acuity contrast test (FACT) scores in terms of logarithmic values between the 2 groups were nearly similar at all spatial frequencies.

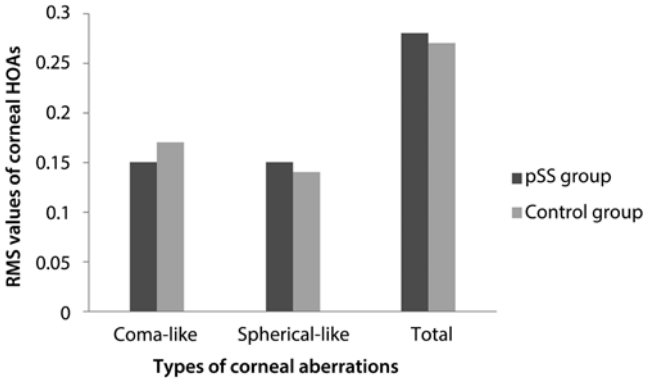

Figure 3. The mean root mean square (RMS) values of all types of corneal high-order aberrations (HOAs) were similar between the 2 groups.

DISCUSSION

The B-cell activating factor of the tumor necrosis factor family (BAFF) is considered to be an important cytokine in the pathogenesis of autoantibody-associated immune pathologies, and it has an important role in B-cell maturation, plasma cell survival, and autoantibody production. Studies that have investigated the pathophysiological mechanisms of pSS have also revealed the significant effect of BAFF on the development of pSS[10,11]. Overproduction of BAFF in transgenic mice has been shown to lead to pathological findings resembling those observed in pSS[12]. On the other hand, higher levels of BAFF that have been detected either in the serum or saliva of pSS patients may support this association in humans[13,14].

Besides playing a crucial role in salivary gland inflammation and in the pathophysiological mechanisms of pSS, the increased expression of BAFF may also participate in ocular surface disorders that are frequently observed in pSS patients. Mariette et al. reported enhanced levels of BAFF mRNA both in the salivary glands and ocular surface of pSS patients[15]. Higher levels of BAFF have previously been observed in the cerebrospinal fluid of patients with multiple sclerosis (MS) or neuromyelitis optica (NMO)[16]. In addition, a strong relationship between pSS and NMO had been demonstrated in numerous case reports[17-21]. Thus, we postulated that apart from participating in pSS, BAFF may also be responsible for the development of optic neuropathy in pSS patients.

In the literature, although the mechanism of optic neuropathy in pSS patients has been attributed to vasculitis[22], we believe that the increased expression of BAFF may additionally participate in the optic nerve damage of pSS patients in 2 ways. First, the increased expression of BAFF may contribute to optic nerve damage by modulating the production levels of autoantibodies such as anti-Ro and anti-La, which are the hallmarks of pSS. It has been reported previously that anti-Ro autoantibodies can play a role in mediating or potentiating vascular injury in the central nervous system[23]. A study by Yang et al. indicated that these autoantibodies may also lead to improper apoptotic removal of the retinal ganglion cells (RGCs) by binding to the apoptotic RGCs, resulting in optic nerve damage[24]. Furthermore, in the same study, according to the OCT findings of pSS patients, a correlation was demonstrated between the thinning of pRNFL and mGCIPL and increased numbers of autoantibodies such as anti-Ro and anti-La[23]. Second, increased serum levels of BAFF may also lead to optic nerve damage by inducing the serum levels of anti-aquaporin-4 antibody (anti-AQP4), which is an important antibody in the development of NMO[25]; overproduction of anti-AQP4 may result in the exposure of neurons to the cytotoxic effects of increased levels of glutamate[26].

The optic neuropathy observed in pSS patients can sometimes begin as an initial manifestation even in the absence of xerostomia and dry eye symptoms[1]; therefore, along with observing the ocular surface structures, these patients should also be evaluated in terms of their optic nerve functions. For this, the CS test can be a valuable method, as it allows detection of visual quality disturbances that arise from optic nerve dysfunction even in the early phases of the associated diseases. However, the CS test in pSS patients can additionally be impaired by an increased amount of corneal HOAs due to dry eye disease[27]. Therefore, this factor should be taken into consideration when evaluating the CS function in pSS patients.

Zhang et al. reported a modest effect of instilling artificial tears on CS in pSS patients, primarily at medium spatial frequencies[28]. In this current study, although none of the participants were using artificial tears, there were no significant differences between the pSS group and control group either in terms of CS tests measured at all spatial frequencies or in terms of total, coma-like, and spherical-like HOAs. These similar results may be attributed to the use of HQ in pSS patients, because the alleviating effect of HQ (reducing the levels of BAFF in the tear fluid of pSS patients) has been demonstrated in a previous study[29]. In another study, the beneficial effect of HQ on xerostomia has also been demonstrated in pSS patients[30].

In this current study, although we could not measure the levels of BAFF in the serum of the participants, we postulated that the similarity between the pSS patients and healthy subjects with respect to the thickness of mGCIPL and pRNFL, except in the inferior quadrant, may have been a consequence of the reduced effects of HQ on the serum levels of BAFF in pSS patients[31]. This association may also be supported by the findings of Yang et al. who found significant thinning of pRNFL in both the inferior and temporal quadrants as well as the thinning of mGCIPL in nearly all quadrants except the superonasal portion of the macula in pSS patients not under treatment with HQ[21,24]. In the current study, we determined that significant thinning of pRNFL in the inferior quadrant in pSS patients may have arisen from mild macular toxicity of HQ; this finding agreed with that reported by Pasadhika[32]. Based on these findings, it may be postulated that pSS patients who are under treatment with HQ may also be protected from optic nerve damage apart from corneal surface irregularities. Moreover, it may be hypothesized that HQ has a possible effect on preventing relapses of MS by reducing the levels of BAFF[33]. However, these hypotheses need to be clarified by further studies.

Because this study was planned for the evaluation of possible factors that may affect the CS function in pSS patients and there were only 14 patients who had been followed-up in our faculty, we could not involve additional pSS patients, particularly who were not under treatment with HQ. In this study, we could not measure the serum levels of BAFF in the participants; we consider this to be another major limitation of this study. However, we believe that the current

study provides interesting associations related to pSS patients, which should be further evaluated in future studies.

In conclusion, the CS function in pSS patients can be maintained with normal thicknesses of pRNFL and mGCIPL and lack of increased corneal HOAs even in the absence of artificial tear usage. However, further studies involving larger sample sizes are required for verifying these associations.

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Intraocular lens explantation or exchange: indications, postoperative interventions, and outcomes

Remoção ou troca de lentes intraoculares: indicações, intervenções pós-operatórias e resultados

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ABSTRACT

Purpose: To analyze the indications for explantation or exchange of intraocular lenses (IOLs), which were originally implanted for the correction of aphakia during cataract extraction.

Methods: All cases that involved intraocular lens explantation or exchange in one institution between January 2008 and December 2014 were analyzed retrospectively.

Results: In total, 93 eyes of 93 patients were analyzed. The median time interval between implantation and explantation of the anterior chamber intraocular lenses (AC IOL) and posterior chamber intraocular lenses (PC IOL) was 83.40 ± 83.14 months (range: 1-276 months) and 55.14 ± 39.25 months (range: 1-168 months), respectively. Pseudophakic bullous keratopathy (17 eyes, 38.6%) and persistent iritis (12 eyes, 27.8%) in the AC IOL group and dislocation or decentration (30 eyes, 61.2%) and incorrect IOL power (nine eyes, 18.4%) in the PC IOL group were the most common indications for explantation of IOLs. The mean logMAR best corrected visual acuity (BCVA) improved significantly from 1.30 preoperatively to 0.62 postoperatively in the PC IOL group (p<0.001) but did not improve significantly in the AC IOL group (p=0.186).

Conclusions: The primary indication for IOL explantation or exchange was pseudophakic bullous keratopathy in the AC IOL group and was dislocation or decentration in the PC IOL group. PC IOL explantation or exchange is safe and improves visual acuity.

Keywords: Cataract extraction; Lenses, intraocular; Reoperation; Device removal; Lens implantation, intraocular; Pseudophakia; Corneal diseases; Patient satisfaction; Visual acuity

RESUMO

Objetivo: *Analisar as indicações para a remoção ou troca de lentes intraoculares (IOL), que foram originalmente implantadas para a correção de afacia após a extração da catarata.*

Método: *Todos os casos que envolveram remoção ou troca de lentes intraoculares em uma única instituição, entre janeiro de 2008 e dezembro 2014 foram analisados retrospectivamente.*

Resultados: *No total, foram analisados 93 olhos de 93 pacientes. O intervalo de tempo médio entre o implante e a remoção das LIOs de câmara anterior (AC IOL) e de câmara posterior (PC IOL) foi 83,40 ± 83,14 meses (variando de 1 a 276 meses) e 55,14 ± 39,25 meses (variando de 1 a 168 meses), respectivamente. Ceratopatia bolhosa pseudofácica (17 olhos, 38,6%) e irite persistente (12 olhos, 27,8%) no grupo AC IOL, e deslocamento ou descentralização (30 olhos, 61,2%) e poder incorreto da IOL (nove olhos, 18,4%), no grupo PC IOL, foram as indicações mais comuns para a remoção das IOLs. A média logMAR da melhor acuidade visual corrigida (BCVA) melhorou significativamente a partir de 1,30 no pré-operatório para 0,62 no pós-operatório no grupo PC IOL (p<0,001), mas não melhorou significativamente no grupo AC IOL (p=0,186).*

Conclusões: *A principal indicação para remoção ou troca de lentes intraoculares foi a ceratopatia bolhosa pesudofácica no grupo AC IOL e deslocamento ou descentralização no grupo PC IOL. A remoção ou troca de PC IOLs é segura e melhora a acuidade visual.*

Descritores: *Extração de catarata; Lentes intraoculares; Reoperação; Remoção de dispositivo; Implante de lente intraocular; Pseudofacia; Doenças da córnea; Satisfação do paciente; Acuidade visual*

INTRODUCTION

Cataracts are one of the most common eye diseases associated with blindness (visual acuity worse than 20/400 in the better eye with best correction) worldwide, with an estimated 18 million people thought to be affected, and cataract surgery is the intraocular procedure performed most often worldwide. Over the years, the techniques of cataract surgery have evolved into a safe and successful procedure for visual rehabilitation. The incidence of most complications has significantly decreased with the development of better instrumentation and affordable, high-quality intraocular lens (IOL) implants[1]. Various aspects of cataract surgery that make it safer have changed considerably in the past decade with the evolution of both surgical techniques and IOL designs.

Although cataract surgery is safe for the majority of patients, some complications that involve the anterior and posterior segment can occur. Surgical procedures involving the use of the modern anterior chamber (AC) IOLs (AC IOLs) and posterior chamber (PC) IOLs (PC IOLs) have reduced the risk of complications necessitating IOL explantation/exchange. Although older types of both AC IOLs and PC IOLs are no longer implanted since the advent of the new generation IOLs, we still see complications associated with those implanted many years ago. The aim of this study was to analyze the indications and outco-

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mes of AC and PC IOL explantation conducted at a single institution between 2008 and 2014.

METHODS

This retrospective interventional case series study has been conducted in accordance with the tenets of the Declaration of Helsinki and with the approval of the Ethics Committee of Necmettin Erbakan University School of Medicine. The medical records for 93 eyes of 93 patients who had an AC or PC IOL explantation/exchange performed at Necmettin Erbakan University School of Medicine from 2008 to 2014 were reviewed for data including gender, age, the mean interval between cataract surgery and IOL explantation, the presence of pseudoexfoliation (PEX), glaucoma, corneal edema, uveitis, the presence of myopia or hyperopia, and best corrected visual acuity (BCVA) before and after the explantation/exchange. The exclusion criteria were a follow-up period shorter than 1 month and patients with incomplete medical records. Otherwise, all the patients with IOL explantation/exchange were included. Descriptive statistics were calculated for various clinical characteristics, and all data were analyzed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Ninety-three patients with AC and PC IOL explantation/exchange were recruited. Forty-four patients had AC IOLs and 49 patients had PC IOLs. The patients were evaluated in two groups accordingly. Table 1 shows the characteristics of patients in each group. The median time intervals between implantation and explantation of the AC IOL and PC IOL groups were 83.40 ± 83.14 months (range: 1-76 months) and 55.14 ± 39.25 months (range: 1-168 months), respectively.

AC IOL group

The mean preoperative intraocular pressure in the AC IOL group was 18.05 ± 8.49 mmHg (range: 6-44). Four patients used timolol + dorzolamide (Cosopt, MSD, Turkey), while two patients used timolol + dorzolamide (Cosopt, MSD, Turkey) and brimonidine tartrate (Alphagan P, Abdi Ibrahim, Turkey).

The most common reasons for explantation of the AC IOLs were pseudophakic bullous keratopathy (PBK) (17 eyes, 38.6%) and persistent iritis (12 eyes, 27.8%) (Table 2). After AC IOL explantation, a scleral fixated PC IOL was placed in 12 eyes (27.3%), and a PC IOL was implanted in six eyes (13.6%) above the remnant of the capsule at the sulcus without suturing. Finally, 26 (59.1%) eyes were left aphakic (Table 3). The mean logMAR BCVA had improved from 2.00 preoperatively to 1.80 postoperatively, but the difference did not reach statistical significance (p=0.186). The BCVA improved in 21 eyes (47.7%), remained stable in 17 eyes (38.6%), and decreased in six eyes (13.6%). The BCVA improved in patients with PBK and persistent iritis in two eyes (11.8%) and eight eyes (66.7%), respectively. The mean intraocular pressure of all the subjects was within the normal range, with 15 (34.1%) patients requiring topical anti-glaucomatous medication. Intraoperative and postoperative complications are shown in table 5.

Table 1. Characteristics of patients with AC and PC IOL explantation

Characteristics	AC IOL group	PC IOL group
Sex, n (%)		
Male	19 (43%)	37 (75.5%)
Female	25 (57%)	12 (24.5%)
Age (y)		
Mean ± SD	65.9 ± 17.0	52.84 ± 24.60
Range	20-83 years	3-86 years
Interval between surgeries		
Mean ± SD	83.14 ± 83.40	55.14 ± 39.25
Range	1-276 months	1-168 months

AC IOL= anterior chamber intraocular lens; PC IOL= posterior chamber intraocular lens, SD= standard deviation.

PC IOL group

The mean preoperative intraocular pressure was 16.69 ± 7.42 mmHg (range: 7-40). Three patients used timolol + dorzolamide (Cosopt, MSD, Turkey), while two patients used timolol + dorzolamide (Cosopt, MSD, Turkey) and brimonidine tartrate (Alphagan P, Abdi Ibrahim, Turkey).

The most common indications for explantation of the PC IOLs were dislocation/decentration (30 eyes, 61.2%) and postoperative residual refractive error due to incorrect IOL power calculation (nine eyes, 18.4%). Other indications were IOL opacification (six eyes, 12.2%), persistent iritis (three eyes, 6.1%), and uveitis glaucoma hyphema (UGH) syndrome (one eye, 2%) (Table 4). After the PC IOL explantation, a new PC IOL could be implanted into the capsular bag in 15 eyes (30.6%) and above the remnant of the capsule without suturing in 13 eyes (26.5%). If the capsular remnant did not offer adequate support for a PC IOL, a scleral fixated IOL was placed (17 eyes, 34.7%). Finally, four eyes (8.2%) were left aphakic (Table 3). The mean logMAR BCVA had improved significantly from 1.30 preoperatively to 0.62 postoperatively (p<0.001). The BCVA improved in 37 eyes (75.5%), remained stable in four eyes (8.2%), and decreased in eight eyes (16.3%). Although 12 patients required topical anti-glaucomatous medications, the mean intraocular pressure of all the subjects was within the normal range. Intraoperative and postoperative complications are shown in table 5.

DISCUSSION

Cataract extraction ranks among the most commonly performed surgical procedures in the United States[2]. As a consequence of the large number of operations performed worldwide, increased use of IOLs leads to an increase in the number of complications requiring explantation of the IOLs, despite the marked improvement in surgical procedures and IOL technologies.

Table 2. Indications for AC IOL explantation and relation to age and intervals between surgeries

Indications	Eyes n (%)	Age, year (mean ± SD)	Interval between surgeries, month (mean ± SD)
Pseudophakic bullous keratopathy	17 (38.6)	68.88 ± 15.84	121.06 ± 87.73
Persistent iritis	12 (27.8)	67.50 ± 13.57	41.75 ± 34.71
IOL decentration	6 (13.6)	66.00 ± 18.06	64.50 ± 90.23
Glaucoma	5 (11.4)	61.20 ± 18.21	121.40 ± 82.84
UGH	2 (4.5)	78.50 ± 4.95	1.00 ± 0.00
Refractive error	1 (2.3)	20.00	180.00
Glare	1 (2.3)	39.00	2.00

AC IOL= anterior chamber intraocular lens; UGH= uveitis glaucoma hyphema syndrome.

Table 3. IOL fixation technique used after IOL explantation

Fixation technique	AC-IOL group	PC-IOL group
PC IOL in bag	0 (0%)	15 (30.6%)
PC IOL in sulcus	6 (13.6%)	13 (26.5%)
PC IOL with scleral fixation	12 (27.3%)	17 (34.7%)
Aphakia	26 (59.1%)	4 (8.2%)

AC IOL= anterior chamber intraocular lens; PC IOL= posterior chamber intraocular lens.

Table 4. Indications for PC IOL explantation and relation to age and intervals between surgeries

Indications	Eyes n (%)	Age, year (mean ± SD)	Interval between surgeries, month (mean ± SD)
IOL dislocation/ decentration	30 (61.2)	58.60 ± 22.89	65.06 ± 41.21
Incorrect IOL power	9 (18.4)	31.44 ± 28.34	48.00 ± 32.86
IOL opacification	6 (12.2)	59.00 ± 8.79	40.00 ± 22.34
Persistent iritis	3 (6.1)	45.67 ± 27.75	32.67 ± 35.80
UGH	1 (2.0)	57.00	2.00

PC IOL= posterior chamber intraocular lens; UGH= uveitis glaucoma hyphema syndrome.

Table 5. Intraoperative and postoperative complications of intraocular lens explantation

	AC IOL group	PC IOL group
Intraoperative complications		
Vitreous loss	8 (18.2%)	6 (12.2%)
Bleeding to the anterior chamber	4 (9.1%)	3 (6.1%)
Suprachoroidal hemorrhage	2 (4.5%),	-
Postoperative complications		
Bullous keratopathy	2 (4.5%)	-
Cystoid macular edema	1 (2.3%)	-
Corneal melting requiring evisceration	1 (2.3%)	-
Endophthalmitis	-	1 (2.0%)

AC IOL= anterior chamber intraocular lens; PC IOL= posterior chamber intraocular lens.

In a series of 102 patients who had IOL explantation or exchange, AC IOLs comprised 66.7% of the removed lenses. PBK, followed by UGH syndrome and cystoid macular edema were the most frequent indications for explantation or exchange[3]. Similarly, PBK and UGH were the most common indications for AC IOL explantation (53.9%), followed by iris-fixated lenses (33.7%)[4]. Marques *et al.* reported that their rate of PBK was only 6.7%, while the main indication was inflammation (UGH and persistent iritis) with a rate of 53.3%[5]. In this study, PBK (17 eyes, 38.6%) was the most common indication, in accordance with Mamalis *et al.*[3] and Doren *et al.*[4], for AC IOL explantation, which had a rate of 47.3%. Preventing the need for penetrating keratoplasty, AC IOL explantation has been indispensable in eyes with signs of progressive corneal endothelial damage[6]. In our series, intervals between surgeries in patients with PBK and persistent iritis were 126.7 ± 89.7 months (range: 6-276 months) and 41.4 ± 38.6 months (range: 2-120 months), respectively. Early explantation of the AC IOLs may prevent progressive endothelial cell loss, as observed in the fact that BCVA improved in only two eyes (11.8%) in patients with PBK who had a longer time interval between surgeries and improved in eight eyes (66.7%) in patients with persistent iritis who had a shorter time interval between surgeries[7,8].

In the latest survey update in 2007 of members of the American Society of Cataract and Refractive Surgeons and the European Society of Cataract and Refractive Surgeons, Mamalis *et al.* reported that dislocation/decentration, incorrect IOL power calculation, glare/optical aberrations, and IOL calcification were the most common reasons for PC IOL explantation[9]. Furthermore, Jones *et al.* investigated indications of IOL exchange and found that IOL dislocation (46%) was the most common indication and that PC IOLs accounted for 88.5% of all decentered IOLs[10].

IOL dislocation is a rare complication in which the patient complains of blurred vision, glare, and possibly diplopia. The visual symptoms can be potentially disabling to the patient, and the condition requires intervention in either repositioning or even removing the lens. Patients with PEX are at risk for IOL dislocation after uncomplicated cataract surgery. Although IOLs can be well secured in the capsular bag, the possibility of progressive loss of zonular integrity may cause late endocapsular subluxation of PC IOLs. In our series, nine patients with PEX had IOL extraction because of delayed dislocation; the mean interval between implantation and exchange was 78 months. The current study at a single institution demonstrated that PC IOL dislocation (61.2%) was the most common indication for extracting PC IOLs, followed by incorrect IOL power (18.4%). This was similar to the findings reported by Mamalis *et al.*[9] and Jones *et al.*[10]. According to the time interval between cataract surgery and IOL dislocation, IOL dislocation can be classified as early dislocation if it occurs within 3 months and late dislocation if it occurs after more than 3 months. Improper fixation within the capsular bag and instability of the capsular bag-IOL complex are the major causes of IOL dislocation[10]. The major causes of early IOL dislocation are improper support of the capsular bag and ciliary sulcus due to zonular or capsular damage, rupture, or both[11]. Late dislocations are often accompanied by trauma or progressive zonular dehiscence caused by contraction of the capsular bag many years after routine cataract surgery[12]. In the present study, early IOL dislocation was present in six eyes after complicated cataract surgery with vitreous loss, in one eye after ocular trauma, and in one eye with a broken IOL haptic. Of the 22 eyes with late IOL dislocation, the major predisposing factors were PEX in nine eyes (40.9%), trauma in seven eyes (31.8%), and capsule contracture syndrome in three eyes (13.6%). No predisposing factor could be found in the remainder (three eyes, 13.6%).

Unpredicted postoperative refractive error due to preoperative incorrect IOL power calculation is a disturbing complication for cataract surgeons. Improved IOL calculation formulas and preoperative measurement of axial length and corneal curvature reduce the risk of this complication. In our study, nine (18.4%) eyes required IOL explantation due to incorrect IOL power. The IOLs were exchanged because of postoperative myopia in five eyes and hyperopia in four eyes. Our results were in accordance with a recent study in which IOL dislocation (46%) followed by incorrect IOL power (23%) were the most common causes of IOL exchange[10].

IOL opacification is a rare but possible event. The exact reason for opacification is unknown. Using microscopic analyses of explanted hydrophilic acrylic IOLs, Werner *et al.* revealed multiple fine, calcified granular deposits of variable sizes within the lens optics[13]. Neuhann *et al.* concluded that it was important to determine whether the calcium deposits formed because of a problem in IOL manufacturing (properties of the polymer, its surface, or the IOL packaging) or were the result of environmental causes that can catalyze calcification[14]. In the present study, five of the six patients with IOL opacifications had a history of diabetes mellitus, which may have contributed to IOL opacifications by catalyzing calcification.

By using a proper IOL stabilizing technique, intraocular tissues should be protected from damage that could be caused by IOLs, and appropriate refractive outcomes should therefore be achieved. Secondary scleral fixated IOL implantation after IOL removal was the dominant procedure used to avoid further corneal complications in both the AC IOL and PC IOL groups in our study.

Postoperative corneal decompensation after IOL explantation was heavily dependent on the initial measurement of endothelial cell density[15,16]. It is important to bear in mind that IOL explantation has a risk of additional damage to corneal endothelial cells. Coli *et al.* showed progression of corneal decompensation in 23.5% of eyes after AC IOL explantation[17]. In the current study, only two eyes (4.5%) developed postoperative PBK in the AC IOL explantation group, and postoperative PBK was not observed in the PC IOL explantation group. The low incidence of progression to PBK in the AC IOL explantation group, compared with Coli *et al.*[17] may be attributed to the higher proportion of patients that were left aphakic in our study. With the application of proper techniques, BCVA improved in 21 eyes (47.7%) in the AC IOL group and in 37 eyes (75.5%) in the PC IOL group.

This study had several shortcomings, including its retrospective nature and a lack of information on the IOL types that were explanted, lack of measurements of preoperative and postoperative endothelial cell density, and the highly variable follow-up times. Although the mean follow-up time was 7.2 ± 9.6 months and some of the cases had 48 months of follow-up, some cases had 1 month of follow-up, which was insufficient to detect some of the postsurgical complications.

In conclusion, the main indications for IOL explantation/exchange in the AC IOL and PC IOL groups were PBK and IOL dislocation/decentration, respectively. PC IOL explantations/exchanges have more favorable outcomes with an increase in BCVA than AC IOL explantations/exchanges, in which inflammation and corneal complications were much more common.

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Insulin replacement restores the vesicular secretory apparatus in the diabetic rat lacrimal gland

Reposição de insulina restaura o mecanismo secretório da glândula lacrimal de ratos diabéticos

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ABSTRACT

Purpose: In the lacrimal gland (LG) acinar cells, signaling regulates the release of secretory vesicles through specific Rab and SNARE exocytotic proteins. In diabetes mellitus (DM), the LGs are dysfunctional. The aim of this work was to determine if secretory apparatus changes were associated with any effects on the secretory vesicles (SV) in diabetic rats as well as the expression levels of constituent Rab and members of the SNARE family, and if insulin supplementation reversed those changes.

Methods: DM was induced in male Wistar rats with an intravenous dose of streptozotocin (60 mg/kg). One of the two diabetic groups was then treated every other day with insulin (1 IU). A third control group was injected with vehicle. After 10 weeks, Western blotting and RT-PCR were used to compared the Rab and SNARE secretory factor levels in the LGs. Transmission electron microscopy evaluated acinar cell SV density and integrity.

Results: In the diabetes mellitus group, there were fewer and enlarged SV. The Rab 27b, Rab 3d, and syntaxin-1 protein expression declined in the rats with diabetes mellitus. Insulin treatment restored the SV density and the Rab 27b and syntaxin expression to their control protein levels, whereas the Vamp 2 mRNA expression increased above the control levels.

Conclusions: Diabetes mellitus LG changes were associated with the declines in protein expression levels that were involved in supporting exocytosis and vesicular formation. They were partially reversed by insulin replacement therapy. These findings may help to improve therapeutic management of dry eye in diabetes mellitus.

Keywords: Diabetes mellitus/chemically induced; Lacrimal apparatus; Exocytosis; secretory vesicles; R-SNARE proteins; Animals; Rats

RESUMO

Objetivo: *Células acinares da glândula lacrimal (GL) sinalizam a regulação da liberação através de vesículas secretórias específicas Rab proteínas exocitóticas SNARE. No diabetes mellitus (DM), as glândulas lacrimais são disfuncionais. O objetivo deste trabalho foi determinar se em ratos diabéticos, alterações dos aparatos secretórios estão associados a efeitos sobre vesículas secretoras (VS) e sobre os níveis de expressão do constituinte Rab, bem como membros da família SNARE, e se a suplementação de insulina reverte as alterações.*

Métodos: *DM foi induzido em ratos Wistar machos com uma dose intravenosa de estreptozotocina (60 mg/kg). Um dos dois grupos diabéticos foi então tratado a cada dois dias com insulina (1 UI). Um terceiro grupo controle foi injetado com o veículo. Após 10 semanas, western blot e RT-PCR comparou níveis de fatores secretórios de Rab e SNARE na glândula lacrimal. Microscopia eletrônica de transmissão (MET) avaliaram a densidade e integridade de VS de célula acinar.*

Resultados: *No grupo diabetes mellitus , houve poucas e alargadas VS. Rab27b, Rab 3d e Sintaxina-1 diminuiu a expressão da proteína em ratos com Diabetes Mellitus. O tratamento com insulina restaurou a densidade das VS e expressão de Rab 27b e Sintaxina para seus níveis de proteína controle, enquanto a expressão de Vamp 2 RNAm aumentou em relação aos controles.*

Conclusões: *Alterações na glândula lacrimal de diabetes mellitus estão associadas a reduções nos níveis de expressão de proteínas envolvidas no apoio a exocitose e formação vesicular. Eles são, em parte, revertida por terapia de reposição de insulina. Estes resultados podem ajudar a melhorar a conduta terapêutica do olho seco no diabetes mellitus.*

Descritores: *Diabetes Mellitus/induzido quimicamente; Aparelho lacrimal; Exocitose; Vesículas secretórias; Proteínas R-SNARE; Animais; Ratos*

INTRODUCTION

Lacrimal gland (LG) secretion of proteins and fluid into the tear film is essential for maintaining the health of the ocular surface (OS). With regard to the corneal epithelium, its smooth optical properties, its transparency, and its protective effect against pathogenic infiltration are sustained by lacrimal gland functions[1,2]. Tears are a complex mixture of various constituents containing more than a thousand different proteins[3]. Lysosomal hydrolases, secretory IgA[4], lactoferrin, transferrin[5], and growth factors are secreted through vesicles or granules in a regulated or constitutive manner[6].

Diabetes mellitus (DM) impairs tear secretion and induces LG and OS changes[7]. Although the effects of DM-induced hyperglycemia, oxidative stress, nerve damage, and impaired insulin signaling have been described in the LG, changes in the secretory mechanism caused by this disease are not clearly understood[8,9]. A recent work revealed that high glucose levels reduced the expression of secretory

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granule-associated vesicle-soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) in the pancreatic beta-cells[10].

Metabolic and neurogenic inputs are needed to sustain LG function. Specifically, they control secretory and anti-oxidant mechanisms[11,12]. Such support is needed to enable the secretory products in the lacrimal acini to go through sorting into immature secretory vesicles in the trans-Golgi network and to acquire the external proteins characteristic of mature secretory vesicles (SVs) as they move towards the apical membrane prior to their exocytotic release[13].

Local and systemic pathways highly control the LG exocytosis of tear fluid components. The exocytosis is modulated by cholinergic and adrenergic stimuli, through changes in protein-kinase A (PKA) activity and intracellular calcium transients[14]. This process has several diverse roles, including the release of neurotransmitters, hormones, enzymes, and cytokines. It is regulated in the intracellular environment by a group of cytosolic proteins that include receptors specific for anchoring vesicles. SNAREs and some Rab GTPases participate in this process and comprise proteins responsible for mediating secretion from neural, endocrine, and other exocrine tissues[15]. They include vesicle-associated membrane protein 2 (Vamp2), Rab 3d, and syntaxin 1, which are responsible for the docking of molecules and the driving of the plasma membrane vesicle fusion that leads to the release of their soluble components into tears[16].

In the LG, the most abundant protein in the acinar secretory pathway is Rab3, which is localized to mature SVs. This protein drives vesicular docking and apical membrane fusion and it can also play a role in determining vesicular size[17] (Figure 1). In previous studies, aging rats had presented with dry eye disease, an insulin-signaling impairment, oxidative stress, and declines in the parasympathetic control of LG function; this revealed an interesting similarity with DM dry eye[18,19]. Some SNARE and Rab family members were also altered in aged LG; particularly, Rab 3 expression was reduced at both the mRNA and protein levels[20]. In addition, advanced glycation end products can accumulate in aged and diabetic rat LGs[7,18].

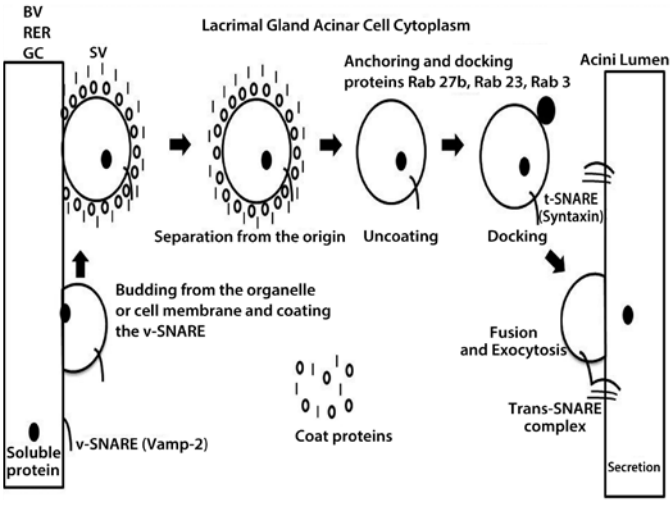

Figure 1. Schematic figure of the protein trafficking in the acinar cell cytoplasm of the lacrimal gland (ACLG) that showed the role of the following SNARE proteins (**SNA**P (**S**oluble **N**SF, *N*-ethylmaleimide sensitive fusion proteins, **A**ttachment Protein **Re**ceptor"), Vamp-2 and syntaxin, and the Rab proteins 3, 23, and 27 b, that were previously described in this tissue. The figure indicates the caption of protein from the blood vessel (BV), the rough endoplasmic reticulum (RER), or the Golgi complex (GC) by a vesicle SNARE (v-SNARE), Vamp-2; this was transported into the secretory vesicle (SV) to the GC (where they were modified) or ready in the acinar cell cytoplasm, but coated by proteins that protected them for secretion (storage and regulated secretion). Once ready or requested by extracellular triggers, the SV was uncoated, and SNARE-v was anchored to target the SNARE (t-SNARE), syntaxin, where the docking and exocytosis included the protein in the tear secretion (regulated and constitutive).

In the current study, we characterized the impact of DM on rat LG acetylcholine (ACh) content, the expression of Rab and SNARE family proteins, and the structure of secretory vesicles (SV) as well as the protective effects rendered by insulin supplementation on such changes.

METHODS

Animal model

Eight-week-old male Wistar rats were obtained from the Animal Breeding Center of the Faculty of Medicine of Ribeirão Preto (Ribeirão Preto, São Paulo, Brazil). The animals had free access to standard rodent chow and water. Food was withdrawn 12 h before the experiments and diabetes was induced with a single dose of streptozotocin (Sigma, St. Louis, MO, USA), 60 mg/kg body weight, diluted in 1 mL of 0.01 M citrate buffer that was administered through the caudal vein. Controls were injected with citrate buffer alone. Each of the three different groups used 10 rats.

Two days later, the diabetic status was verified with a glucose meter test (Accu-check, Roche Diagnostica Brazil Ltda., São Paulo, SP, Brazil) of blood obtained from the caudal veins of rats that had fasted for 12 h. A fasting hyperglycemia of over 200 mg/dL was thought to indicate the presence of diabetes; on the 4th day, insulin treatment was initiated in part of the diabetic group (subcutaneous injections of 1 IU every other day). This dose was not sufficient to maintain adequate glycemic control, but was enough to avoid body weight loss and growth retardation[21].

Comparative studies of the three groups, i.e., control (C), diabetic (DM), and diabetic with insulin treatment (IT), were performed 10 weeks later.

The animals were weighed, anesthetized with intraperitoneal injection comprising a combination of ketamine (5 mg/100 g b.w.) (União Química Farmacêutica S.A, Embu-Guaçu, SP, Brazil) and xylazine (2 mg/100 g b.w.) (Laboratorio Callier S.A., Barcelona, Spain). LGs were extirpated after ensuring that the corneal and caudal reflexes were abolished. Thereafter, the rats were euthanized with excess anaesthesia.

Tissue collection and storage

Each LG obtained from the right side of a rat was dissected into two parts and processed according to the protocol for each set of experiments. LGs were collected and homogenized in a buffer containing 50 mM Tris at a pH of 7.5, 500 mM NaCl, 0.1% Triton, and the protease inhibitor cocktail set III (Calbiochem, San Diego, CA) with a Polytron (Virsonic, Biopharma, Winchester, UK). RNA from the LGs was extracted with Trizol after homogenization, according to the manufacturer's protocol. The left LG was used for transmission electron microscopy (EM). This tissue was fixed in 2% glutaraldehyde and 2% paraformaldehyde (Sciences, Hatfield, PA, USA) in 0.1 M of phosphate buffer at a pH of 7.4, for 40 min at room temperature.

Acetylcholine (ACh) measurements in LG

ACh was measured in LG using an ACh assay kit (Amplex Red; Molecular Probes, Eugene, OR, USA) to compare the amounts of this neurotransmitter in LGs of the three groups (n=5/group)[22]. In brief, 0.1 mL of medium and tissue aliquots of homogenates containing 200 µg of protein were spotted in duplicate onto 96-well microplates. Standard ACh curves were constructed to evaluate the ACh content in each experiment. A 0.1 mL aliquot of assay buffer (50 mM Tris-HCl at a pH of 7.5) containing 0.2 M of reagent (Amplex Red; Molecular Probes), 2 U/mL of horseradish peroxidase, 0.2 U/mL of choline oxidase, and 10 U/mL of acetylcholinesterase was added to each well. After incubation, absorbance was determined with a spectrophotometer (Beckman Instruments, Inc., Fullerton, CA) at 530 nm. The ACh levels were expressed on a millimolar (mM) basis.

Transmission electron microscopy

LG tissues from the three groups that were fixed for TEM were rinsed in a 0.1 M phosphate buffer, dehydrated through a graded ethanol series, rinsed in acetone, and embedded in an Embed 812 (EM Sciences). Sections (60-70 nm) were cut with a diamond knife and stained for 25 min each in 2% uranyl acetate and 5 min in Reynolds'lead citrate. Sections were examined with a TEM (Jeol, Jem 100cx, Tokyo, Japan). Pictures were taken and converted to digital files (Hamamatsu, ORCA-HR Amtv542, Hamamatsu City, Japan). The intracellular organelles, including secretory vesicles and nuclei, were evaluated in each group.

RT-PCR for Rab3d, Rab 23, Rab 27b, and Vamp2

The reverse transcriptase polymerase chain reaction (RT-PCR) compared the Rab3d, Rab 23, Rab 27b, and Vamp 2 mRNA levels in the three rat LG groups. In addition, beta-actin mRNA was used for internal normalization. The resulting RNA was quantified by spectrophotometry at 260 nm and the RNA integrity was evaluated on 6.6% formaldehyde and 1% agarose (Gibco/BRL) gels. Reverse transcriptase, oligo dT priming, and the Advantage RT-for-PCR kits from Clontech Laboratories Inc. (Palo Alto, CA, USA) were used for the cDNA transcription.

PCR amplification of cDNA was performed with a GeneAmp polymerase chain reaction (PCR) System 9700 (Applied Biosystems, Foster City, CA, USA) using 1.5 units of Taq DNA polymerase (Gibco/BRL), 0.3 mM each of dATP, dCTP, dGTP, and dTTP (Invitrogen), PCR buffer (Tris -Hcl 60 mM, MgCl2 1.5 mM, NH_4 SO_4 pH10 15 mM) (Invitrogen), and 10 mM of 5' and 3' primers corresponding to rat Rab 3d, Rab 23, Rab 27b, Vamp2, and beta-actin cDNA (Life Technologies, Gaithersburg, MD, USA), after the preliminary assays identified the parameters to ensure that the products were in the linear range (Table 1). In all PCR procedures, the positive and negative control cDNAs were run in parallel. Our attempts to detect syntaxin 1 mRNA were unsuccessful as in a previous study[23].

The PCR program used the following cycle profile: denaturation for 1 min at 94°C, annealing for 1 min at the indicated temperatures, extension for 1.5 min at 72°C, and maximization of strand completion for 7 min at 72°C. Following amplification, the cDNA fragments were analyzed on 1% agarose gels containing a 100 bp DNA molecular weight ladder (Gibco/BRL) and were post-stained with ethidium bromide to confirm the anticipated base pair (bp) sizes for Rab 3d, Rab 27b, Rab 23, and Vamp 2, and beta-actin products.

Positive controls for Rab3d, Rab 23, Rab 27b, and Vamp 2 included cDNA isolated from rat pancreatic islets. Negative controls included samples without reverse transcriptase or samples of cDNA. The results were recorded on the Gel Doc system (Bio-Rad Laboratories, Richmond, CA, USA). The membranes were scanned and analyzed by Scion Image Analysis Software (Scion Corp, Frederick, MD, USA).

Western blotting

Western blots evaluated Rab 27b, Rab 3d, Vamp 2, and syntaxin 1 protein expression in cell lysates obtained from the rat LGs from the three different groups (n=5/group). LGs were solubilized in 1 mL of homogenization buffer containing the following: 100 mM-2-amino-2-hydroxymethyl-propane-1,3-diol (Tris) (pH 7.5), 10 mM-sodium pyrophosphate, 100 mM-sodium fluoride, 10 mM-EDTA, 10 mM-sodium vanadate, 2 mM-phenylmethylsulfonyl fluoride, and 1% Triton-X 100. LGs were disrupted using a Polytron PT 1200C homogenizer (Brinkmann Instruments, Westbury, NY, USA). The extracts were then centrifuged at 12,000 rpm at 4°C for 15 min to remove insoluble materials. Protein concentrations in the supernatant fractions were assayed with the Bradford dye method. For SDS gel electrophoresis and Western blotting, the samples were treated with a Laemmli sample buffer containing dithiothreitol. After heating at 95°C for 5 min, the proteins were separated by electrophoresis (70 µg protein/lane, 10%-12% gels). Following electrophoresis, the proteins were trans-

Table 1. RT-PCR primers and parameters for SNARE and Rab mRNA detection in LG. of control, DM, and insulin-treated DM rats

	Accession number	Primers sequence	Number of cycles	BP size	Annealing temperature
B-actin	NM 031144	Sense: 5' agagggaaatcgtgcgtgaca 3' Antisense: 5' cgatagtgatgacctgaccgtca 3'	33	202	59°C
Rab 3 d	NM 080580	Sense: 5' actgatggtgacaatgatgc 3' Antisense: 5' acggaagtgaagaaagcaac 3'	37	340	59°C
Rab 23	NM 016277	Sense: 5' tgagccaaattgtgctgttc 3' Antisense: 5' gggcaataatttttccacca	37	270	57°C
Rab 27b	NM 053459	Sense: 5' cggagctcgagaagactaga 3' Antisense: 5' ggccaggagtttaatcaggt 3'	37	225	60°C
Vamp 2	NM 012663	Sense: 5' gcatctctcctacccttttca 3' Antisense: 5' tttaggggtctgagggtaca 3'	34	141	58°C
Syntaxin	NM 053788	Sense: 5' gtacaacgccactcagtcag 3' Antisense 5' agcatgtcttccaactcctc 3'	37	260	60°C

ferred to nitrocellulose membranes. The nitrocellulose filters were treated with a blocking buffer (5% non-fat dried milk, 10 mM-Tris, 150 mM-NaCl, and 0.02% Tween 20) overnight and were subsequently incubated with rabbit polyclonal antibody anti-Rab 3d, Vamp 2, Rab 27b, syntaxin 1, and GAPDH as internal controls (Table 2). Visualization of specific protein bands was performed by incubating the membranes for 2 h with a peroxidase-conjugated secondary antibody (1:10.000; Zymed Laboratories, Inc., San Francisco, CA, USA), followed by detection with enhanced chemiluminescence reagents (Pierce Biotechnology, Rockford, IL, USA) and exposure to X-ray film (Kodak, Manaus, AM, Brazil). The band intensities were quantified by optical densitometry (Scion, Image, Frederick, MD, USA).

Statistical analysis

Data were reported as mean ± SEM. Comparisons were made using the Kruskal-Wallis test followed by Dunn's *post hoc* test (GraphPad 5.0 software; Prism, San Diego, CA). Densitometry values were reported as ratios of beta-actin in RT-PCR and GAPDH in the Western blot assays, respectively. The ratio of densitometric values of one control sample of each blot was defined as 1.0 (100%), and the subsequent values were expressed as a ratio relative to its control value and submitted to statistical analysis with the Kruskal-Wallis test followed by the Dunn's *post hoc* test.

RESULTS

Body and LG weight were significantly lower in the DM group than in its control group whereas insulin treatment prevented such declines. The ACh levels remained unchanged at 10 weeks after DM induction (Table 3).

In the apical areas of the acinar cells in the DM group, there were fewer and enlarged secretory vesicles (SV) predominantly encapsulating the white content and there were fewer dark vesicles than in the controls. On the other hand, the cell size and nuclear appearance were unchanged in the DM group. In the insulin-treated group, the predominant white vesicular coloration in the DM group was less evident, but there were fewer black SVs than in the apical areas of the acinar cells of the control LGs (Figure 2).

RT-PCR revealed that the Rab 3d, Rab 27b, and Rab 23 mRNA levels were not changed by DM or insulin treatment, but the Vamp 2 level was higher in the insulin-treated group (Figure 3).

Western blotting revealed that the expression of syntaxin 1, Rab 27b, and Rab 3d were significantly lower in the DM group, whereas the decline in Vamp 2 was insignificant. However, insulin treatment prevented the declines in Rab 27b, syntaxin 1, and Rab 3d expression as they remained at levels similar to those in the control group (Figure 4).

Table 2. Antibodies used for Western blot analysis of SNARE and Rab protein detection in LG of control, DM, and insulin-treated DM rats

Protein	Catalog #	Type	Molecular weight	Concentration
GAPDH	Santa Cruz SC 367715	Rabbit polyclonal	37 KDa	200 µg/mL
Rab 3 d	Santa Cruz SC 26392	Goat polyclonal	25 KDa	200 µg/mL
Rab 27b	Santa Cruz SC 22993	Goat polyclonal	30 KDa	200 µg/mL
Vamp 2	Calbiochem 627724	Rabbit polyclonal	12 KDa	1 mg/mL
Syntaxin	Santa Cruz SC 12736	Mouse monoclonal	35 KDa	200 µg/mL

Table 3. Changes in parameters of the control, DM, and insulin-treated DM rats. Data is expressed as mean ± standard error, *denotes $p<0.05$

	Control	DM	DM-ins
Body weight (g)	699.8 ± 25.02	205.20 ± 11.37*	504.0 ± 54.67
LG weight (mg)	128.2 ± 4.83	50.10 ± 1.87*	97.0 ± 8.61
Glycemia (mg/dL)	156.5 ± 12.65	542.30 ± 53.53*	295.3 ± 38.15
Acetylcholine (µM)	110.6 ± 18.60	86.70 ± 13.5	117.6 ± 16.50

DISCUSSION

The present study indicated that there was a correspondence between changes in the secretory mechanisms in LGs that were iso-

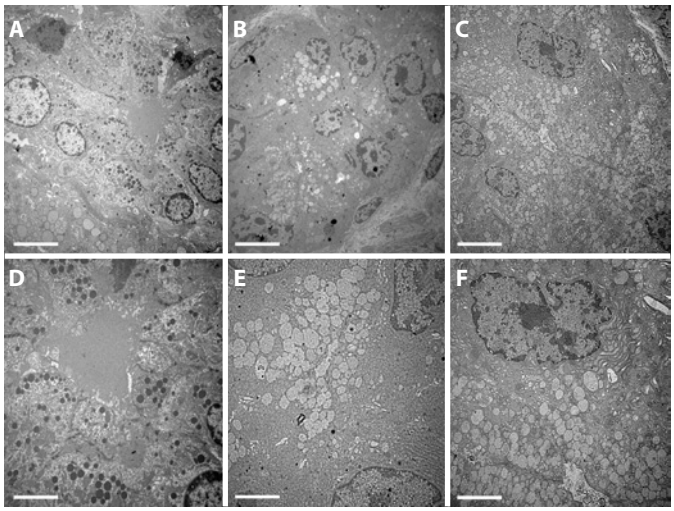

Figure 2. Transmission electron microscopy of the acinar cells in the exorbital LG of control (A, D), DM (B, E), and insulin-treated (C, F) DM groups. The images are representative of sections of LGs from 5 animals/group. Magnification ×2000 in the upper lane and ×4000 in the lower lane (scale bar=5 µm and 2.5 µm, respectively).

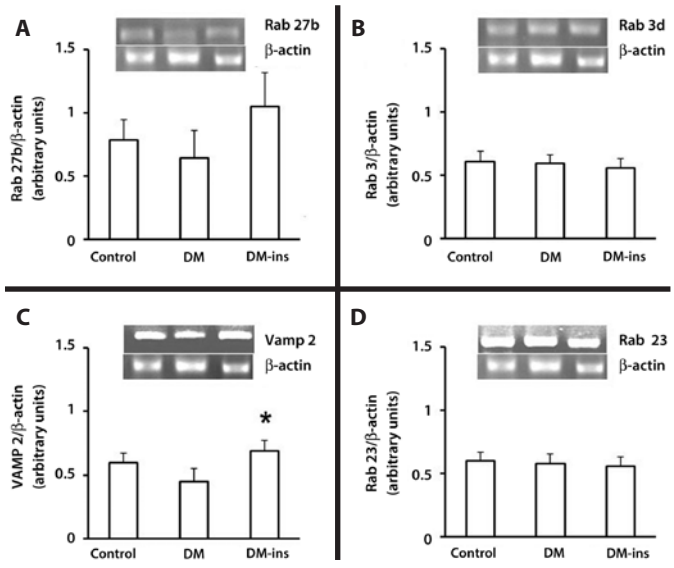

Figure 3. Insulin replacement increased the mRNA content of Vamp2. RT-PCR of (A) Rab27b, (B) Rab3d, (C) Vamp2, and (D) Rab 23 in LGs of the control, DM, and insulin-treated DM rats. Densitometric arbitrary units were normalized to β-actin expression and were expressed as mean ± standard error of the mean (*denotes p value <0.05). Results are representative of three independent experiments (n=5/group/experiment).

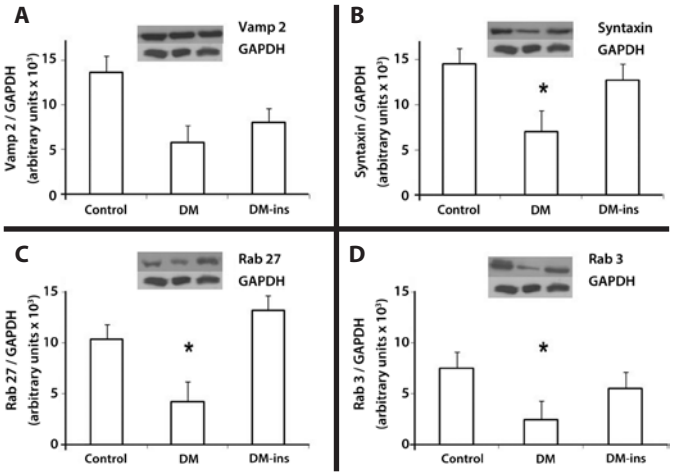

Figure 4. Impaired expression of SNARE and Rab proteins was rescued by insulin treatment in LG of diabetic rats. Western blotting of (A) Vamp2, (B) syntaxin 1, (C) Rab27b, and (D) Rab3d in LGs of control, DM, and insulin-treated DM rats. Densitometric arbitrary units were normalized to GAPDH expression. Data are expressed are means ± standard error of the mean; * $p<0.05$. Results are representative of three independent experiments (n = 5/group/experiment).

lated from DM rats and the dry eye syndrome manifestations. Such an insight will provide a better understanding of dry eye pathophysiology[7,12,21]. The major current finding was that lower intracellular transport protein expression levels in the DM group were associated with declines in delimited SV density and their ultra-structural appearance of the acinar apical cell membranes.

Different animal models of DM have found that LG secretory product content changes can accompany OS neuronal and structural damage[24]. Taken together, the present findings, in particular, the similar levels of ACh among the diabetic and control groups, suggested that the damage in the signaling machinery of diabetic LG preceded the neurogenic damage to the LG and OS[25]. These results are consistent with a previous study where LG synaptic junctional ultrastructure of the DM rats were preserved after 4 weeks of disease, although the insulin signaling cascade was already impaired just 1 week after DM onset[8,26].

Although animal models in general have some limitations in fully simulating a disease condition (e.g., dry eye syndrome), in streptozotocin-diabetic rats, these structural changes were described in the secretory granules of the acinar cells of LGs along with the functional impairment[24]. Moreover, in different models of diabetic rodents, mechanisms other than those described here triggered declines in tear secretion and corneal epithelial damage associated with inflammation, lower proliferative capacity, and oxidative damage[27].

The fact that in LGs of DM rats there is a discrepancy between the declines in Rab 3d and Rab 27 protein expression and the lack of changes in their mRNA expression suggested that DM promoted changes at a post-transcriptional level. They may be caused by a reduction in translational events or a decline in the protein half-life. Such decreases could be attributable to hyperglycemia or a secondary vascular disturbance[28].

In an aging rodent, which is another model of the dry eye syndrome, similar alterations in SV appearance and declines in their density were associated with lower Rab 3d levels[20]. Similar to the DM model used here, this model had high levels of oxidative stress and insulin resistance[19,21]. As in that study, we were unable to identify syntaxin 1 at the mRNA levels, but detected it with Western blotting. A possible explanation was that the antibody that we used cross-reacted with another LG acinar cell syntaxin isoform, which we did not probe for at the mRNA level.

A recent publication revealed that SV were highly expressed in human LGs with dry eye induced by prolonged visual display terminal exposure compared to controls and Sjögren's syndrome patients. Taken together, those findings indicated that distinct diseases differentially affected the LG secretory mechanisms, as did evaporative, inflammatory, and diabetic dry eye. In agreement with those findings in humans subject to video display terminals or Sjogren's syndrome, the present work revealed that Vamp-2 increased in a DM model of dry eye and the SV were dimorphic; their localization was changed in the acinar cells of LG. This observation may indicate that therapeutic measures to prevent such changes could compensate for the abnormal secretory changes induced by DM. Insulin induced multiple responses through a myriad of interacting intracellular signaling cascades[29]. It was demonstrated that either systemic insulin or topical treatment prevented LG damage and reduced ocular surface damage in DM animal models with dry eye[21]. In the present work, systemic insulin was sufficient to protect against body and LG weight loss due to increases in catabolism and more severe SV content and ultra-structural changes along with modified secretory protein profiles[30].

In conclusion, the present work demonstrated that the LG secretory impairment secondary to DM was involved in reducing the expression of some Rab and SNARE protein family members that were responsible for intracellular SV trafficking that could be prevented by insulin treatment. The consequent reduction in tear secretion and content in the untreated DM rats may help to explain early ocular surface epithelial damage in DM[21]. Moreover, the present findings may help to identify new therapeutic measures in DM for use in the dry eye syndrome, including insulin hormone therapy.

Ethical standards

All experimental procedures adhered to the Principles of Laboratory Animal Care (NIH publication no. 85 to 23) and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the committee on animal experimentation of the School of Medicine at Ribeirão Preto, University of São Paulo.

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Diode laser-assisted transcanalicular dacryocystorhinostomy: the effect of age on the results

Dacriocistorrinostomia transcanalicular auxiliada por laser de diodo: o efeito da idade sobre os resultados

Fahrettin Akay[1], Abdullah Ilhan[2], Ümit Yolcu[3], Fatih C. Gundogan[4], Yildiray Yildirim[1], Sami Toyran[1]

ABSTRACT

Purpose: The aim of this study was to explore the effect of age on the success of transcanalicular diode laser-assisted dacryocystorhinostomy (TCDCR).

Methods: Seventy patients (70 eyes) who underwent transcanalicular diode laser-assisted dacryocystorhinostomy for the treatment of nasolacrimal duct obstruction as a primary surgery were included in this retrospective, nonrandomized study. The patients were divided into two groups according to age. Mean ages were 21.3 ± 3.3 in group 1 and 60.3 ± 7.3 in group 2. The records of the 3-, 6-, and 12-month follow-up examinations were evaluated, and the anatomical and functional outcomes were noted. Functional success was defined as the absence of epiphora as indicated by the patient. Anatomical success was determined as patency of the neo-ostium with irrigation.

Results: At the 3-month follow-up, 67% cases in group 1 showed anatomical success and 52% showed functional success; in group 2, the rates were 100% and 92%, respectively. Functional and anatomical success rates were the same for both the 6- and 12-month visits; 46% in group 1 and 76% in group 2. The results in group 2 were significantly better at all three follow-up visits ($p<0.05$).

Conclusions: This study clearly showed that the older patients experienced better transcanalicular diode laser-assisted dacryocystorhinostomy results than the younger patients. The diminished inflammatory response in the older population may be a possible contributing factor to these results.

Keywords: Dacryocystorhinostomy; Diagnostic technique ophthalmological; Lacrimal duct obstruction; Nasolacrimal duct; Silicones; Lasers semiconductor

RESUMO

Objetivo: *O objetivo deste estudo foi explorar o efeito da idade sobre o sucesso de dacriocistorrinostomia transcanalicular auxiliada por laser de diodo (TCDCR).*

Método: *Setenta olhos de setenta pacientes submetidos dacriocistorrinostomia transcanalicular auxiliada por laser de diodo para o tratamento da obstrução nasolacrimal como cirurgia primária foram incluídos neste estudo retrospectivo, não randomizado. Os pacientes foram divididos em dois grupos segundo a idade. As idades médias foram 21,3 ± 3,3 no grupo 1 e 60,3 ± 7,3 no grupo 2. Os registros do acompanhamento pós-operatório aos três, seis e 12 meses, foram avaliados, observando resultados anatômicos e funcionais. Sucesso funcional foi definido como a ausência de lacrimejamento, conforme informado pelo paciente. Sucesso anatômico foi determinado como a permeabilidade do novo óstio à irrigação.*

Resultados: *Nos três meses de acompanhamento, 67% dos casos no grupo 1 apresentou sucesso anatômico, e 52% mostraram sucesso funcional. No grupo 2, as taxas foram de 100% e 92%, respectivamente. Taxas de sucesso funcionais e anatômicas foram as mesmas para ambos os seis e 12 meses de visitas: 46% no grupo 1 e 76% no grupo 2. Os resultados do grupo 2 foram significativamente melhores em todas as três visitas pós-operatorias ($p<0,05$).*

Conclusões: *Este estudo mostra claramente que os pacientes mais idosos apresentam melhores resultados à dacriocistorrinostomia transcanalicular auxiliada por laser de diodo comparados aos mais jovens. A resposta inflamatória diminuída na população mais velha é um possível fator que contribuiu para estes resultados.*

Descritores: *Dacriocistorinostomia; Técnicas de diagnóstico oftalmológico; Obstrução dos ductos lacrimais; Ducto nasolacrimal; Silicones; Lasers semicondutores*

INTRODUCTION

Primary acquired nasolacrimal canal obstruction (NLDO), which presents with persistent epiphora and with or without dacryocystitis, is commonly observed in ophthalmology practice. For approximately 100 years, the gold standard treatment for NLDO has been conventional external dacryocystorhinostomy (DCR)[1,2]. The goal of DCR surgery is to re-establish tear flow from the lacrimal system into the nasal cavity.

With the advances in laser and endoscopic techniques, endocanalicular and endonasal surgical procedures have become increasingly popular over the past decade. Cosmesis, short recovery time, the lower risk of morbidity, and the lack of impairment of the orbicularis oculi pump mechanism are some advantages of minimally invasive surgical approaches such as external DCR[3]. Transcanalicular (or endocanalicular) laser DCR (TCDCR) is a recently developed surgical approach for treating NLDO based on the canalization of the upper lacrimal system[4-6]. Typically, a laser probe is inserted through both canaliculi and advanced along the nasolacrimal duct to the lateral wall of the nasal fossa, where a transcanalicular nasolacrimal ostium can be created using laser energy. Different types of laser can be used in TCDCR but diode laser is one of the most useful[7] because it ablates the bone and the mucosa of the nasal fossa with less collateral damage[8]. Different success rates have been reported in various studies[8,9].

This study aimed to investigate the effect of age on the final success rates with TCDCR.

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METHODS

Seventy consecutive diode laser DCR operations of 70 patients within a 16-month period were included in this study. The patients were divided into two groups based on age. Group 1 (under 45 years) consisted of 33 patients with a mean age of 21.3 ± 3.3 years (range, 20-25); 25 members of this group were enlisted soldiers in the Turkish army. Group 2 consisted of 37 patients with a mean age of 60.3 ± 7.3 years (range, 45-70).

The records of patients who underwent TCDCR as a primary surgery for NLDO at the Izmir Military Hospital between January 2010 and January 2013 were retrospectively reviewed after approval of the study by our Institutional Ethics Committee. The patients, all of whom complained of epiphora, underwent standard ophthalmic examinations, including nasolacrimal drainage system probing and irrigation. Indications for DCR were determined based on a history of epiphora and NLDO diagnosed by the irrigation of the nasolacrimal canal. The patients were referred to an otorhinolaryngologist prior to undergoing surgery to explore any nasal anatomical variations and pathologies that may have complicated the surgeries. Patients with a history of septoplasty, ethmoidectomy, or other nasal surgeries; significant sinus pathologies; septal deviation; concha bullosa; or middle turbinate hypertrophy were excluded. Patients with a postoperative follow-up period of at least 12 months were included. Informed consent was obtained for each patient, and the tenets of the Declaration of Helsinki were followed.

All procedures were scheduled on an outpatient basis. Preoperative screening was conducted for bleeding issues and systemic hypertension. If present, the bleeding tendency and systemic arterial hypertension issues were controlled before the surgery. Diabetic patients were excluded. The surgical procedure was performed under local anesthesia by the same two ophthalmologists (FA and YY).

One hour before the surgical intervention, a mixture of 10% xylocaine (Xylocaine pump spray 10%; Astra Zeneca, Istanbul, Turkey) and adrenaline- (Adrenalin 0.5 mg; Osel, Istanbul, Turkey) soaked cotton plugs were inserted into the nasal cavity. The operations were conducted with a transcanalicular 940-nm diode laser (Quanta System, Solbiate Olona, Italy). The inferior and superior puncta were dilated, and a 600-µm laser fiber was passed through the canaliculi up to the sac. A 4-mm, 0-degree, angled, rigid nasal endoscope (Storz, Tübingen, Germany) was introduced into the nasal cavity, and the aiming beam was transmucosally identified (Figure 1 A). The lacrimal bone and nasal mucosa were evaporated using a laser with 8-12 W of power and a 450-ms pause between pulses. The osteotomy diameter sizes were approximately 8 mm vertically and 5 mm horizontally (Figure 1 B). The burned debris around the osteotomy was cleaned with forceps. The total laser energy in joules and operation time were noted. Silicon tubes were inserted into both canaliculi and tightened in the nose (Figure 1 C). The anatomical success was controlled by irrigating the lacrimal system in both canaliculi. Antibiotic-soaked cotton plugs were inserted into the nose and removed after 2 days at the first follow-up visit. The patients were postoperatively treated with mometasone furoate nasal spray (Nasonex; Schering-Plough, Istanbul, Turkey), q 1 h for 1 month, and with 0.1% dexamethasone eye drops (Maxidex; Alcon, Istanbul, Turkey) q 6 h, and 0.3% ofloxacin eye drops (Exocin; Abdi İbrahim, Istanbul, Turkey) q 6 h for 10 days.

The silicon tube was removed during the third month after visualizing the neo-ostium with a nasal endoscope. The patients were examined during the sixth and twelfth months to evaluate the success of the surgery. Anatomical success was defined as patency of the neo-ostium with irrigation. Functional success was defined as the absence of epiphora as indicated by the patient.

Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Group 1 included 28 male and five female patients and group 2 included 15 male and 22 female patients. The statistical difference in gender was significant ($p<0.001$). Differences between the groups for the duration and side of the operation, laser power, and total energy used were insignificant (Table 1).

The mean follow-up durations were 13.1 ± 1.3 months in group 1 and 15.9 ± 3.6 months in group 2.

The anatomical and functional success rates are shown in table 2. In all three examination periods, the older patients had significantly better anatomical and functional success rates ($p<0.05$).

Covariate analyses (ANCOVA) showed that operation duration, laser power, and total energy did not significantly affect the anatomical or functional success results during any of the examination periods ($p>0.05$). Similarly, logistic regression analysis showed that gender had an insignificant effect on the results ($p>0.05$).

DISCUSSION

In recent years, diode laser has emerged as the preferred laser for performing TCDCR. Eloy *et al.* first described TCDCR using a diode laser in 2000[10]. This method is cost effective and can be utilized by a single ophthalmologist. The diode laser produces a wavelength of 980 nm and 7-20 W of power[3], and it can ablate bone and soft tissues without causing excessive collateral damage by using a 400-600-µ optical fiber. Variable success rates have been reported for TCDCR with diode lasers ranging from 64% to 90%; these values were based

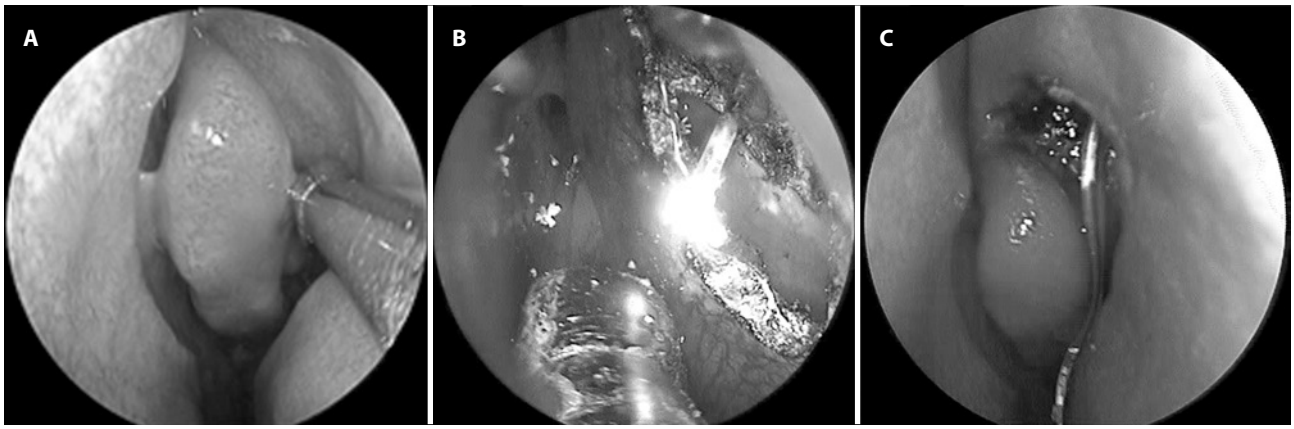

Figure 1. A) Red reflex of the laser probe at lacrimal fossa. B) Ostium created by the diode laser. C) A silicon tube passing through the ostium.

Table 1. Differences in operation duration, laser power, total energy, and side of the operation

	Operation duration (min)	Power (watt)	Energy (joule)	Side (right/left)
Group 1	25.8 ± 3.1	10.1 ± 1.5	1037 ± 109.4	17/16
Group 2	25.2 ± 3.5	10.1 ± 1.3	1074 ± 95.9	17/20
p	0.543*	0.839*	0.139*	0.811†

*= independent samples t test; †= Chi-square test.

Table 2. Anatomic and functional success ratios between the groups

		Anatomic success		Functional success	
Examination time	**Group**	**Ratio (%)**	***p****	**Ratio (%)**	***p****
Third month	Young patients	22/33 (67)	<0.001	17/33 (52)	<0.001
	Elderly patients	37/37 (100)		34/37 (92)	
Sixth month	Young patients	15/33 (46)	0.001	15/33 (46)	0.014
	Elderly patients	31/37 (84)		28/37 (76)	
Twelfth month	Young patients	15/33 (46)	0.014	15/33 (46)	0.014
	Elderly patients	28/37 (76)		28/37 (76)	

*= Chi-square test.

on an absence of epiphora 3 months after surgery[8,9]. However, the rates have improved over the years and have reached over 80%[8,10]. Toti's classic transcutaneous approach has shown higher success rates than minimally invasive procedures, as evidenced by a wider neo-ostium and less fibrosis. This may be explained by thermal damage from the laser energy causing more fibrosis at the neo-ostium and resulting in obstruction of the nasolacrimal pathway[11,12].

In this study, we investigated the effect of age on the success of TCDCR surgery. One of the most common reasons for TCDCR failure is stenosis and scarring of the ostium[7,13]. A patent ostium with minimal scar tissue is the most critical factor for achieving final surgical success. This study showed that clinical outcomes were worse in the younger patient group than in the patients ≥45 years of age, probably due to more severe ostium fibrosis.

A recent study demonstrated that a high expression of heat shock protein 47 (a regulator of fibrosis) in scar formation was associated with the failure of endoscopic DCR[14]. Camara and Santiago reported a high rate of surgical success with the use of mitomycin C[15]. Because the number of fibroblasts decreases or because the fibroblasts degenerate with age, milder fibrovascular proliferations can be expected in older patients, which results in less scar tissue[16]. In addition to a decline in cell number and function, diminished microcirculation contributes to poor tissue regeneration in older patients. Microcirculation provides the tissue with oxygen and supportive nutrients and regulates temperature and inflammatory responses; microcirculation can worsen with age[17]. There is further evidence to support the adverse effects of age on wound healing. Fleming *et al.* stated that an accumulation of methylglyoxal and increased formation of advanced glycation end products during physiological aging could result in a retardation of wound healing[18].

In the literature, the number of studies primarily aimed at exploring the effect of age on DCR procedures has been rather small. Erdol *et al.* reported better external DCR results in older patients, while Kashkouli *et al.* found that age had no significant effect on the success of external DCR[19,20]. Zenk *et al.* found that age did not have a significant effect on endonasal DCR[21], while two other studies reported that age had no effect on TCDCR[8,13]. In short, no studies have reported that age has a proven effect on endocanalicular or transcanalicular surgery. However, it is important to remember that the age differences of the groups in those studies were not as clear-cut as the age differences in this study.

In this study, we found a very significant difference in TCDCR results between the younger and older patients. At the end of the twelfth month, both functional and anatomical success rates were 46% and 76% in the younger and older patients, respectively. The success rates, regardless of age, were 88%, 84%, and 83% in three different studies[8,22,23]. Compared with those studies, the success rate of the younger group in this study was small.

In conclusion, this study clearly showed better TCDCR results in patients ≥45 years than younger patients. We believe that a possible contributing factor may be a diminished inflammatory response in the older population.

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Anatomical and visual outcomes of ranibizumab injections in retinal pigment epithelium tears

Resultados anatômicos e visuais de injeções de ranibizumab em roturas do epitélio pigmentado da retina

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ABSTRACT

Purpose: To report the anatomical and visual results in patients diagnosed as having retinal pigment epithelium (RPE) tears after receiving ranibizumab injections.

Methods: Eyes diagnosed as having RPE tears with a minimum 6-month follow-up were retrospectively evaluated. Each eye was treated with at least three doses of ranibizumab at monthly intervals. Best-corrected visual acuity (BCVA), anterior segment findings, intraocular pressure, and fundus examination results were evaluated during control visits. Color fundus photography, fundus fluorescein angiographies, fundus autofluorescence, and spectral domain optical coherence tomography (SD-OCT) images were obtained. The height of pigment epithelial detachment (PED) was measured by SD-OCT.

Results: Twelve eyes with RPE tears were studied. Nine eyes (75%) developed RPE tears during ranibizumab injections for choroidal neovascularization (eight eyes with vascularized PED and one eye with choroidal osteoma), and tears occurred in three eyes before any injections. The median number of ranibizumab injections after diagnosis of RPE tears was 3 (min 2, max 5). In the most recent follow-up visit, there was no statistically significant correlation between the grade of RPE and logMAR of BCVA (p>0.05, r=0.112). Eight of twelve eyes had PED, and seven of these had irregular PED contours before injection therapy. The mean PED height was 447 ± 122 µm.

Conclusions: In this series, RPE tears developed mostly after intravitreal anti-VEGF injections for vascularized PED. Increased vertical height and irregular contours of the PEDs can be risk factors for the formation of RPE tears. The continuation of anti-VEGF therapy after tear formation is beneficial for vision improvement in eyes with RPE tears.

Keywords: Macular degeneration; Retinal detachment; Retinal pigment epithelium; Intravitreal injections; Antibodies, monoclonal, humanized; Tomography, optical coherence; Vascular endothelial growth factor; Fluorescein angiography

RESUMO

Objetivo: *Apresentar os resultados anatômicos e visuais de injeções de ranibizumab em pacientes que foram diagnosticados com roturas do epitélio pigmentado da retina (RPE).*

Métodos: *Olhos com um mínimo de seis meses de acompanhamento após diagnóstico de roturas do RPE foram avaliados retrospectivamente. Cada olho foi tratado com, pelo menos, três doses de ranibizumab em intervalos mensais. Acuidade visual com a melhor correção (BCVA), achados do segmento anterior, pressão intraocular e exames de fundo de olho foram avaliados nas visitas de controle. Retinografia colorida, angiografias fluoresceínicas, autofluorescência de polo posterior e tomografia de coerência óptica imagens de domínio espectral (SD-OCT) foram obtidos. A altura do descolamento do epitélio pigmentado (PED) foi medida com SD-OCT.*

Resultados: *Doze olhos com roturas do epitélio pigmentado da retina foram incluídos no estudo. Nove olhos (75%) desenvolveram roturas do epitélio pigmentado da retina durante as injeções ranibizumab para neovascularização de coroide (oito olhos com descolamento do epitélio pigmentado vascularizado e um olho com osteoma de coroide), a rotura ocorreu em três olhos antes de quaisquer injeções. A mediana do número de injeções de ranibizumab após o diagnóstico da rotura do RPE foi de 3 (mínimo 2, máximo 5). Na visita de acompanhamento mais recente, não houve correlação estatisticamente significante entre o grau de RPE e logMAR de BCVA (p>0,05, r=0,112). Oito dos doze olhos tinham descolamento do epitélio pigmentado, desses, 7 olhos tinham PEDs com contornos irregulares antes da injeção. A altura média do PED foi 447 ± 122 µm.*

Conclusões: *Nesta série, as roturas de epitélio pigmentado da retina aconteceram principalmente após a injeção intravítrea anti-VEGF para descolamento do epitélio pigmentado vascularizado. O aumento da altura vertical e contornos irregulares dos PEDs podem ser considerados fatores de risco para a formação da rotura de epitélio pigmentado da retina.*

Descritores: *Degeneração macular; Descolamento retiniano; Epitélio pigmentado da retina; Injeções intravítreas; Anticorpos monoclonais humanizados; Tomografia de coerência óptica; Fator A de crescimento do endotélio vascular; Angiofluoresceinografia*

INTRODUCTION

Retinal pigment epithelium (RPE) tear is a rare devastating complication of age-related macular degeneration (AMD). An RPE tear develops when the pigment epithelium detaches from the neurosensorial layer with its basement membrane and retracts[1]. RPE tears may develop spontaneously in eyes with AMD or after photocoagulation and photodynamic therapy. There are also cases reported to occur after nd:YAG laser capsulotomy and cataract surgery[2-4]. After anti-vascular endothelial growth factor (VEGF) therapies became widely used for choroidal neovascularization, the incidence of RPE tears has increased recently[5-7]. Some authors have stated that the contraction of choroidal neovascularization lying beneath the RPE after anti-VEGF injection causes this complication[8].

RPE tears are diagnosed by clinical examination, fluorescein angiography, optical coherence tomography (OCT), and fundus autofluorescence imaging of the macula. RPE tears have a characteristic appea-

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rance on fluorescein angiography. During fluorescein angiography, the bare area is hyperfluorescent in the early phase and leakage does not occur, unlike choroidal neovascularization. The scrolled region of the RPE is particularly dark and blocks the underlying fluorescence. On occasion, the scrolled area of the RPE has been termed "doubly hypofluorescent." OCT scans through the retracted RPE show a very intense hyperreflectivity. A deep hyperreflectivity under the line corresponding to the RPE is evident in the area of the bare choroid. Fundus autofluorescence shows patchy or hazy hyperfluorescence[1-8].

The incidence of RPE tear formation following anti-VEGF treatment has been reported to range between 1.8% and 27% in recent studies[9]. Different treatment protocols and follow-up periods may explain the wide incidence range and difficulties in diagnosing RPE tears. In previous case studies, the spontaneous healing of RPE tears has been demonstrated by using time-domain OCT[10,11]. In a study conducted by Caramoy et al., the use of anti-VEGFs was proposed to slow down the scarring process, prevent photoreceptor damage, and give RPE a chance to heal[12].

In this study, we evaluated the anatomical and visual results in patients diagnosed as having RPE tears after receiving ranibizumab injections as anti-VEGF treatment.

METHODS

The charts of 12 eyes of 12 choroidal neovascularization patients with at least 6 months follow-up after being diagnosed with RPE tears were retrospectively evaluated. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients signed an informed consent form before undergoing any treatment.

Full ophthalmic examination, including best-corrected visual acuity (BCVA), anterior segment, and fundus and intraocular pressure were evaluated at the initial visit. Spectral domain (SD)-OCT was taken by using a Cirrus HD-OCT (Carl Zeiss Meditec Inc., Germany). The height of pigment epithelial detachment (PED) was evaluated by using SD-OCT, as previously described by Chan et al.[5]. Fundus photos, fundus autofluorescent images, and fundus fluorescein angiographies of the eyes were obtained by using a Visucam NM/FA fundus camera (Carl Zeiss, Dublin, California) in 45° mode.

In our clinic, patients diagnosed with choroidal neovascularization receive ranibizumab (Lucentis, Genentech Inc., San Francisco, CA, USA) injections (0.5 mg/0.5 ml) at monthly intervals for the first 3-month period. After the third injection, eyes with more than a 50-µm increase in central foveal thickness and/or one or more lines of visual acuity loss on a Snellen chart receive repeated injections. This treatment protocol was not changed for patients who developed RPE tears during ranibizumab therapy.

RPE tears were graded as described by Sarraf et al.[13]. The grading was performed on the basis of the greatest length of a defect in the vector direction of the tear and foveal involvement by using fluorescein angiographic analysis: Grade 1 tears (diameter <200 µm), Grade 2 tears (diameter between 200 µm and 1 disc diameter), Grade 3 tears (diameter >1-disc diameter), and Grade 4 tears (Grade 3 tears that involved the foveal center).

Statistical analysis

Statistical analysis was performed by using a computer program (SPSS 18.0; SPSS Inc., Chicago, IL, USA). Results are reported as the mean ± standard deviation (SD), median, minimum (min), maximum (max), frequency, or percentage. BCVA results were converted to logMAR for statistical evaluation. The Wilcoxon signed rank t-test was used for comparisons. The correlations between the grade of the RPE tear and BCVAs in the first and last follow-ups were assessed by using Spearman's rank correlation coefficient. A p value of <0.05 and an r value of >0.5 were considered to indicate statistical significance.

RESULTS

Twelve eyes of 12 patients were diagnosed as having RPE tears. The demographic properties of the patients are shown in table 1. Seven (58%) of the 12 patients were females. The mean age of the patients was 68.5 ± 14.5 years. Nine eyes (75%) developed RPE tears during ranibizumab injections. The median number of ranibizumab injections before RPE tears for nine eyes was 2 (min 1, max 3). Eight of the nine eyes with RPE tears had choroidal neovascularization with vascularized PED secondary to AMD, and the other one had choroidal neovascularization secondary to choroidal osteoma. The other three eyes with RPE tears were referred to our clinic from another hospital. Therefore, it was unknown whether PED existed before RPE tear formation. The patient histories of these patients showed that there were developments of choroidal neovascularization after cataract surgery (in one eye 15 days later and in two eyes 1 year later).

The mean follow-up time after the diagnosis of RPE tears was 12.1 ± 4.9 months. The median ranibizumab injection after the diagnosis of RPE tears was 3 (min 2, max 5). In all of the patients, ranibizumab was used as an anti-VEGF treatment agent. In the last follow-up visit, the BCVAs of the patients (logMAR 0.60 ± 0.52) were better than

Table 1. Characteristics, best-corrected visual acuity, grade of RPE tears, and numbers of ranibizumab injections of the patients

Patient no	Age	Sex	First BCVA (logMAR)	Last BCVA (logMAR)	Grade of RPE tear	Number of ranibizumab injections before RPE tear	Number of ranibizumab injections after RPE tear	Mean PED height (micron)
1	72	M	1.0	0.1	1	0	4	No PED
2	76	F	0.2	0.1	1	2	3	344
3	57	M	0.3	0.1	2	2	3	387
4	71	F	0.7	0.5	3	1	3	402
5	75	F	0.7	0.7	2	2	2	498
6	70	F	1.8	1.3	3	1	4	689
7	75	M	0.7	0.4	4	0	4	No PED
8	75	F	0.7	1.3	4	0	5	No PED
9	74	M	0.4	0.4	3	2	3	230
10	29	F	1.0	0.7	2	2	2	No PED
11	68	F	1.0	0.7	3	2	5	455
12	81	M	2.0	0.9	2	3	3	578

M= male; F= female; BCVA= best-corrected visual acuity; RPE= retinal pigment epithelium; PED= pigment epithelial detachment.

those at the first follow-up visit (logMAR 0.85 ± 0.45); however, the difference was not statistically significant (p=0.12). The median grade of the RPE tears was 2.5 (range, 1-4). In the last follow-up visit, there was a positive correlation between the RPE grade and logMAR BCVA, but the correlation was not statistically significant (p>0.05, r=0.112).

In five of the nine eyes that developed RPE tears during ranibizumab therapy, subretinal hemorrhages were evident. Five of these eyes developed RPE tears after the second injection, and two eyes hemorrhaged after the first dose. After tear development, hemorrhage was observed in only two eyes.

During the follow-up period, the RPEs (one Grade 1 and one Grade 2) in two eyes reattached. In these eyes, reattachments of RPE tears were observed by using SD-OCT and fundus autofluorescence imaging. Initially, the RPE tear areas were hypoautofluorescent and the tear borders were hyperautofluorescent. However, in the last visit, it was observed in two eyes that the hypoautofluorescence initially observed in the tear area had changed to hyperautofluorescence, and in one of the eyes, hyperautofluorescent spots were still evident in the hypoautofluorescent area. Eight of the twelve eyes with RPE tears had PED. The mean PED height of the eight eyes was 447 ± 122 µm initially. The PEDs of seven of these eyes had irregular contours.

Representative case examples

Case 3: A 57-year-old man was admitted to our clinic with vision loss in the left eye. The BCVA in the left eye was 1.0 logMAR. On the basis of the OCT and fundus fluorescein angiography findings, he was diagnosed with AMD, and an intravitreal ranibizumab treatment protocol was started. When his BCVA improved to 0.3 logMAR after the second dose, a Grade 2 RPE tear was observed in the inferior macula. Two doses of ranibizumab were administered after tear formation. Six months later, his BCVA improved to 0.1 logMAR. In fundus autoflorescence imaging, there was hyperautofluorescent spotting in the denuded RPE area, and subretinal and intraretinal hyper-reflective spots were seen in the OCT (Figure 1).

Case 9: A 74-year-old male was with vision loss in both eyes was examined. His BCVA indicated the ability to count fingers at 1 m in the right eye and to count fingers at 2 m in the left eye. Fundus examination in the right eye revealed two disc-sized subretinal hemorrhages on the macula. He was diagnosed with AMD. After the second dose of ranibizumab, the subretinal hemorrhage was resorbed, BCVA increased to 0.4 logMAR (Figure 2 A), but OCT revealed an RPE tear (Figure 2 B). Three additional ranibizumab injections were administered after tear formation, and his BCVA remained stable at 0.4 logMAR (Figures 2 C and 2 D).

DISCUSSION

We observed that nine of the 12 eyes developed RPE tears during the treatment of choroidal neovascularization with ranibizumab injections. We continued to inject intravitreal ranibizumab after the development of RPE tears. After all injections, two of the 12 eyes appeared to be stable, nine of the 12 eyes showed improvement, and only one eye showed worsening of visual acuity at the end of the follow-up periods. At the last follow-up visits, however, the visual acuity had decreased in the patients with a high degree of tears, but the decrease was not statistically significant. According to our experience, continuation of anti-VEGF injections for patients who developed RPE tears during injection therapy appears to be necessary. In our study population, the heights of the PEDs were >400 microns, and PEDs in seven of the eight eyes had irregular contours.

The pathogenesis of RPE tears is not fully understood. Contraction of the choroidal neovascularization under the weak RPE, increased fluid transport secondary to exudative AMD under the RPE, globe deformation, vitreous syneresis, vitreo-macular traction due to vitreous incarceration in the injection hole, and detachment of the tight junctions between RPE cells are some of the mechanisms that have been considered[14,15].

RPE tears usually develop from the temporal edge of the PED. The separated part of the RPE folds parallel to the PED and reveals the

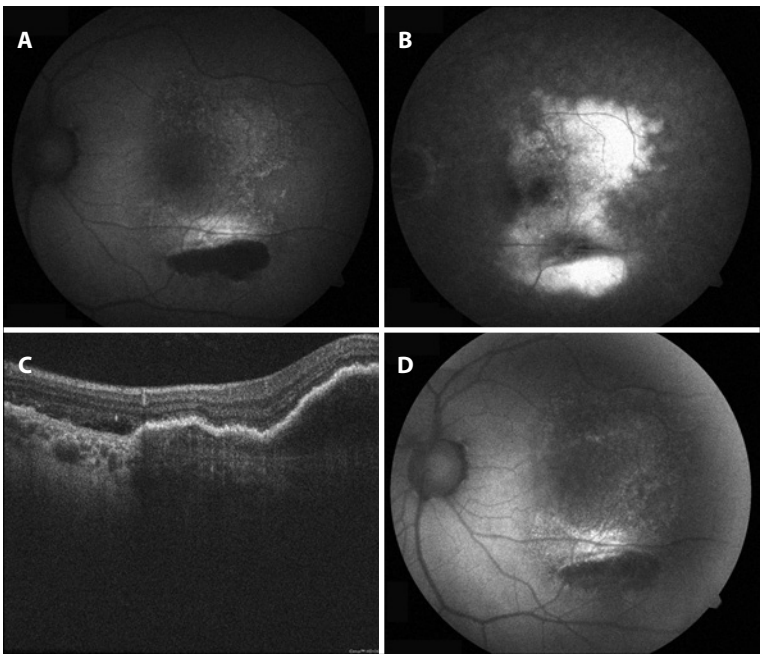

Figure 1. A) Fundus autofluorescent imaging of the left eye in case 3. The retinal pigment epithelium (RPE) tear in the inferior macula is hypoautofluorescent, and the denuded RPE area shows spotted hyperautofluorescence. B) In fluorescein angiography, the RPE tear in the inferior macula is hyperfluorescent, and the denuded RPE area is hypofluorescent. C) The spectral domain optical coherence tomography (SD-OCT) section passes through the RPE tear and pigment epithelial detachment (PED). D) Fundus autoflorescence imaging 3 months after the RPE tear formation.

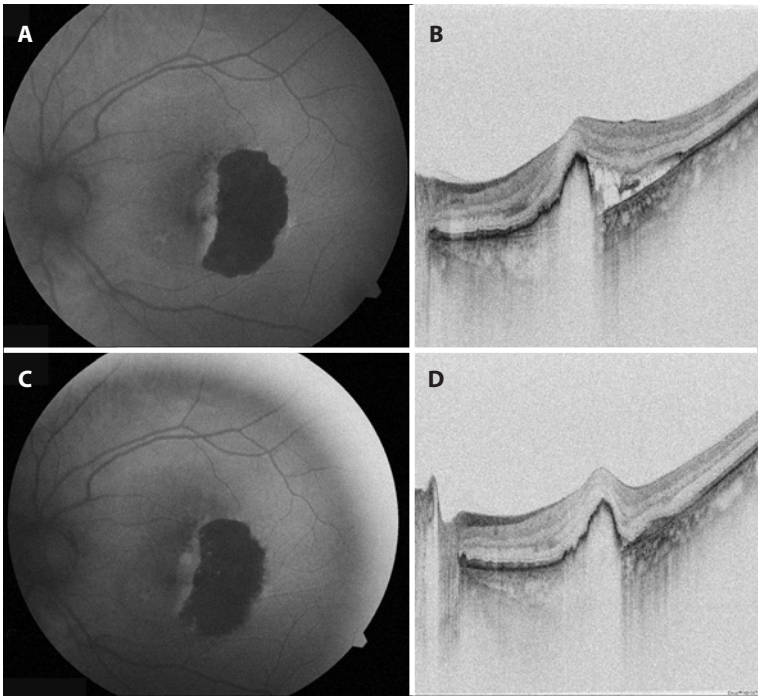

Figure 2. A) The initial fundus autofluorescent imaging of the RPE tear with two disc-sized hypoautofluorescent areas. B) The initial spectral domain optical coherence tomography (SD-OCT) with retinal pigment epithelium (RPE) tear. C) After three ranibizumab injections, hyperautofluorescent spots were observed in the hypoautofluorescent area, and D) the height of the pigment epithelial detachment (PED) was decreased.

bare Bruch's membrane for a few days[2,8,12]. After RPE tear formation, the PED usually becomes flat spontaneously. Reattachment of the free RPE edges to the Bruch membrane at a different location has recently been reported[2]. There is a possibility of improvement in patients with lower grade RPE tears[12].

Overexpression of new tissue from the tear border provides solidity to the RPE layer. The intraretinal hyper-reflective spots in SD-OCT and the corresponding hyperfluorescent spots in fundus autoflorescence may be secondary to RPE migration[12]. The existence of the hyperautofluorescent spots may be similar to the ones in central serous retinopathy[16]. The reason for this is the corrupted pump mechanism in the RPE denuded region and phagocytosis in the outer segment. The hyperreflective spots in fundus autoflorescence imaging may represent the subretinal or intraretinal outer photoreceptor segments that are phagocytized by the macrophages because the photoreceptor cells can live up to 325 days in the RPE denuded area[17]. Moreover, it has been demonstrated that the precipitates in the subretinal outer segment layer acted as hyperreflective spots in OCT ophthalmoscopy of central serous retinopathy[18,19].

Previous studies have reported repopulation and reattachment of RPE cells after tear formation, but these studies did not demonstrate healing of the hypoautofluorescence in the tear region[2,8]. Pece et al. used OCT to show that reattachment of the margins of an RPE tear were healed by tissue remodeling and described how the disease can recur[20]. In our study, reattachment of the RPE tear was demonstrated by using SD-OCT and fundus autofluorescence imaging only in 2 eyes. In addition, the hypoautofluorescent area in the tear region healed partially in one eye after 6 months. In another eye, hyperautofluorescent spots had appeared in the hypoautofluorescent area. Similarly, Caramoy et al. reported a case in which healing in the hypoautofluorescent area was observed after 2.5 years. In that study using SD-OCT, 7 (19.4%) of 36 eyes showed patchy or hazy hyperfluorescent areas in fundus autofluorescence imaging, and the majority of the eyes (83.3%) showed hyperreflective dots that possibly represented hard exudates and intraretinal RPE migration. The authors stated that fundus autofluorescence imaging showed a considerable amount of RPE proliferation, repopulation, and migration[12].

In a recent study that included 1298 AMD patients, the pooled rate of RPE tears was 1.8% in the 0.5-mg ranibizumab group, 3.0% in the 0.3-mg ranibizumab group, and 1.6% in the control group. Better visual acuity results were achieved with ranibizumab treatment versus control treatment in patients with RPE tears. Moreover, the potential benefit of continued ranibizumab therapy was suggested for patients with RPE tears secondary to neovascular AMD[21]. Garg et al. reported that 15 eyes from 15 patients developed an RPE tear, which gave an incidence of 1.6% in 920 eyes with exudative AMD treated with intravitreal bevacizumab. Six of the 15 eyes were continued to be injected with bevacizumab/ranibizumab after tear development, and four of these six eyes showed visual improvement[22]. The risk for RPE tear after bevacizumab injection in eyes with PED seems to be moderate. Weinberger et al. investigated RPE tears after intravitreal bevacizumab in 31 eyes with PED and observed RPE tears in four eyes without vision loss. The authors concluded that continuation of anti-VEGF injections for patients who develop RPE tears during injection therapy seems to be necessary[23].

In a few studies, certain factors, such as large PED diameter, vertical height, and subretinal fluid, have been associated with an increase in RPE tear rate[5,24]. The contour of the PED is an important factor for predicting RPE tear formation risk. Moroz et al. retrospectively evaluated 24 consecutive patients with choroidal neovascular membrane associated with PED, and reported the development of RPE tears after the first injection in six patients. They described two typical patterns in the eyes, which developed tears. One pattern was multifocal wrinkles and waves with RPE elevations, and the second was step-like interruptions of the continuity of the RPE line[25]. Knowing these risk factors is important for identifying eyes that are likely to develop this complication. The anatomical SD-OCT characteristics of a PED leading to RPE tear after anti-VEGF therapy has recently been descri-

bed by Nagiel et al. and has been prospectively described by Sarraf et al.[26,27]. Eyes with vascularized PEDs secondary to AMD have a risk for RPE tear following intravitreal anti-VEGF injection. Those authors explained that the contraction of neovascular tissue adhering to the undersurface of the RPE and rapid involution may cause a substantial contractile force that tears this already-strained tissue layer[26]. A baseline PED height >550 µm, presence of a Grade 1 tear, and positive ring sign are high-risk factors for the subsequent development of an RPE tear[27]. In our study, the mean PED height of eyes with RPE tears was 447 µm. In addition, before the development of tear formation, irregularity in the PED area was detected in seven of eight eyes with PED.

One of the patients in our study had choroidal neovascularization secondary to choroidal osteoma. Choroidal osteomas may decalcify and cause degeneration in the underlying retina, including the RPE. In this patient, the RPE tear occurred between the decalcified and calcified regions, which can be explained by the fragility of the area caused by degeneration of the RPE[28]. The RPE tear mechanism may be different for choroidal neovascularization secondary to choroidal osteoma. Sen et al. demonstrated that multiple anti-VEGF injections caused Bruch membrane rupture in angioid streaks in which the Bruch membrane was calcified and brittle, as in choroidal osteoma[29]. To our knowledge, our case is the first choroidal osteoma case to show the development of an RPE tear after ranibizumab therapy.

The limitations of this study included the limited sample size, lack of a comparison with a control group, lack of standard etiological and anatomical classifications, short follow-up period, and retrospective design. On the other hand, this was a single-center study and the same technicians performed the fundus autoflorescence imaging and SD-OCT, which may have helped to standardize the input. For distinguishing risk factors and mechanisms for RPE tear formation either spontaneously or after VEGF therapy, randomized studies in larger patient series are needed.

CONCLUSION

In our series, RPE tears developed mostly after intravitreal anti-VEGF injections administered to treat vascularized PED. The study results demonstrate that SD-OCT, along with fundus autoflorescence imaging, provided valuable information about the healing process of RPE tears. The continuation of anti-VEGF therapy after tear formation is beneficial for vision improvement in eyes with RPE tears. The PED height and irregularity in the edges of PED areas can be an early indicator of RPE tear formation.

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Safety of warfarin therapy during cataract surgery under topical anesthesia

Segurança da terapia com varfarina durante cirurgia de catarata com anestesia tópica

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ABSTRACT

Purpose: To analyze the safety of warfarin therapy during cataract surgery under topical anesthesia.

Methods: This was a prospective nonrandomized comparative study of 60 eyes of 60 patients treated with or without concurrent oral warfarin anticoagulant therapy, referred for cataract surgery under topical anesthesia. The sample included a treatment (*n*=30) and a control (*n*=30) group.

Results: There were no records of intraoperative or postoperative intracameral bleeding complications in both the groups. At 1-month postoperative follow-up, 90.0% of patients presented spectacle-corrected visual acuity of at least 20/40.

Conclusion: Cataract surgery by phacoemulsification with topical anesthesia can be successfully conducted without discontinuing warfarin.

Keywords: Cataract extraction; Anticoagulants; Warfarin/adverse effects; Hemorrhage

RESUMO

Objetivo: *Avaliar a segurança da cirurgia de catarata com anestesia tópica em pacientes em uso de varfarina.*

Métodos: *Estudo comparativo não aleatorizado, prospectivo de 30 olhos de 30 indivíduos sob terapia anticoagulante por via oral com Varfarina que se submeteram à cirurgia de catarata com anestesia tópica. O grupo controle foi composto por 30 olhos de 30 pacientes, com indicação de cirurgia de catarata, que não faziam uso de terapia anticoagulante.*

Resultados: *Não houve registro de complicações hemorrágicas intracamerais transoperatórias ou pós-operatórias em ambos os grupos. Na visita pós-operatória de 30 dias, 90,0% dos pacientes apresentavam acuidade visual corrigida por óculos de pelo menos 20/40.*

Conclusão: *A cirurgia de catarata por facoemulsificação com anestesia tópica pode ser realizada com sucesso sem interrupção da terapia com varfarina.*

Descritores: *Extração de catarata; Anticoagulantes; Varfarina/efeitos adversos; Hemorragia*

INTRODUCTION

Most patients undergoing cataract surgery are elderly and are on regular systemic medications[1]. Important classes of drugs include antiplatelet and anticoagulant medications, which may increase the risk of hemorrhagic anesthetic, or operative complications. These medications are taken to reduce the incidence of potentially life-threatening thromboembolic events in patients with cardiovascular conditions[1].

The Royal College of Ophthalmologists Cataract Surgery Guidelines recommends that patients taking warfarin should continue it before cataract surgery but that the international normalized ratio (INR) should be maintained within the therapeutic level[2]. Some studies have demonstrated that uncomplicated cataract surgery can be safely performed during oral anticoagulant therapy[3-5].

This prospective study aimed to analyze the safety of warfarin therapy during cataract surgery under topical anesthesia.

METHODS

A prospective comparative study was conducted with 60 consecutive eyes of 60 patients treated at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo for cataract surgery. The sample included 30 consecutive patients on oral anticoagulant therapy with warfarin and 30 controls who were not on anticoagulant therapy. The exclusion criterion was any ocular disease other than cataract.

The variables analyzed were international normalized ratio (INR) of the warfarin group, dosage of warfarin, postoperative visual acuity, and intraoperative and postoperative complications.

All patients underwent complete ophthalmic examination prior to cataract extraction by phacoemulsification with clear corneal incision and intraocular lens implantation, under topical anesthesia. No patient required intraoperative mechanical pupil dilation or corneal suture.

In the warfarin group, INR was determined 1 week prior to and on the day of surgery; INR between 1.9 and 2.7 was a prerequisite for undergoing cataract extraction according to our surgical protocol.

Data were analyzed by descriptive statistical methods, and categorical variables are expressed as absolute frequencies.

RESULTS

Among the 30 patients undergoing anticoagulant therapy with warfarin, 23 were taking a 5.0-mg dose per day and seven were taking 2.5 mg per day. The mean INR value was 2.04.

No intracameral perioperative bleeding or postoperative hemorrhagic complications were observed in the treatment or control group. With regard to the postoperative visual outcome, 90% of the patients had a visual acuity of 20/40 or better at 1-month follow-up.

DISCUSSION

Prophylactic anticoagulation has been of paramount importance in preventing coronary ischemic events, stroke, and peripheral arte-

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rial obstruction. However, it is well known that patients on anticoagulation therapy are exposed to a greater risk of hemorrhage when undergoing surgical treatment[6].

This increased risk makes these patients represent a challenge to cataract surgeons. Continuing antiplatelet and anticoagulation therapies may place these patients at risk of bleeding complications, whereas discontinuing these medications puts them at risk of thromboembolic complications[7-9].

Annually, 10% of patients receiving oral anticoagulants require treatment interruption for surgery or an invasive procedure[4]. A multicenter audit has shown that 5.1% of 48,862 patients subjected to cataract surgery were on concurrent warfarin therapy[1]. Considering the long and variable half-life of vitamin K antagonists, some guidelines recommend that patients should discontinue warfarin at least 5 days before major procedures[10-12].

The incidences of subconjunctival hemorrhage and microscopic hyphema were significantly higher in patients undergoing phacoemulsification without warfarin interruption compared with the discontinuation subgroup, although most of such bleeds were self-limiting and did not significantly decrease visual acuity[13-15]. Most members of the Canadian Society of Cataract and Refractive Surgery do not recommend suspending warfarin prior to cataract surgery[16]. However, it has been presented that most glaucoma surgeons discontinue the use of anticoagulants (warfarin or aspirin) before antiglaucoma surgery[17].

The results of the present study are in agreement with reports in the literature that state that there is no significant increase in bleeding that could potentially afflict vision in patients undergoing cataract surgery while using antiplatelet or anticoagulant therapy[1,18,19], particularly when the surgery is conducted under topical anesthesia[20,21]. Thus, in this series, phacoemulsification cataract surgery under topical anesthesia was safely performed without discontinuing warfarin anticoagulation in uncomplicated eyes. However, larger studies are required to elucidate this issue.

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Factors affecting visual loss and visual recovery in patients with pseudotumor cerebri syndrome

Fatores que influenciam na perda e na recuperação visual de pacientes com a síndrome do pseudotumor cerebral

Clara L. Afonso[1], Aley Talans[1], Mário Luiz Ribeiro Monteiro[1]

ABSTRACT

Purpose: To investigate the frequency of visual loss (VL), possible predictive factors of VL, and improvement in patients with pseudotumor cerebri (PTC) syndrome.

Methods: We reviewed 50 PTC patients (43 females, seven males) who underwent neuro-ophthalmic examination at the time of diagnosis and after treatment. Demographic data, body mass index (BMI), time from symptom onset to diagnosis (TD), maximum intracranial pressure (MIP), occurrence of cerebral venous thrombosis (CVT), and treatment modalities were reviewed. VL was graded as mild, moderate, or severe on the basis of visual acuity and fields. Predictive factors for VL and improvement were assessed by regression analysis.

Results: The mean ± SD age, BMI, and MIP were 35.2 ± 12.7 years, 32.0 ± 7.5 kg/cm^2, and 41.9 ± 14.5 cmH_2O, respectively. Visual symptoms and CVT were present in 46 and eight patients, respectively. TD (in months) was <1 in 21, 1-6 in 15, and >6 in 14 patients. Patients received medical treatment with (n=20) or without (n=30) surgery. At presentation, VL was mild in 16, moderate in 12, and severe in 22 patients. Twenty-eight patients improved and five worsened. MIP, TD, and hypertension showed a significant correlation with severe VL. The best predictive factor for severe VL was TD >6 months (p=0.04; odds ratio, 5.18). TD between 1 and 6 months was the only factor significantly associated with visual improvement (p=0.042).

Conclusions: VL is common in PTC, and when severe, it is associated with a delay in diagnosis. It is frequently permanent; however, improvement may occur, particularly when diagnosed within 6 months of symptom onset.

Keywords: Pseudotumor cerebri; Visual loss; Intracranial hypertension; Papilledema

RESUMO

Objetivo: *Investigar a frequência de perda visual (PV) e os possíveis fatores preditivos para perda e para melhora visual em pacientes com a síndrome do pseudotumor cerebral (SPC).*

Métodos: *Foram revisados 50 pacientes com SPC submetidos a exame neuroftalmológico no momento do diagnóstico e após o tratamento. Dados demográficos, índice de massa corpórea (IMC), tempo decorrido entre o início dos sintomas e o diagnóstico (TD), pressão intracraniana máxima (PIM), ocorrência de trombose venosa cerebral (TVC), e as modalidades de tratamento foram revisadas. PV foi graduada em discreta, moderada e grave, baseada na acuidade e no campo visual. Fatores preditivos para perda e melhora visual foram avaliados por análise de regressão linear.*

Resultados: *Quarenta e três pacientes eram do sexo feminino. A média de idade, o IMC e a PIM (± desvio padrão) foram: 35,2 ± 12,7 anos, 32,0 ± 7,5 kg/cm^2 e 41,9 ± 14,5 cmH_2O, respectivamente. Sintomas visuais estavam presentes em 46 e TVC em 8 pacientes. TD (em meses) foi <1 em 21, 1-6 em 15 e >6 em 14 pacientes. Pacientes receberam tratamento clinico apenas (n=30) ou associado a tratamento cirúrgico (n=20). Na apresentação a PV era discreta em 16, moderada em 12 e grave em 22 pacientes. Vinte e oito pacientes melhoraram e 5 pioraram. PIM, TD e hipertensão arterial correlacionaram significativamente com PV grave. O melhor fator preditivo para PV grave foi o TD>6 meses (p=0,04; razão de chances 5,18). TD entre 1 e 6 meses foi o único fator significativamente associado com melhora visual após tratamento (p=0,042).*

Conclusões: *Perda visual é comum na SPC e quando grave se mostra relacionado a atraso no diagnóstico. É usualmente permanente mas pode haver melhora visual especialmente quando a doença é diagnosticada nos primeiros 6 após o início dos sintomas.*

Descritores: *Pseudotumor cerebral; Perda visual; Hipertensão intracraniana; Papiledema*

INTRODUCTION

Pseudotumor cerebri (PTC) syndrome is a term used to describe patients with raised intracranial pressure (ICP) without localizing neurological findings, ventriculomegaly, or evidence of intracranial tumor. The diagnosis is currently applied to patients with either (1) idiopathic intracranial hypertension in the absence of an identifiable cause of intracranial hypertension or (2) cerebral venous outflow system obstruction or impairment[1-3]. Idiopathic intracranial hypertension (IIH) is diagnosed on the basis of criteria originally described by Dandy[4], with modifications proposed by Friedman and Jacobson[5], including the following: 1) symptoms and signs attributable to increased ICP or papilledema; 2) elevated ICP recorded during lumbar puncture in the lateral decubitus position; 3) normal cerebrospinal fluid (CSF) composition; 4) no imaging evidence of ventriculomegaly or a structural cause for increased ICP, such as a brain parenchymal, ventricular, meningeal, or venous sinus abnormality; and 5) no other cause of intracranial hypertension identified, such as the use of certain medications. Increased ICP without brain tumor or ventriculomegaly and attributable to cerebral venous sinus thrombosis (CVT), sinus stenosis, or venous hypertension from other causes is referred to as secondary PTC[6,7].

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The main morbidity of PTC, visual loss (VL) from acute or chronic papilledema, has been described and studied in detail by several authors[8-11]. The incidence of visual impairment varies across studies; however, the VL field may occur in up to 92% of eyes of patients with PTC.[11] Although VL may initially be reversible, it tends to be permanent once retinal nerve fiber layer (RNFL) loss and retinal ganglion cell (RGC) atrophy develop[8-10,12]. VL may also be caused by retinal complications such as retinal hemorrhage, choroidal folds, or the development of a peripapillary neovascular membrane[13-15].

The occurrence and severity of PTC-related VL are quite variable and very often do not correlate well with other findings of the disease. Few studies have evaluated predictive factors for the occurrence and severity of VL in PTC[8,9,16,17], making early diagnosis and timely treatment difficult, despite the importance of minimizing permanent disability. Although VL is frequently permanent in advanced cases of PTC, visual improvement may occur in the early stages, although at an incidence that is not well defined in the literature at present. Therefore, this study aimed to determine the incidence of VL and visual improvement and investigate possible predictive factors associated with its occurrence in a series of patients with PTC who underwent detailed clinical and neuro-ophthalmic evaluation at the time of diagnosis and after treatment.

METHODS

This study included data from 50 patients (43 females, seven males) diagnosed with and treated for PTC, with papilledema that resolved at least 6 months prior to the final evaluation. This included patients with IIH and intracranial hypertension secondary to elevated intracranial venous pressure[2]. IIH was defined on the basis of previously published criteria, with high CSF opening pressure (ICP >25 cmH_2O) measured by lumbar puncture at the time of diagnosis; normal magnetic resonance imaging (MRI) and magnetic resonance venography (MRV); normal CSF composition; and normal neurological examination, except for papilledema and possible sixth cranial nerve palsy[3,5]. In patients with cranial sinus thrombosis, the diagnosis was based on neuroimaging studies, including MRV and/or cerebral angiography.

Inclusion criteria for this study consisted of a complete ophthalmological examination, including VF testing using standard automated perimetry (SAP) with the 24-2 SITA-Standard strategy (Humphrey Field Analyzer, Carl-Zeiss Meditec, Dublin, CA) or Goldman perimetry at the time of diagnosis. Patients were also required to have undergone a complete neurological examination, spinal tap with manometry, and CSF analysis as well as normal MRI and/or computed tomography (CT) scan study at the time of diagnosis in addition to evaluation by MRV and/or arteriography to confirm or rule out the presence of CVT. In addition, all the study subjects were older than 15 years, had no ocular abnormalities other than acute or chronic papiledema, and had ametropia of less than 5 spherical diopters and 3 cylindrical diopters. Patients were also required to have a post-treatment ophthalmic examination, including VF assessment, after the treatment for PTC and at least 6 months after the resolution of papilledema. After treatment, patients were required to have clinically resolved papilledema (grade 0 according to the Frisen Scale[18]). The study was approved by the Institutional Ethics Committee.

The study parameters included age, sex, weight, body mass index (BMI), history of systemic hypertension, presenting symptoms, presence of visual complaints such as blurred vision and transient visual obscurations (TVO), time from symptom onset to diagnosis of PTC (TD), best-corrected visual acuity (VA) using a Snellen chart, presence and severity of papilledema or optic atrophy, and types of treatment. The maximum intracranial pressure (MIP), defined as the highest measurement of ICP on a lumbar puncture obtained at the time of diagnosis or during follow-up, was recorded.

In total, 100 eyes were evaluated and submitted to VA and VF analysis. The VA decimal measurements were categorized in three groups: A: worse than 0.1, B: between 0.1 and 0.9, and C: 1.0 (normal acuity). Visual field was measured with either manual or standard automated perimetry (SAP). Manual perimetry was performed using Goldmann equipment (Haag-Streit AG, Bern, Switzerland) with the use of the V/4e, I/4e, I/3e, and I/2e targets. SAP was performed with Humphrey Field Analyzer (Carl-Zeiss Meditec, Dublin, CA) using the Swedish Interactive Threshold Algorithm (SITA-standard 24-2 program) and a Goldmann size III stimulus on a 31.5-apostilb background. A grading system was used to classify VF defects documented with Humphrey or Goldmann perimetry and was slightly modified from a previously published article (11); the classification was either normal (grade 0) or graded from 1 to 4 in terms of VL severity. VF abnormalities on manual perimetry were either normal (grade 0) or classified into four grades as follows: grade 1: nerve fiber layer-type defect encompassing the blind spot and the central VF with normal I/2e isopter; grade 2: VF defect including abnormality in the I/2e isopter, with a VF defect greater than 20°; grade 3: absence of isopter I/2e in the central area, with a total field greater than 20°; and grade 4: VF of <20°. When using SAP, VF defects were classified as follows: grade 0: normal field; grade 1: mean deviation worse than -4.0 decibels (dB) with a nerve fiber layer VF defect; grade 2: mean deviation between -4.0 and -12.0 dB; grade 3: mean deviation between -12.0 and -20.0 dB; and grade 4: mean deviation worse than -20.0 dB. When both types of VF defects were present, the classification was based on SAP.

Patients were also classified taking into consideration the visual function of both eyes, with a bilateral visual score as follows: *Mild VL:* normal VA, VF better than grade 3 in each eye, and sum of scores ≤3; *Moderate VL*: VA better than 0.1 in each eye, VF defect better than grade 4 in each eye, and sum of scores of both eyes ≤4; and *Severe VL:* VA <0.1 in at least one eye, VF grade 4 in at least one eye or sum of scores ≤5.

At the final post-treatment examination, improvement in visual function was defined as a ≥0.1 decimal increase in VA or any downgrade on the bilateral VL scale (e.g., from moderate to mild VL). Worsening of visual function was defined as a ≥0.1 decimal decrease in VA or any upgrade on the bilateral VL scale. Visual function was considered unchanged when the VA and visual score remained the same.

Findings were expressed as mean and standard deviation (SD) for continuous variables and as proportions for categorical variables. To identify possible predictive factors for VL, categorical variables were analyzed using the chi-square test, whereas continuous variables were evaluated using Student's *t* test. McNemar's test was used to compare the percentage of eyes with VA reduction and the score of VF loss before and after treatment. Using the variables with $p<0.10$ in the univariate model, a multivariate stepwise logistic regression model was adjusted for investigating factors associated with VL. The level of statistical significance was set at 5% ($p=0.05$).

RESULTS

Table 1 shows the clinical data of all patients. The mean ± SD age, BMI, and MIP were 35.2 ± 12.7 years, 32.0 ± 7.5 kg/cm^2, and 41.9 ± 14.5 cmH_2O, respectively. Headache was present in 80% of patients and visual symptoms in 92%, including TVO, diplopia, and blurred vision. Time from symptom onset to diagnosis of PTC (TD) was <1 month in 21, 1-6 months in 14, and >6 months in 14 patients. Seven and nine patients had a history of oral contraceptive use and hypertension, respectively. CVT was present in eight patients (16%).

On the initial examination, VA was normal in 18 patients, 0.1-0.9 in at least one eye in 20 patients, and worse than 0.1 in at least one eye in 12 patients. Diplopia from sixth nerve paresis was present in 12 patients. The grading of VF loss for each of the 100 eyes in the sample is shown in table 1. Combining VA and VF data, VL was considered mild in 16, moderate in 12, and severe in 22 patients. Most patients (68%) had moderate or severe VL at presentation. Visual function improved in 28 patients, worsened in five, and remained unchanged in 17.

After treatment, VL was classified as mild in 24, moderate in 10, and severe in 16 patients (Table 1). The mean follow-up time was 4 years (1345 days). Forty-four patients received treatment with carbon anhydrase inhibitors, eight received anticoagulant treatment, six underwent shunting procedures, and 14 received optic nerve sheath fenestration.

The ability of each parameter to predict severe VL was statistically evaluated. In table 2, patients with severe VL are compared with patients with mild or moderate VL. Using the severity of VL as a dependent variable, univariate regression analysis was performed investigating possible predictive factors. An association (p<0.1) was found for maximum ICP, TD >6 months, and high blood pressure. As shown by our multivariate logistic regression analysis, the most important predictive factor for severe VL was TD >6 months [p=0.04; odds ratio (OR)=5.18]. We also tested for possible associations between each parameter and visual improvement after treatment. According to univariate logistic regression, the only predictive factor for visual improvement was TD 1-6 months (p=0.042).

Table 1. Demographic data and clinical findings of 50 patients (100 eyes) with pseudotumor cerebri syndrome

Characteristic	Number (%) or mean ± SD
Sex	
Male	7 (14%)
Female	43 (86%)
Age at first diagnosis mean ± SD, years	35.2 ± 12.7
Body mass index mean ± SD, kg/m^2	32.0 ± 7.5
Maximum intracranial pressure mean ± SD, cmH_2O	41.9 ± 14.5
Main clinical manifestation at onset	
Headache	40 (80%)
Transient visual obscurations	24 (48%)
Time from first symptom and diagnosis, months	
<1	21 (42%)
1-6	15 (30%)
>6	14 (28%)
Medical history	
Use of birth control pills	7 (80%)
Hypertension	9 (48%)
Visual acuity at time of diagnosis	
Worse than 0.1 in at least one eye	12 (24%)
Between 0.1 and 0.9 in at least one eye	20 (40%)
Normal in both eyes (1.0)	18 (36%)
Visual field at presentation (100 eyes)	
Grade 0	12 (12%)
Grade 1	31 (31%)
Grade 2	20 (20%)
Grade 3	15 (15%)
Grade 4	22 (22%)
Classification of visual loss at presentation (patients)	
Mild	16 (32%)
Moderate	12 (24%)
Severe	22 (44%)
Classification of visual loss after treatment (patients)	
Mild	24 (48%)
Moderate	10 (20%)
Severe	16 (32%)
Outcome of visual function after treatment	
Improvement	28 (56%)
Stable	17 (34%)
Worsening	5 (10%)

*= see methods for grading of visual function loss; SD= standard deviation.

DISCUSSION

The epidemiologic findings of our study confirm that PTC is a disorder with a distinct preponderance in women, with approximately 6 women for every man afflicted. Patients were predominantly overweight women (average BMI of 32 kg/cm^2, Class I obesity) of childbearing age (average, 35 years). This profile has been extensively described in the literature, particularly for patients with IIH[9,11,16,19]. Headache, present in 80% of our patients, was the most prevalent symptom, matching figures reported in other studies (72%-94%)[8,9,11,20,21]. The incidence of TVO in our series (48%) was within the range provided in the literature (44-72%)[8,9,11,20-22]. Most of our patients (58%) had symptoms for >1 month before the diagnosis was established. In 28%, symptoms were present for >6 months. The fact that PTC is often diagnosed late may explain why only 36% of our patients had normal VA in both eyes at presentation; 88% of the eyes in the sample had VF defects and 68% of these presented with moderate or severe VL. Our finding of VL in 88% of the eyes on the initial examination is comparable with the indices reported by Wall and George (91% of patients; 87% of eyes) in a prospective study of 50 patients[11] and slightly higher than the indices (49-72%) reported in several other studies employing appropriate perimetry techniques[8,9,12,20-23].

In addition to analyzing the distribution of symptoms and signs and the occurrence of VF in a series of PTC patients, we evaluated risk factors possibly associated with VL. Because blindness is the most significant complication of PTC, despite great variations in incidence and severity, it is very important to identify factors that directly influence disease outcome. Nevertheless, few authors have attempted such factor identification[8,9,11,16].

In our study, as shown by univarate analysis, TD >6 months, MIP, and hypertension were significantly associated with severe VL. Despite the low prevalence of hypertension in our study (18%), this condition proved to be a statistically significant predictor for VL severity (p=0.014). Similarly, in a study by Corbett et al.[24], hypertension was the only statistically significant risk factor for VL; in their series, the prevalence of hypertension was 22%, and 61% of hypertensive patients had severe unilateral or bilateral VL. Therefore, our findings are in agreement with those of Corbett et al.[24], who consider hypertension to be the single most important risk factor for VL in a patient with PTC. We agree with their suggestion that hypertensive vascular narrowing compounds the mechanical and vascular compromise that occurs at the optic disc in eyes with papilledema[24]. We also found a positive correlation between MIP and VL. It is important to consider that because ICP widely varies in PTC patients, it is impossible to accurately define MIP in a study such as ours. However, by defining MIP, we at least had an estimate of ICP grade elevation in our patients. Although no other study has specifically addressed this issue, Corbett et al.[9] suggested that the absolute magnitude and constancy of CSF pressure elevation may play a mechanical role in VL.

The time from symptom onset to PTC diagnosis was <1 month in 42%, 1-6 months in 28%, and >6 months in 28% of our patients. Using multivariate logistic regression, the most important factor for the occurrence of severe VL in our study was TD >6 months, with a p value of 0.04 and OR of 5.18. Although no previous study has specifically correlated TD with VL, the association was expected and draws attention to the importance of an early diagnosis to reduce the incidence of severe VL. In our study, when univariate analysis was used to verify other possible risk factors for VL, neither headache nor TVO or BMI was associated with severe VL. Although headache was present in 80% of cases in our study, it was not found to be a predic-

Table 2. Severe versus mild/moderate visual loss after treatment in 50 patients with pseudotumor cerebri syndrome

Clinical data	Severe visual loss, *n*=16	Mild or moderate visual loss, *n*=34	*p* value
Female sex (*n*=43)	14	29	0.834*
Age (mean ± SD)	39.4 ± 15.8	33.3 ± 10.7	0.176†
Body mass index (mean ± SD)	32.9 ± 7.3	30.1 ± 7.6	0.231†
Headache (*n*=40)	12	28	0.544*
Visual symptoms (*n*=46)	16	30	0.153*
TVO (*n*=29)	7	22	0.161*
Symptoms for 6 months or more (*n*=14)	8	6	0.021*
Cerebral venous thrombosis (*n*=8)	2	6	0.676*
Hypertension (*n*=9)	6	3	0.014*
Maximum intracranial pressure (mean ± SD)	47.9 ± 16.6	39.1 ± 12.7	0.048†

*= Chi-square test; †= Student's *t* test; Significant values are in italic; TVO= transient visual obscuration.

tive factor for severe VL (*p*=0.544), a finding supported by previous studies[8,9]. This is possibly because patients with headache are likely to be diagnosed earlier, before severe VL is established. Our findings for TVO were also in agreement with the literature: despite elevated frequency (48%), no significant association between TVO and severe VL was observed[8,9].

Other risk factors for VL have been proposed. Wall and George identified two factors significantly correlated with deterioration: small optic cup size and weight gain over the year preceding diagnosis. Most patients had high-grade papilledema, and the authors considered the possibility that a crowded disc with small scleral canals increases the vulnerability of the axons. Szewka et al.[16] found a trend toward more severe VL in one or both eyes at last follow-up among patients with BMI > 40. Logistic regression modeling revealed that 10-unit (kg/m^2) increases in BMI increased the odds of severe VL by 1.4 times (*p*=0.03) after controlling for sex, race, diagnosed hypertension, and diagnosed sleep apnea.

Permanent VF in PTC patients has been extensively discussed in the literature; however, the possibility of visual improvement has not received the same attention. Corbertt et al. found that 58% eyes of 57 patients had permanent VA or VF loss at follow-up; however, they did not specify how many eyes had improved with treatment. Orcutt et al.[8] found that throughout their study, 49% of eyes of 68 patients had VL, including 18% that did not deteriorate and 31% that worsened during follow-up. According to the authors, 51% had normal acuity and VF throughout the study; however, the question of improvement was not addressed. Wall and George[11] followed 50 patients with IIH prospectively and found that VF loss was initially present in 87% of eyes but only in 51% at the final visit. Visual improvement occurred in 60% of patients, while 10% worsened. Visual improvement occurred in 60% of patients, whereas 10% worsened. Craig et al.[21] observed improvement of VF in 39% of 42 patients in a retrospective study. Yri et al.[20] prospectively evaluated 20 patients with IIH followed for a mean period of 21 months. In total, 50% of the eyes with accurate VF findings had some degree of VL at presentation; however, only 21.2% did not have normal VF after treatment. Hung et al.[25] followed 10 patients with IIH and found visual function improvement in all but two eyes during follow-up. At the last visit, 40% of eyes had normal VF; however, it was mild or minimal in 40% and severe in two patients[25].

In the present study, visual improvement occurred in 56% of 50 patients with PTC, 34% remained unchanged, and 10% worsened. Our findings match the figures published by Wall and George[11] for a cohort of 50 patients. We also tested whether any study parameters were associated with visual improvement after treatment. Logistic regression revealed that the only factor associated with visual improvement was time from symptom onset to diagnosis between 1 and 6 months (*p*=0.042). However, it is important to consider that although visual improvement occurred in more than half of our patients, VL was still moderate or severe in 52% on the final examination. The fact that visual improvement is more likely to occur when diagnosis is made within 6 months of symptom onset and the high number of patients with significant VL despite adequate treatment emphasize the importance of early diagnosis and appropriate treatment of this condition.

In conclusion, our study confirms that VL is a frequent and potentially serious complication of PTC. Although hypertension and MIP have been shown to be significantly associated with VL severity, the most important predictive factor was the time from symptom onset to diagnosis. Thus, efforts should be made to diagnose patients with PTC early to prevent permanent VL.

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Refraction and eye anterior segment parameters in schizophrenic patients

Refração e parâmetros do segmento anterior ocular em pacientes com esquizofrenia

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ABSTRACT

Purpose: To evaluate the difference in terms of refractive errors and anterior segment parameters between schizophrenic patients and healthy volunteers.

Methods: This study compared 70 patients (48 men) who were diagnosed with schizophrenia with a control group of 60 (35 men) who were similar in terms of age, gender, education, and socioeconomic level. Anterior segment examination was performed using a Scheimflug system. Axial length and lens thickness (LT) were measured using optic biometry. The following tests were administered to the psychiatric patient group: Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and Scale for the Assessment of Positive Symptoms (SAPS).

Results: Mild myopia was detected in both the schizophrenic and control groups, with no statistically significant difference ($p>0.005$). Corneal volume (CV), anterior chamber volume (ACV), anterior chamber depth (ACD), and central corneal thickness (CCT) values were lower in the schizophrenic group, and there was a statistically significant between-group difference ($p=0.026$, $p=0.014$, $p=0.048$, and $p=0.005$, respectively). LT was greater in schizophrenics, and the difference was found to be statistically significant ($p=0.006$). A statistically significant negative correlation was found between SAPS and cylinder values ($p=0.008$). The axial eye length, cylinder value, pupil diameter, mean keratometric value, and anterior chamber angle revealed no statistically significant difference between the groups ($p>0.05$).

Conclusion: No statistically significant difference was detected in terms of refraction disorders between schizophrenics and the healthy control group, while some differences in anterior chamber parameters were present. These results demonstrate that schizophrenics may exhibit clinical and structural differences in the eye.

Keywords: Schizophrenia; Refractive errors/complications; Anterior eye segment/pathology; Biometry

RESUMO

Objetivo: *Avaliar se existem diferenças em relação aos erros refracionais e parâmetros do segmento anterior entre pacientes com esquizofrenia e voluntários saudáveis.*

Métodos: *Este estudo comparou 70 pacientes diagnosticados com esquizofrenia (48 homens) com um grupo controle de 60 pacientes, semelhantes em relação à idade, sexo, escolaridade e nível socioeconômico (35 homens). O exame do segmento anterior foi realizado com o sistema Scheimflug; os comprimentos axiais do olho e a espessura do cristalino foram avaliadas por meio de biometria óptica. Os seguintes testes foram aplicados ao grupo de pacientes psiquiátricos:* Brief Psychiatric Rating Scale *(BPRS),* Scale for the Assessment of Negative Symptoms *(SANS), e* Scale for the Assessment of Positive Symptoms *(SAPS).*

Resultados: *Miopia leve foi detectada em ambos os grupos de esquizofrenia e de controle, sem diferença estatisticamente significativa (p>0,005). Volume de córnea (CV), volume da câmara anterior (ACV), profundidade da câmara anterior (ACD) e paquimetria central da córnea (CCT) apresentaram valores menores no grupo de esquizofrênicos e houve diferença estatisticamente significativa entre os dois grupos (p=0,026, p=0,014, p=0,048 e p=0,005, respectivamente). A espessura do cristalino (LT) foi maior em esquizofrênicos e a diferença foi estatisticamente significativa (p=0,006). Foi encontrada uma correlação negativa estatisticamente significativa entre SAPS e os valores cilíndricos (p=0,008). O comprimento axial do olho, o valor do cilindro, o diâmetro pupilar, a ceratometria média e o ângulo da câmara anterior não revelaram nenhuma diferença estatística entre os grupos (p>0,05).*

Conclusões: *Não foi detectada diferença estatisticamente significativa em relação aos transtornos de refração entre os esquizofrênicos e o grupo controle, enquanto algumas diferenças nos parâmetros de câmara anterior estavam presentes. Estes resultados demonstram que esquizofrênicos podem apresentar diferenças clínicas e estruturais do olho.*

Descriotres: *Esquizofrenia; Erros de refração/complicações; Segmento anterior do olho/patologia; Biometria*

INTRODUCTION

Schizophrenia is characterized by distorted thought, hallucinations, and reduced ability to feel normal emotions. It has a lifetime prevalence of approximately 1% and has long been associated with the environment and hereditary factors[1,2]. Dopamine may be involved in the pathophysiology as all effective pharmacological treatments for the disorder affect dopamine neurotransmission[2].

Myopia is a visual disorder where nearby objects are seen clearly but distant objects appear blurred, and it is the most common refractive error[3].

Studies have demonstrated that genetic factors make an important contribution to the etiology of both myopia and schizophrenia[4,5]. In addition, the suggested role of dopamine in the emmetropization process and pathophysiology of schizophrenia is known[2,6]. According to the dopamine hypothesis, the lack of dopamine in the brain may interfere with the emmetropization process[6].

Recently, Caspi et al.[7] reported that the presence of refractive errors in adolescence is related to a lower risk of schizophrenia in light of the dopamine hypothesis and genetic factors. However, anterior segment parameters related with refraction were not evaluated in schizophrenic patients in their study.

This study aimed to evaluate differences between schizophrenic patients and healthy volunteers with regard to refractive errors and anterior segment parameters. To the best of our knowledge, there is

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no study on anterior segment parameters in schizophrenic patients, and only one study has reported refractive errors in schizophrenic patients[7].

METHODS

The study group included 70 schizophrenic patients evaluated at the Eye Outpatient Clinic of Inonu University, Department of Ophthalmology in Turkey. All 130 subjects provided informed consent to participate in the study after they were informed about the aim and details of the cross-sectional study. The control group included 60 age-, sex-, and educational level-matched subjects who were other patients visiting the same institution. This study was approved by the local ethics committee. The Institutional Review Board of the Inonu University School of Medicine approved the study protocol, which specified study conduct in compliance with the tenets of the Declaration of Helsinki.

Inclusion criteria

The inclusion criteria for schizophrenic patients included age of 18-65 years, diagnosis of schizophrenia on the basis of the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition Revised Form (DSM-IV-TR) criteria, treatment with antipsychotic drug (typical, atypical or combined) for at least 2 years, no exposure to electroconvulsive therapy (ECT), and the absence of a comorbid medical condition or disease.

Exclusion criteria

Exclusion criteria for both schizophrenic and control groups included anamnesis of eye surgery or eye trauma, refractive surgery, corneal pathology, uveitis, glaucoma, posterior segment pathology, or a topical drug usage that affects anterior segment parameters. Patients who were physically impaired and had difficulties in conversing or completing the scale, patients who received treatment for any other psychiatric disorders according to the DSM-IV-TR, patients with dementia, and patients who had undergone intraocular surgery, had corneal pathologies, or had a history of ocular trauma were excluded from the study. Subjects who had a history of refractive surgery or amblyopia were also excluded from the study.

Patient assessment

Each subject underwent a complete ophthalmic evaluation, including detailed ophthalmic history, visual acuity testing using Snellen's chart, slit-lamp examination, Goldmann's applanation tonometry, gonioscopy using Goldmann's three-mirror lens, visual field examination, and dilated fundus examination.

The patient group consisted of schizophrenic patients aged 18-65 years who had been taking antipsychotic medication for at least 2 years and whose schizophrenia diagnosis was based on the DSM-IV-TR diagnostic criteria[8].

All subjects in the study and control groups were interviewed by a psychiatrist. The dynamic refraction assay of patient and control groups was applied, and it was accepted ± 0.25 D and below as emmetropia.

All patients were evaluated using Pentacam (Oculus®, Pentacam, Germany). All measurements were obtained under standard dim light conditions and without dilation. The Pentacam CES system is based on a 180° rotating Scheimpflug camera that can take 12-50 single images to reconstruct the anterior chamber. Anterior segment reconstructions were produced with 25 single captures in this study. After completing a scan, the Pentacam software constructs a three-dimensional image of the anterior segment and calculates the anterior chamber parameters[9]. This imaging provides measurements of anterior chamber depth (ACD), anterior chamber volume (ACV), anterior chamber angle (ACA) width, and pupil size.

The software-provided values, automatically calculated using 25 images from each patient eye, were used for ACA width, ACV, and ACD evaluation. The Pentacam system measures ACD from the endothelium to the anterior lens surface without including the corneal thickness, whereas ACV is measured from the posterior cornea to the anterior lens surface[10].

The axial length (Alx) measurements and lens thickness (LT) were determined by optic biometry (Lenstar LS 900; Haag Streit Köniz, Switzerland). Alx measurement was accepted as the distance from the anterior cornea to the retina. The Lenstar LS 900 biometer uses optical low-coherence reflectometry (OLCR) with an 820 µm superluminescent diode. Alx measurements were performed with the non-contact method using Lenstar LS 900[11].

Sociodemographic and Disorder Inquiry Form: This inquiry was prepared by the investigators and included questions on gender, age, education, any physical disorder requiring continuous treatment, psychiatric history, and family history of associated disorders. The form was read out to participants and their family members, and the information was recorded by the investigators.

Brief Psychiatric Rating Scale (BPRS): BPRS is a rating scale for measuring psychiatric symptoms such as depression, anxiety, hallucinations, and unusual behavior. Each symptom is rated between 1 and 7, and 18 or 24 symptoms are scored depending on the version. BPRS was developed by Overall and Gorham in 1962, and a validated Turkish translation is available[12].

Scale for the Assessment of Negative Symptoms (SANS): SANS, developed by Andreasen[13], assesses negative symptoms, including affective blunting, alogia (impoverished thinking), avolition/apathy, anhedonia/asociality, and disturbance of attention, in schizophrenic patients. The final symptom complexes seem to have less obvious relevance to negative symptoms than the other four complexes. Assessments are conducted on a six-point scale (0= not at all to 5= severe). The Turkish version was validated and reported to be reliable by Erkoç et al.[14].

Scale for the Assessment of Positive Symptoms (SAPS): This scale is designed to assess positive symptoms, principally those that occur in schizophrenia, and it is intended to serve as a complementary instrument to the SANS. Positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorder. SAPS was developed by Andreasen in 1984[15]. The Turkish version was validated and reported to be reliable by Erkoç et al.[16].

Sample size

Based on post hoc power analysis for LT and outcome variables, group sample sizes of 60 and 70 were considered necessary to achieve 84% power to detect a difference of -0.2 between the null hypothesis that both group means are 3.8 and the alternative hypothesis that the mean of Group 2 is 4.0, with estimated group standard deviations of 0.3 and 0.4 and a significance level (alpha) of 0.05 using a two-sided two-sample *t*-test.

SPSS version 17.0 was used for statistical analysis of data. The chi-square test was used for between-group evaluation of the categorical variables of gender, education level, and economic level between the two groups. The mean, standard deviation, and percentage values were calculated. An independent samples *t*-test was used to determine the difference between the two groups. Pearson Correlation test was used to determine the amount and direction between variables, with $p<0.05$ considered statistically significant.

RESULTS

The mean age was 35.34 ± 10.13 years in the schizophrenic group and 32.63 ± 7.90 years in the control group. The 70 subjects in the schizophrenic group had a women: men distribution of 22 (31.4%) to 48 (68.6%), whereas there were 25 (41.7%) women and 35 (58.3%) men in the control group. There was no significant between-group difference with regard to age, sex, and duration of education ($p>0.05$). Sociodemographic data of the groups are presented in table 1.

A comparison of the data for the study groups for refractive errors, Alx measurements, and anterior segment parameters is presented in table 2.

The mean BPRS, SAPS, and SANS values were 28.77 ± 10.91, 41.52 ± 15.59, 50.45 ± 23.89, respectively, in schizophrenic men, whereas they were 33.86 ± 27.41, 49.95 ± 24.28, and 56.90 ± 27.74, respectively, in schizophrenic women.

The correlation between age, refraction, Alx, and anterior segment parameters and the BPRS, SAPS, and SANS values in the schizophrenic group is presented in table 3. Only the correlation between cylindrical equivalent and the SAPS values was statistically significant. This means there is an increased tendency for astigmatism when the negative symptoms of the disease increase.

There were 18 subjects (25.7%) with emmetropia and 52 subjects (74.3%) with ametropia in the schizophrenic group and 24 subjects (40%) with emmetropia and 36 subjects (60%) with ametropia in the control group. When the patient and control groups were compared with regard to the incidence of refractive errors, there was no statistically significant difference between the groups (p=0.082).

The mean duration of disease was 10.40 ± 6.66 (range 2-22) years in the patient group. Correlations between the duration of disease and refractive error, Alx, and anterior segment parameters are presented in table 4.

Table 1. Sociodemographic data of study groups

	Patient (*n*=70)	Control (*n*=60)	*p* value
Age (years)	35.34 ± 10.13	32.63 ± 7.90	
Mean ± SD (95% CI)	(32.92-37.75)	(30.59-34.67)	0.09
Sex, *n* (%)			
Female	22 (31.4%)	25 (41.7%)	
Male	48 (68.6%)	35 (58.3%)	0.22
Socioeconomic status, *n* (%)			
Low	23 (32.9%)	23 (38.3%)	
Moderate	37 (52.9%)	28 (46.7%)	
High	10 (14.3%)	9 (15.0%)	0.76
Levels of education, *n* (%)			
Primary school	20 (28.6%)	21 (35.0%)	
High school	39 (55.7%)	30 (50.0%)	
University	11 (15.7%)	9 (15.0%)	0.72

Note= mean ± SD (95% CI for mean).
t= independent samples test; n= number of subjects; SD= standard deviation.

Eight patients were on treatment with only typical antipsychotics (11.4%), 37 patients with only atypical antipsychotics (52.8%), and 25 patients with both typical and atypical antipsychotics (35.7%). The dosage of typical and atypical antipsychotic drugs at a chlorpromazine-equivalent (mg/day) was 307.41 ± 180.60 and 386.47 ± 281.51, respectively.

In addition to antipsychotics, 18 patients (25.7%) were on treatment with biperiden. Benzodiazepines (alprazolam and diazepam) were used by four patients (5.7%). Two patients (2.8%) were on treatment with a selective serotonin reuptake inhibitor (escitalopram).

The percentage of patients of this study using each antypsychotic drug was determined. Typical antipsychotic drug use was as follows: four patients (5.7%) on zuclopentixol, 26 patients (37.1%) on haloperidol, and three patients (4.3%) on flupentixol. Atypical antipsychotic usage included: 28 patients (40%) on risperidone, 13 patients (13%) on olanzapine, 10 patients (14.3%) on aripiprazole, eight patients (11.4%) on amilsulpiride, 14 patients (20%) on clozapine, five patients (7.1%) on quetiapine, and one patient (1.4%) on ziprasidone.

DISCUSSION

There are many hypotheses for the etiology of schizophrenia such as genetic factors and imbalance of biochemical mediators, of which the most important one is dopamine[17,18]. Genetic factors and dopamine have been determined to play a role in the etiologies of both refractive errors and schizophrenia[7]. Dopamine plays an important role in the emmetropization process and inhibits the development of myopia[7]. In addition, Caspi et al.[7] have reported a lower frequency of myopia in schizophrenic patients than in healthy subjects. In that study, the rate of refractive errors in schizophrenic patients, their nonschizophrenic siblings, and control siblings was 1.00%, 3.58%, and 5.07% respectively. Caspi et al.[19] have reported a lower incidence of refractive errors in schizophrenic patients and their nonschizophrenic twins, suggesting an important role of genetics in the development of refractive errors. Saw et al. reported that the low prevalence of myopia could be related to the reduced tendency for near work in schizophrenic patients. In our study, we did not find any difference between the groups in terms of refractive error.

Many studies have reported differences with regard to various parts of the body in schizophrenic patients[20-22]. The frequencies of specific dermatoglyphic patterns were found to be statistically significantly different between schizophrenics and healthy controls with respect to hand and gender[20]. The incidence of agenesis of the corpus callosum, large cavum septum pellicidum, or absence of adhesio interthalamica gray matter heterotopia is higher in schizophrenic patients[21,22]. Similarly, we found many differences in the anterior seg-

Table 2. Between-group comparison of refractive errors, axial length measurements (Alx), and anterior segment parameters

	Patient (*n*=70)	Control (*n*=60)	
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	*p* value
Spherical equivalent	-0.84 ± 2.13 (-1.35-0.33)	-0.73 ± 1.90 (-1.22-0.24)	0.760
Cylindrical equivalent	-0.67 ± 0.57 (0.54-0.81)	-0.63 ± 0.60 (0.48-0.79)	0.700
Axial length (mm)	23.57 ± 1.04 (23.32-23.82)	23.58 ± 1.22 (23.26-23.89)	0.960
Lens thickness (mm)	3.99 ± 0.36 (3.90-4.07)	3.82 ± 0.29 (3.74-3.90)	0.006*
Corneal volume (mm^3)	59.78 ± 4.27 (58.76-60.79)	61.31 ± 3.30 (60.45-62.16)	0.026*
Anterior chamber volume (mm^3)	169.44 ± 36.55 (160.72-178.16)	187.75 ± 47.38 (175.50-199.99)	0.014*
Anterior chamber depth (mm)	2.94 ± 0.34 (2.86-3.02)	3.07 ± 0.38 (2.97-3.17)	0.048*
Anterior chamber angle	35.15 ± 5.72 (33.79-36.52)	35.60 ± 5.03 (34.30-36.90)	0.630
Pupil diameter (mm)	2.79 ± 0.48 (2.67-2.90)	2.93 ± 0.48 (2.80-3.05)	0.100
Central corneal thickness	538.55 ± 31.26 (531.10-546.01)	555.56 ± 36.17 (546.22-564.91)	0.005*
Mean keratometric value	43.30 ± 1.65 (42.91-43.70)	43.44 ± 1.76 (42.99-43.90)	0.630

t= independent samples test; *n*= number of subjects; SD= standard deviation; mean ± SD (95% CI for Mean).

Table 3. Correlation between age, refraction, axial length (Alx), and anterior segment parameters and the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS) values in the schizophrenic group

	BPRS (n=70)		SAPS (n=70)		SANS (n=70)	
	r	p	r	p	r	p
Age	-0.09	0.45	0.004	0.970	-0.190	0.10
Spherical equivalent	-0.03	0.80	0.100	0.370	-0.210	0.07
Cylindrical equivalent	-0.15	0.19	-0.310	0.008*	-0.020	0.84
Alx	-0.01	0.89	-0.120	0.300	0.004	0.97
Lens thickness	-0.15	0.19	-0.080	0.470	-0.060	0.58
Corneal volume	0.13	0.28	-0.050	0.460	-0.110	0.33
Anterior chamber volume	0.03	0.77	-0.100	0.370	-0.050	0.67
Anterior chamber depth	0.01	0.92	-0.110	0.330	-0.120	0.29
Anterior chamber angle	-0.03	0.78	-0.050	0.670	0.020	0.85
Pupil diameter	0.14	0.24	0.010	0.870	-0.090	0.42
Central corneal thickness	0.20	0.09	0.080	0.460	-0.140	0.24
Mean keratometry	-0.13	0.28	-0.190	0.110	-0.170	0.15

r= Pearson's correlation Test; *n*= number of subjects.

Table 4. Correlation between duration of disease and refractive error with Alx and anterior segment parameters

	Duration of disease	
	r	*p*
Spherical equivalent	0.32	0.0060*
Cylindrical equivalent	0.023	0.8500
Axial length	-0.19	0.1000
Lens thickness	0.73	0.0001*
Corneal volume	-0.14	0.2300
Anterior chamber volume	-0.55	0.0001*
Anterior chamber depth	-0.48	0.0001*
Anterior chamber angle	-0.23	0.0050*
Pupil diameter	-0.29	0.0130*
Central corneal thickness	0.032	0.7900
Mean keratometry	0.29	0.0130*

*= statistically significant, $p<0.05$.

ment parameters of the eye such as central corneal thickness (CCT), ACV, ACD, LT, and CV.

Some ocular problems in schizophrenic patients such as dysfunction of saccadic eye movements and stereopsis disorders (particularly in schizophrenic patients with visual hallucinations) have been reported in the literature[23,24]. Recently, Meier et al. demonstrated a microvascular abnormality in schizophrenia by retinal imaging[25]. According to this study, retinal venules were wider in schizophrenic patients than in controls, suggesting a microvascular abnormality reflective of insufficient brain oxygen supply. In addition, Shiloh et al. have reported a decrease in the corneal temperature in patients with treatment-resistant paranoid schizophrenia and concluded that this situation may be attributable to the thermoregulation effect of dopamine[26]. Compared with controls, we also found a statistically significant decrease in CV and CCT in schizophrenic patients, which may be attributable to genetic factors and/or the emmetropization effect of dopamine. In addition, the decreased ACA, ACD, and increased LT in schizophrenic patients may be associated with these factors. We have demonstrated changes in ACD, LT, CV, and CCT and no difference in Alx, ACA, PD, and Km in schizophrenic patients.

Shiloh et al. have reported a lower corneal temperature in schizophrenics who use antipsychotic drugs than in those who do not use them[27]. Because all the schizophrenic patients in our study had used antipsychotic drugs, we could not compare anterior segment parameters between patients who did and did not use antipsychotics. One limitation of our study is that our patient group had received antipsychotic drugs and this may have affected some of the parameters assessed. However, we believe it would be ethically incorrect to discontinue drug use in this patient population for the purpose of scientific study. Only two patients had started using antipsychotic drugs before the age of 20 years; however, there were no problems detected on ophthalmologic examination in these two patients. Emetropization is expected to be completed by this age, although we believe that the refractive status will not be affected.

BPRS, SAPS, and SANS have been used in psychiatry clinics for the evaluation of schizophrenics. We found only one statistically significant correlation between the cylindrical equivalent and the SAPS values. An increase in negative symptoms may increase the tendency for astigmatism. On the other hand, there was no statistically significant correlation between the spherical equivalent and BPRS, SAPS, or SANS.

The correct diagnosis and management of patients with glaucoma is dependent on an accurate determination of intraocular pressure (IOP). Kruse Hansen et al. have reported a positive linear correlation between CCT and IOP[28]. IOP measured by applanation may be overestimated or underestimated in thick or thin corneas, respectively. CCT measurements were lower in schizophrenic patients than the control group in the present study; however, we could not find any difference between the two groups with regard to IOP measurements. We also found no difference between the two groups with regard to ACA measurements.

In addition, the reduced level of CV and CCT is clinically important in schizophrenic patients who require refractive surgery. Moreover, the reduced level of CV and CCT indicates that refractive surgery involves a higher risk in schizophrenic patients[29].

Furthermore, in the present study, the LT level was found to be increased, whereas the ACV and ACD levels were reduced in schizophrenic patients. These findings are very important for glaucoma, cataract, and anterior segment surgeries. In addition, this condition reflects an increased risk potential for glaucoma, cataract, and anterior segment surgeries in schizophrenic patients[29]. We found no statistically significant between-group difference with regard to the frequency of refractive error or measured values in our study. Caspi et al. have reported a lower frequency of myopia in schizophrenic patients than in healthy subjects[7]. Moreover, we found a slight myopic shift but no statistically significant difference between the groups in the present study.

Finally, this study pioneers the investigation of anterior segment parameters (CV, CCT, LT, ACV, ACD, ACA, and Alx) in schizophrenic patients.

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Visual loss resulting from immunosuppressive therapy in patients with syphilitic uveitis

Perda visual resultante do uso de terapia imunossupressora em pacientes com uveíte por sífilis

Vivian Cristina Costa Afonso[1], Heloisa Nascimento[1], Rubens M. Belfort[1], Emilia Inoue Sato[2], Cristina Muccioli[1], Rubens Belfort Jr.[1]

ABSTRACT

Permanent visual loss can be caused by improper use of immunosuppressive therapy in cases of uveitis without differential diagnosis of syphilitic uveitis. We present four cases of syphilitic uveitis that were incorrectly diagnosed as being secondary to rheumatic diseases and were subsequently treated with immunosuppressive therapy, leading to permanent visual loss. These cases highlight the importance of ruling out syphilis in the differential diagnosis of inflammatory ocular diseases before starting use of immunosuppressive therapy.

Keywords: Syphilis; Uveitis/drug therapy; Immunosuppressive agents/therapeutic use; Immunosuppressive agents/adverse effects; Vision disorders/etiology; Case reports

RESUMO

Elucidar os efeitos adversos do uso de medicações imunossupressoras em pacientes com uveíte não diagnosticada por sífilis. Avaliação de quatro pacientes com uveíte por sífilis submetidos a tratamento com drogas imunossupressoras por suspeita de uveíte secundária a doenças reumáticas, que desenvolveram perda visual permanente. Sífilis deve ser sempre um diagnóstico diferencial nas doenças inflamatórias oculares, principalmente antes do início de terapia imunossupressora.

Descritores: *Sífilis; Uveítes/quimioterapia; Imunossupressores/uso terapêutico; Imunossupressores/efeitos adversos; Transtornos da visão/etiologia; Relatos de casos*

INTRODUCTION

Syphilis can affect the eyes in the secondary and tertiary stages of the disease, and ocular syphilis can be difficult to diagnose due to variation in presentation. The most common presentation is uveitis[1], which can be in the posterior or diffuse form, as well as unilateral or bilateral.

Biologic immunosuppressant agents have been used to treat non-uveitis[2], but the evidence supporting this approach is not strong. In addition, the use of immunosuppressant agents has been related to exacerbation of infectious uveitis[3]. Non-treponemal serologic tests, such as the venereal disease research laboratory (VDRL) test, followed by tests to identify *Treponema*, such as enzyme-linked immunosorbent assay, fluorescent *Treponema* antibody (FTA-ABS), and the microhemagglutination assay for *Treponema pallidum* antibodies, are the gold standard for diagnosing syphilis[1]. The non-treponemal tests are important for monitoring disease progression, because they are quantitative and can identify titer level, determining the response to antibiotic treatment. Given the differences in uveitis etiology, it is important that treatment decisions are based on the results of both treponemal and non-treponemal tests[4] (Table1).

The purpose of this report is to raise awareness in the medical community of the possibility of permanent ocular damage caused by the inappropriate use of immunosuppressive therapy in cases of uveitis associated with undiagnosed syphilis.

CASE REPORTS

A 61-year-old woman presented with a bilateral decrease in visual acuity, with best-corrected visual acuity (BCVA) levels of 20/400 and 20/800 in the right and left eyes, respectively. Examination showed 2+ inflammatory anterior chamber (AC) cells bilaterally, granulomatous keratic precipitates, vasculitis, and intense vitritis bilaterally.

The patient had skin lesions on the palms of her hands and soles of her feet, as well as hypoacusis. She was being treated with 60 mg of prednisone daily and had undergone pulse therapy with methylprednisolone, due to ophthalmic and suspected inflammatory disease (anticardiolipin antibody-positive), without clinical improvement. Her VDRL titer was 1\128 and her FTA-ABS test was positive. She was negative for human immunodeficiency virus (HIV), and her cerebrospinal fluid (CSF) was negative for syphilis. She was started on 16 million units of intravenous penicillin daily for 14 days. The vitreitis and vasculitis in her right eye improved; however, optic atrophy was observed and a rhegmatogenous retinal detachment developed in the left eye, causing permanent blindness bilaterally. Her dermatologic clinical signs improved substantially (Figure 1).

A 49-year-old woman presented with progressive visual loss bilaterally for 6 months, with a corrected VA of 20/400 and 20/800 in the right and left eyes, respectively. She also had 2+ AC cells, granulomatous keratic precipitates, intense bilateral vitreitis, oral and genital ulcers, hypoacusia, and mental confusion. After diagnosing her with neuro-Behçet's disease, a rheumatologist prescribed prednisone, micofenolato mofetil, and infliximab. Two ophthalmologists and internists also evaluated the patient. Her VDRL titer was 1/128 and she was negative for HIV. CSF tests revealed that her FTA-ABS test was positive. Sixteen million international units (IU) of IV penicillin were prescribed for 14 days. After treatment, VA improved to 20/20 in both eyes.

A 51-year-old man presented with clinical signs of uveitis for 3 months, with VA of 20/120 and 20/80 in the right and left eyes, res-

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Table 1. Interpretation of diagnostic tests for syphilis in cases of uveitis[6]

Treponemal test	Non-treponemal test	Interpretation
Negative	Negative	Immunologic window or is not syphilis
Positive	Negative	Already treated syphilis or tertiary syphilis; inquire about previous treatment of syphilis. In previously untreated cases or inadequately treated cases, consider retreatment. Evaluate the prozone effect. Dilute sample of non-treponemal test and reassess positivity
Positive	Positive	Evaluate titers of non-treponemal tests. In previously treated cases, the titers probably have declined. In previously untreated or inadequately treated cases, consider retreatment
Negative	Positive	Immunologic window or false positive (consider rheumatic diseases)

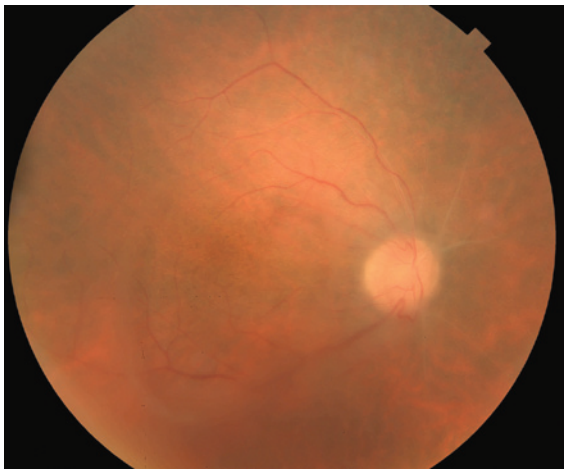

Figure 1. Case 1: funduscopy of right eye after treatment.

pectively. He also had 2+ AC cells, keratic precipitates, and non-granulomatous keratic precipitates. He had undergone pulse therapy with methylprednisolone, but the clinical signs worsened. At the time of his visit, he was taking 200 mg/day of azathioprine and 60 mg/day of prednisone, which was prescribed by a rheumatologist after a previous ophthalmic evaluation. His VDRL titer was 1/128, and his FTA-ABS test was positive. He was also HIV negative, and his CSF test was negative for syphilis. The patient was treated with intramuscular penicillin G benzathine 2,400,000 IU/week for 3 weeks. His VA improved to 20/40 and 20/25 in the right and left eyes, respectively. After 4 months, his VA decreased and the uveitis recurred. Treatment with IV crystalline penicillin was performed for 14 days. This resolved the uveitis and the patient's VA improved to 20/25 in both eyes.

A 51-year-old woman presented with a bilateral BCVA of 20/400, 2+ AC cells in the aqueous humor, granulomatous keratic precipitates, intense vitreitis, and dermatologic symptoms (rashes on the palms and soles). She was treated with 60 mg prednisone, methotrexate, and adalimumab, which was prescribed by a rheumatologist who suspected possible Behcet's disease. The patient's VDRL titer was 1/128, her FTA-ABS was positive, and she was negative for HIV. CSF tests also showed positive FTA-ABS results. She was treated with 16 million units of IV penicillin daily for 14 days. Following treatment, her VA improved to 20/40 in both eyes, but paralytic mydriasis and photophobia persisted.

DISCUSSION

In case 1, we observed systemic involvement associated with the clinical signs of uveitis. However, because the patient was anticardiolipin-positive, the disease was considered rheumatic in nature. A positive test for anticardiolipin antibody can occur in cases with a high *Treponema* load[4], even when VDRL may be negative. Serology for *Treponema*, which would have facilitated a correct diagnosis, had not been performed initially. In addition in cases of antiphospholipid syndrome, steroid pulse therapy is generally not prescribed, although this patient had previously received it.

In case 2, the patient had systemic involvement with neurologic changes and oral and genital ulcers. The systemic clinical signs could have been compatible with neuro-Behçet's disease. However, the differential diagnosis did not include syphilis. In case 3, the patient had clinical signs of uveitis only, with no improvement during the 3 months of immunosuppressant therapy.

Cases 1, 2, and 4 had systemic involvement with dermatologic changes. After immunosuppressant therapy, the symptoms worsened.

The clinical signs of uveitis in these cases were treated with immunosuppressive therapy using corticosteroids and other immunosuppressants, without syphilis being excluded. This led to worsening of the ocular symptoms, because corticosteroids and immunosuppressants can increase *Treponema* load, resulting in increased syphilis-related ocular and non-ocular complications[5,6]. The potential complications following the use of immunosuppressive therapy in syphilitic uveitis, which may lead to blindness, include retinal vasculitis, exudative retinal detachment, retinal chorioretinitis, and optic atrophy.

When the disease is treated early and aggressively, even severe uveitis tends to resolves without major permanent visual loss[7].

In the cases described here, ocular disease became more evident after the use of immunosuppressive drugs. Other studies have reported the development of ocular syphilis after the use of anti-TNFα[8,9]. Moreover, syphilitic uveitis is often associated with neurosyphilis, and patients with symptoms consistent with this diagnosis should be treated according to the recommendations for neurosyphilis[10].

The cases described here demonstrate that syphilis should always be included in the differential diagnosis of inflammatory ocular diseases before a patient receives any immunosuppressive treatment.

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Idiopathic polypoidal choroidal vasculopathy masquerading as choroidal tumors: one year follow-up of a peripheral lesion

Vasculopatia polipoidal idiopática da coroide simulando tumores da coroide: um ano de seguimento de uma lesão periférica

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ABSTRACT

This case report describes peripheral idiopathic polypoidal choroidal vasculopathy (IPCV) with a collection of small aneurysmal dilations that masqueraded as choroidal tumors in an elderly patient. A 68-year-old African American woman was referred to us with a suspected diagnosis of asymptomatic vascular choroidal tumor and choroidal capillary hemangioma, affecting the temporal peripheral fundus. Upon examination, optical coherence tomography (OCT) revealed two large hemorrhagic pigment epithelium detachments (PED), and indocyanine green angiography (ICG) confirmed the diagnosis of IPCV. One year later, there was reduction in the hemorrhagic pigment epithelium detachments and the lesion took on a different appearance, resembling a choroidal osteoma. No treatment was necessary despite the presence of multiple polyps. IPCV is a rare condition that can resemble other choroidal diseases depending on the stage of presentation. OCT is the best tool to determine the characteristics of the lesions, and indocyanine green angiography should be used to confirm the diagnosis. Not all cases require treatment.

Keywords: Choroid hemorrhage/etiology; Choroid diseases/pathology; Fluorescein angiography; Indocyanine green/diagnostic use; Choroid/blood supply; Peripheral vascular diseases; Pigment epithelium of eye; Tomography, optical coherence; Case reports

RESUMO

Relato de um caso de vasculopatia polipoidal idiopática da coroide (IPCV) com múltiplas dilatações aneurismáticas em região temporal periférica da retina, em uma paciente idosa que assemelhou-se com alguns tumores de coroide no seguimento de um ano. Paciente de 68 anos da raça negra, assintomática, foi encaminhada com a hipótese diagnóstica de um tumor vascular de coroide e hemangioma capilar da coroide, em região temporal inferior periférica da retina. Ao exame de tomografia de coerência óptica (OCT) era observado dois grande descolamentos de epitélio pigmentado (DEP), sendo confirmado o diagnóstico de vasculopatia polipoidal idiopática da coroide pela angiografia com indocianina verde (ICG). Após um ano, houve absorção do descolamento do epitélio pigmentado hemorrágico assemelhando-se assim ao osteoma de coroide. Nenhum tratamento foi necessário apesar da quantidade dos pólipos. A vasculopatia polipoidal idiopática da coroide é uma doença rara que, dependendo do estágio da apresentação, pode se assemelhar com algumas doenças da coroide. A tomografia de coerência óptica pode ilustrar melhor as características das lesões e a ICG confirma o diagnóstico. Nem todos os casos necessitam ser tratados.

Descritores: *Hemorragia da coroide/etiologia; Doenças da coroide/patologia; Angiofluoresceinografia; Verde indocianina/uso diagnóstico; Coroide/irrigação sanguínea Doenças vasculares periféricas; Epitélio pigmentado ocular; Tomografia de coerência óptica; Relatos de casos*

INTRODUCTION

Idiopathic polypoidal choroidal vasculopathy (IPCV) is a vascular malformation of the choroid, comprising a network of branching vessels of varying sizes that produce aneurysmal-like enlargements. This disease is generally observed in the peripapillary area, and less commonly as an isolated macular lesion[1].

Frequently, the IPCV vascular network is associated with multiple episodic serosanguineous detachments of the retinal pigment epithelium and neurosensory retina, which occasionally lead to sub-retinal[1-3] and on rare occasions vitreous[4] hemorrhage. When the vascular network is beneath the atrophied pigment epithelium, a clinical diagnosis of IPCV is recommended if reddish orange, spheroidal, or polyp-like structures are observed. Nevertheless, in the majority of cases these lesions are not clearly visible, and indocyanine green angiography (ICG) is required for diagnosis[2,3].

ICG images illustrate two components of vascular abnormalities in the choroidal circulation: 1) a branching vascular network and 2) aneurysmal dilations at the end of the vascular network branch. These dilations can also be divided into two patterns: 1) large solitary round aneurysmal dilations, which usually present a stable and favorable clinical course and 2) a collection of small aneurysmal dilations resembling a cluster of grapes, which tend to bleed or leak and cause severe visual loss[5].

Optical coherence tomography (OCT) is another exam used to characterize the IPCV lesion[6], and is used mainly when retinal pigment epithelium and serous retinal detachment are suspected[7]. However, this approach has not yet been described in peripheral IPCV.

A major problem with the diagnosis of peripheral IPCV is that it masquerades as several mass lesions or tumors, such as acquired vasoproliferative disease, metastatic lesions to the choroid, choroidal melanoma, or choroidal osteoma. The goal of this case report was to elucidate the diagnosis of a temporal lesion that mimicked a tumor mass, as well as describe the follow-up approach for assessing treatment need if the patient's vision becomes threatened or compromised.

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CASE REPORT

A 68-year-old asymptomatic African American woman was referred to us with a suspected diagnosis of vascular choroidal tumor and choroidal capillary hemangioma. The patient had lived with systemic arterial hypertension for 18 years, which was treated with enalapril maleate® at 25 mg per day, and diabetes mellitus for 1 year, which was treated with metformin at 850 mg twice per day.

Upon initial examination, the patient's visual acuity was 20/20 in both eyes, she had no afferent pupillary defects, and had normal intraocular pressure measurements. Slit-lamp examination revealed only pinguecula on the right eye (OD) and asteroid hyalosis in the left eye (OS). Upon fundus examination of OD, there was an elevated lesion in the middle periphery of the inferior temporal region adjacent to multiple areas of pigment epithelium detachment (PED). In addition, at 2 o´clock in relation to the lesion, a peculiar, smaller elevation resembling a vascular tumor (Figure 1A) was observed.

The OCT examination of the major lesion in OD revealed a large PED with adjacent smaller lesions resembling a vascular tumor, and these observations were correlated with retinal serous detachment (Figure 2). Fluorescein angiography of OD showed a patchy area of subretinal staining of undetermined origin, with minimal leakage and a blockage area corresponding to the elevated lesion (Figure 1B). ICG revealed the presence of an inner choroidal vascular abnormality that ended in multiple small, hyperfluorescent polyps with leakage characteristic of IPCV, as well as a permanent blockage area observed during all phases of the angiogram, which corresponded to the major PED (Figure 1C). No macular changes were observed. One year later, there was decreased dimension and discoloration of the lesions, which now resembled a choroidal osteoma (Figure 3). After the initial visit no treatment was administered, because the macula was not threatened.

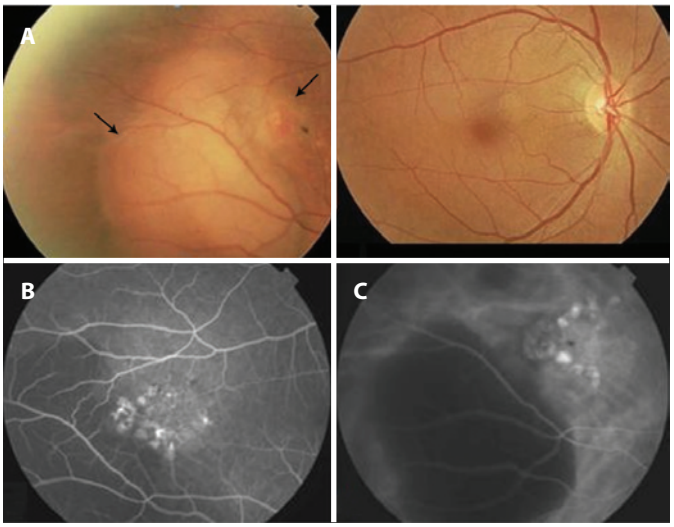

Figure 1. A) Fundus retinography demonstrating an elevated lesion in the mid-periphery of the inferior temporal vascular arcade, as shown by the long black arrow, and a lesion resembling the vascular tumor at the 2 o`clock position, as shown by the short black arrow. B) Right fundus. A middle phase of the fluorescein angiography showing minimal leakage and pooling. C) Indocyanine green angiogram showing the tubular elements ending in aneurysmal or polypoidal dilatations with little leakage of the dye. In both exams, the lack of fluorescence (i.e., black appearance) was due to major hemorrhagic pigment epithelium detachment.

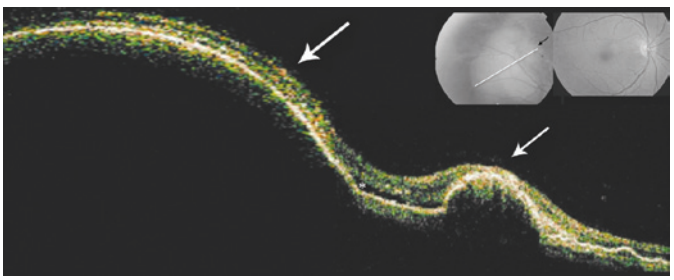

Figure 2. OCT showing the larger lesion, represented by the long white arrow, and the smaller lesion, represented by the short white arrow, corresponding to hemorrhagic pigment epithelium detachments (PED). Note the presence of serous retinal detachment, as shown by the asterisk, and multiples areas of PED on the right.

DISCUSSION

Recent findings have expanded our knowledge surrounding the nature of the vascular lesions that occur during the course of IPCV[4]. The most common region of occurrence is the peripapillary or macular area, and even in these cases the diagnosis is challenging due to variability in disease presentation, as well as the fact that this condition is uncommon and can only be confirmed using ICG[2]. Therefore, patients suffering from this disease are almost always initially diagnosed with malignant tumor lesions.

In the first case of peripheral IPCV[9], the patient demonstrated characteristic peripheral subretinal hemorrhage associated with hard exudates, and was free of systemic disorders. Our patient presented a similar lesion location (temporal inferior), but did not show hemorrhage or hard exudates, possibly due to its benign course.

In the case described here, the use of OCT was important, because it permitted the observation of multiple serosanguineous detachments of the retinal pigment epithelium, and neurosensory retina isolated between the two PED that was not threatened. Moreover, the approach enabled the detection of a major lesion that resembled a tumor, but was instead correctly identified as a major PED.

A major strength of this case, which we followed for one year, was that the differential diagnosis performed early after disease onset included vasoproliferative acquired disease, capillary hemangioma, focal posterior scleritis, and primary tumor. However, in the late phase (Figure 3), due to the appearance of discolored lesions likely associated with the absorption of blood, potential diagnoses suggested were metastatic tumors and choroidal osteoma.

Consistent with a previous report[2], ICG was essential in establishing a diagnosis of IPCV in this patient, because it uncovered polypoidal and aneurysmal dilations at the terminals of the branching vascular network[10]. The patient presented with a peripheral collection of small aneurysmal dilations, which is a risk factor for bleeding that can lead to vision loss and has a poor prognosis. However, the disease course in this patient has been benign and was appropriately identified within a year.

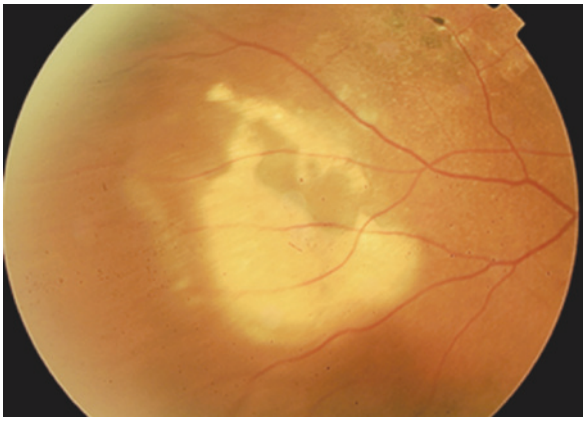

Figure 3. Peripheral retinography of OD a year after diagnosis of the lesion. Note that the lesions changed, showing discoloration and a decrease in dimension.

No treatment was administered to this patient, because there was no subretinal fluid accumulation, hard exudates, or hemorrhage threatening the fovea. This patient is currently under continued observation.

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Treatment of cystoid macular edema secondary to chronic non-infectious intermediate uveitis with an intraocular dexamethasone implant

Tratamento do edema macular cistóide secundário à uveíte intermediária não infecciosa com implante intraocular de dexametasona

Julia Dutra Rossetto[1], Heloisa Nascimento[1], Delia Diana Paola González Fernandes[1], Rubens Belfort Jr.[1], Cristina Muccioli[1]

ABSTRACT

Purpose: To evaluate the use of a slow-release dexamethasone 0.7-mg intravitreal implant for cystoid macular edema (CME) secondary to intermediate uveitis and refractory to systemic steroids.

Methods: A retrospective study of the best-corrected visual acuity (BCVA), intraocular inflammation, intraocular pressure (IOP), fundus photography, optical coherence tomography (OCT), inflammation, and adverse reactions of five patients (women, mean age of 35 years) with cystoid macular edema treated with a dexamethasone implant. Patients were evaluated in seven visits until the 150th day after the implant.

Results: Four patients had bilateral pars planitis and one had bilateral intermediate uveitis associated with juvenile idiopathic arthritis. Six dexamethasone devices were implanted, under topical anesthesia (one each in six eyes, five patients). The mean follow-up time was 5 months. The best-corrected visual acuity improved in all eyes that received an implant, with five having improvements of two or more lines. Optical coherence tomography showed thinning of the macula in all eyes treated, and we saw a correlation between the best-corrected visual acuity and retinal thinning. No serious adverse events occurred and no significant increase in intraocular pressure was observed.

Conclusions: Slow-release dexamethasone intravitreal implants can effectively treat CME secondary to intermediate uveitis and refractory to systemic steroids.

Keywords: Macular edema/etiology; Uveitis/complications; Tomography, optical coherence; Dexamethasone/therapeutic use; Visual acuity

RESUMO

Objetivos: *Avaliar o implante intravítreo de liberação lenta de dexametasona 0,7 mg no tratamento do edema macular cistóide (EMC) secundário à uveíte intermediária refratária a corticosteroides orais.*

Métodos: *Estudo retrospectivo da acuidade visual melhor corrigida, inflamação intraocular, pressão intraocular (PIO), retinografia, tomografia de coerência óptica (OCT), inflamação e reações adversas de cinco pacientes (mulheres, idade média 35 anos) com o edema macular cistóide tratado com implante de dexametasona. Pacientes foram avaliados em 7 consultas até o 150º dia pós implante.*

Rsultados: *Quatro pacientes apresentaram parsplanite bilateral e um, uveíte intermediária bilateral associada à artrite idiopática juvenil. Seis implantes foram inseridos sob anestesia tópica. O tempo médio de acompanhamento foi de 5 meses. A acuidade visual melhorou em todos os olhos. A tomografia de coerência óptica mostrou afinamento da mácula em todos os olhos e houve correlação entre a acuidade visual e a retina mais fina. Não ocorreu evento adverso grave. Não ocorreu aumento significativo na pressão intraocular.*

Conclusão: *O implante intravítreo é eficaz no tratamento do edema macular cistóide secundário a uveíte intermediária refratária a esteróides sistêmicos.*

Descritores: *Edema macular/etiologia; Uveíte/complicacões; Tomografia de coerência óptica; Dexametasona/uso terapêutico; Acuidade visual*

INTRODUCTION

Corticosteroids are the mainstay of non-infectious uveitis treatment. The use of local corticosteroids minimizes systemic adverse effects, but local use can lead to increased intraocular pressure (IOP), cataract, and endophthalmitis[1,2]. Cystoid macular edema (CME) is a major contributor to decreased visual acuity (VA) secondary to uveitis, and is usually treated with systemic, periocular, or intraocular steroids[1,2].

The dexamethasone 0.7-mg implant (Ozurdex® Allergan, Inc., CA, USA) is an innovative slow-release system that is biodegradable. It can be implanted through an injection system, and implantation can be performed on an outpatient basis.

Dexamethasone has potent anti-inflammatory properties and a history of favorable effects for the treatment of macular edema[3,4]. Previous studies have shown that implantation of the slow-release dexamethasone implant can improve visual acuity (VA) and macular thickness[3,4].

We evaluated the tolerability and effectiveness of the biodegradable intravitreal implant of 0.7 mg dexamethasone in patients with refractory CME secondary to intermediate uveitis.

METHODS

We retrospectively reviewed the medical records of patients with chronic CME secondary to non-infectious uveitis and refractory to systemic treatment with corticosteroids and/or cytotoxic drugs. The patients who received the dexamethasone implant had a minimum age of 18 years and a best-corrected VA (BCVA) of 20/60 or worse.

We evaluated patients demographics, etiology of the inflammation, BCVA, previous therapies, results of ocular examinations [inclu-

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ding biomicroscopy, IOP, indirect ophthalmoscopy, and optical coherence tomography (OCT)], and adverse reactions.

All patients had previously received systemic immunosuppressive therapy, including oral corticosteroids and methotrexate for patients 1 and 2; oral corticosteroids and ciclosporin for patients 3 and 4; and intravenous and oral corticosteroids, and azathioprine for patient 5. All patients were refractory to these treatments, as measured as BCVA improvement less than two lines at a minimum follow-up of 5 months.

Two patients had undergone a previous glaucoma surgery. Patient 1 had undergone a trabeculectomy 6 months prior, and on the same eye the dexamethasone device was implanted. Patient 3 had undergone phacoemulsification one year prior, and on the same eye the dexamethasone device was implanted. She had also received an Ahmed valve implant (New World Medical, Inc., CA, USA) 5 years prior, and on the same eye the dexamethasone device was implanted.

To determine the etiologies of the infectious and noninfectious diseases, analysis was performed using clinical, laboratory, and radiographic data.

The biodegradable dexamethasone implant was used according to published data(3-7) and according to the manufacturer's instructions (http://www.allergan.com/assets/pdf/ozurdex_pi.pdf).

After the implantation procedure, 0.3% gatifloxacin drops were administered for 4 days. The patients were evaluated in seven postoperative visits, occurring on days 1, 15, 30, 60, 90, 120, and 150 following implantation. During all visits, BCVA was measured, and anterior and posterior slit-lamp examination, Goldmann tonometry, dilated fundus examination, and OCT were performed. All patients were assessed for ocular inflammation and the need for additional intravitreal injections.

RESULTS

Six eyes of five patients received a dexamethasone 0.7-mg sustained-release intravitreal implant to treat intermediate non-infectious uveitis. Patient demographic data, diagnosis, and examination findings are summarized in table 1. The mean follow-up time post-implantation was 5 months.

BCVA improved in all eyes, with five eyes having an improvement of two or more lines of VA. OCT measurement of macular thickness revealed improvement in all eyes (Figure 1). We identified a correlation between BCVA and thinning of the macula, as evaluated by OCT. The mean duration of implant effectiveness was 3.6 months (range 3-4 months), with a standard deviation of 0.55.

No serious ocular or systemic adverse events occurred during the follow-up period. Subconjunctival hemorrhages developed at the site of implant injection in two cases.

IOP observed during the follow-up visits was 22 mmHg or less in all eyes, and the range of IOP was between 2 and 6 mmHg in all patients. Two patients had a 6 mmHg range in IOP and also previously had glaucoma surgery. The other patients had variations in IOP of 3 mmHg or less (Table 2).

DISCUSSION

Treating patients with severe uveitis, the fifth leading cause of vision loss in the United States, is a major challenge in ophthalmology. Although the administration of systemic corticosteroids, immunosuppressive agents, or a combination of both is considered the gold standard treatment for this disease, complications and side effects may result from long-term treatment and are major concerns. These drugs may also not be available for the treatment of ocular diseases in developing countries.

Systemic corticosteroids are often accompanied by a poor safety profile characterized by multiple adverse effects, such as fluid retention, hypertension, hyperglycemia, osteoporosis, mood changes, psychosis, and greater susceptibility to infections[5]. Immunosuppressive agents can also be unsafe for women of child bearing age, because these drugs increase the risk of fetal malformations.

The Systemic Immunosuppressive Therapy for Eye Diseases study recently reported data on both overall and cancer-related mortality following inflammatory disease treatment with immunosuppressants or biologic drugs[9]. Preliminary findings from this study have suggested that cancer and total mortality may increase with the use of anti-tumor necrosis factor agents, though this must be confirmed in further studies. In addition to these safety concerns, biologic drugs also pose difficulties with respect to third-party payment and their overall cost[9,10]. For these reasons and due to the absence of solid medical evidence, biologic treatments may not be the treatment of choice for uveitis.

Uveitis is particularly difficult to treat due to the blood-retinal barrier, which significantly reduces the ability of topical and systemic medications to reach effective concentrations in posterior ocular structures. In addition, adequate vitreous and retinal concentrations of corticosteroids for the treatment of posterior inflammation should ideally be achieved through local therapies that do not have adverse systemic effects[5]. Due to these concerns, local treatment for uveitis has gained popularity in recent years. Local injections of corticosteroids, such as intravitreal injection of triamcinolone, can effectively control uveitis and eliminate the use of systemic medications[11]. Moreover, the Ozurdex implant is increasingly being used as a local therapy to treat ocular diseases. Safety and efficacy of Ozurdex in the treatment of macular edema due to retinal vein occlusion has been demonstrated,[7] and the US Food and Drug Administration has approved it for intravitreal use in macular edema secondary to non-infectious uveitis or retinal vein occlusion. The implant has also been approved in Brazil. This medication has also been tested off-label in the treatment of non-necrotizing scleritis with positive results[6].

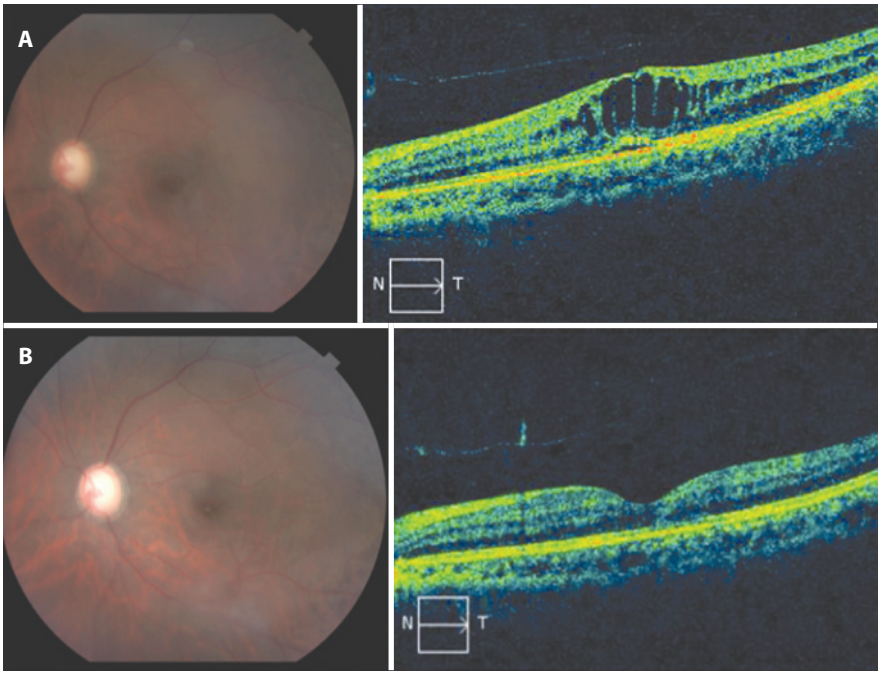
Previous studies, such as the Multicenter Uveitis Steroid Treatment (MUST) trial[8], which were designed to compare the fluocinolone acetonide implant to standard systemic therapy for the treatment of patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis, found that both treatments improved vision similarly over two years.

In this study, we treated five patients with an intravitreal dexamethasone implant (Ozurdex). Four of these patients had idiopathic

Table 1. Patient demographic data

Patient	Age	Diagnosis	Basal VA	OCT (µ)	Follow-up (months)	Final VA	Final OCT (µ)
1	19	IIU	20/400	670	5	20/80	213
			20/60	461		20/40	217
2	22	JIA	20/60	558	5	20/40	259
3	48	IIU	20/160	450	5	20/80	273
4	66	IIU	20/400	472	5	20/100	345
5	20	IIU	20/80	404	5	20/50	261

IIU= idiopathic intermediate uveitis; JIA= juvenile idiopathic arthritis.



N= nasal; T= temporal.
Figure 1. Patient 3 - representative case. A) OCT of the left eye before treatment. B) OCT of the left eye 5 months after treatment.

Table 2. Visual acuity, IOP, and OCT follow-up

Patient	Initial VA	15th day VA	120th day VA	Initial IOP	15th day IOP	120th day IOP	Initial OCT	15th day OCT	120th day OCT
1	20/400	20/200	20/80	12	12	15	670	470	222
	20/60	20/60	20/32	16	22	20	461	298	201
2	20/60	20/60	20/40	16	18	16	558	412	239
3	20/160	20/80	20/60	15	16	14	450	337	244
4	20/400	20/100	20/60	12	14	14	472	309	271
5	20/80	20/40	20/32	14	14	16	404	248	223

IOP= intraocular pressure; OCT= optical coherence tomography.

intermediate uveitis and one had juvenile idiopathic arthritis. In these cases, local treatment is advantageous because systemic diseases are not masked, which enables accurate diagnosis and management in patients with subclinical disease. The dexamethasone implant controlled ocular inflammation and reduced macular edema, and had a mean duration of effect of 3.6 months. This effect duration was lower than the previously reported effect duration of 6 months[5]. One possible contribution to this difference may be related to previous anti-glaucomatous surgery in patients 1 and 3, which may have increased aqueous humor outflow and drug clearance.

Of the patients studied here, IOP only increased in patients with a history of glaucoma, and these increases may be related to steroid responsiveness. However, their IOP measures remained within the range of the general population following implantation. According to the American Academy of Ophthalmology, in normal individuals, IOP varies 2-6 mmHg over a 24-hour period. Perhaps these patients would have a greater increase in IOP if they had not undergone prior surgery. A possible treatment complication that we did not evaluate here is the development of cataract secondary to the use of a corticosteroid. We did not examine this because our follow-up period was not long enough, and controlled prospective studies are needed to examine this potential complication.

CONCLUSION

The dexamethasone 0.7-mg implant is effective and safe for the local treatment of chronic CME secondary to non-infectious intermediate uveitis and refractory to systemic steroids.

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Safety and feasibility of the use of a bevacizumab-methylcellulose mixture as an adjunct to glaucoma surgery: a pilot study

Segurança e viabilidade do uso de uma mistura de bevacizumabe-metilcelulose como terapia adjuvante à cirurgia anti-glaucomatosa: um estudo piloto

Jayter Silva Paula[1], Danilo José Lopes Secches[1], Marcelo Jordão Lopes Silva[1], Maria de Lourdes Veronese Rodrigues[1], Armando da Silva Cunha Junior[2]

ABSTRACT

Bevacizumab, a monoclonal anti-vascular endothelial growth factor antibody, has been suggested as a potential healing therapeutic following glaucoma surgery. Here, we aimed to improve the bioavailability of bevacizumab when used as an adjunct therapy to non-penetrating deep sclerectomy (DS) by using a bevacizumab-methylcellulose mixture (BMM). Ten previously non-operated eyes in ten patients diagnosed with primary open angle glaucoma underwent DS with a subconjunctival injection of 0.3 ml of BMM (bevacizumab 3.75 mg incorporated into 4% methylcellulose) at the surgical site. Bevacizumab release was evaluated *in vitro* using size-exclusion high performance liquid chromatography (HPLC). Intraocular pressure (IOP), bleb morphology, corneal endothelial cell count (CECC), and complications were evaluated at 6 months after surgery. Using HPLC, bevacizumab was detected in BMM for up to 72 h. Moreover, all surgical blebs remained expanded with hyaline material during the first week. A significant IOP reduction (mean ± SD= -10.3 ± 5.4 mmHg, P<0.001) and diffuse blebs were observed at the final follow-up period. Although CECC was slightly reduced (-7.4%), no complications were observed. In conclusion, bevacizumab was released from BMM, and the use of this innovative mixture yielded good results following DS with no complications. Further studies are required to determine its efficacy prior to establishing BMM as an adjunct treatment for penetrating and non-penetrating glaucoma surgeries.

Keywords: Trabeculectomy/adverse effects; Glaucoma/surgery; Sclerectomy; Antibodies, monoclonal, humanized/therapeutic use; Methylcellulose/therapeutic use; Mitomycin/therapeutic use; Chemotherapy, adjuvant; Intraocular pressure/physiology

RESUMO

O bevacizumabe (um agente anti-fator de crescimento endotelial vascular) tem sido sugerido como potencial modulador cicatricial na cirurgia do glaucoma. Este estudo objetivou melhorar a biodisponibilidade do bevacizumabe, investigando a viabilidade de uma nova mistura de bevacizumabe-metilcelulose (BMM) como terapia adjuvante para a esclerectomia profunda não-penetrante (DS). Dez olhos sem cirurgias prévias de 10 pacientes com glaucoma primário de ângulo aberto foram submetidos à DS associada à uma injeção subconjuntival de 0,3 ml da mistura de bevacizumabe-metilcelulose (bevacizumabe 3,75 mg incorporado em metilcelulose 4%) no sítio cirúrgico. A liberação de bevacizumabe foi avaliada in vitro *através de cromatografia líquida de alta performance por exclusão de tamanho (HPLC). A pressão intraocular (PIO), a morfologia da ampola de filtração, a contagem de células endoteliais da córnea (CECC) e as complicações foram estudadas aos seis meses de seguimento. O bevacizumabe foi detectado a partir da mistura de bevacizumabe-metilcelulose por meio do HPLC até 72 horas. Além disso, todas as ampolas cirúrgicas permaneceram expandidas com material hialino durante a primeira semana. Uma redução significativa da pressão intraocular (média ± DP= -10,3 ± 5,4 mmHg, P<0,001) e ampolas difusas foram observadas ao final do período de seguimento. Embora a contagem de células endoteliais da córnea se mostrou discretamente diminuída (-7,4%), nenhuma complicação foi observada. Neste estudo, o bevacizumabe foi liberado da mistura de bevacizumabe-metilcelulose e o uso desta nova mistura se associou com bons resultados cirúrgicos e nenhuma complicação. Estudos futuros serão necessários para determinar sua eficácia, antes de se estabelecer a mistura de bevacizumabe-metilcelulose como um tratamento adjuvante às cirurgias penetrantes e não-penetrantes para o glaucoma.*

Descritores: *Trabeculectomia/efeitos adversos; Glaucoma/cirurgia; Esclerostomia; Anticorpos monoclonais humanizados/uso terapêutico; Metilcelulose/uso terapêutico; Mitomicina/uso terapêutico; Quimioterapia adjuvante; Pressão intraocular/fisiologia*

INTRODUCTION

Non-penetrating deep sclerectomy (DS) is a glaucoma surgery that aims to minimize the complications of trabeculectomy (TRAB), which often arise due to penetration of the anterior chamber. Nevertheless, excessive cicatrization of the surgical site may also limit the success rates of DS[3]. The fibrosis of subconjunctival tissues is considered to be the leading cause of failure of glaucoma surgery. This problem is mitigated by using mitomycin C (MMC) and 5-fluorouracil (5-FU) as adjunctive treatments[1]. However, complications frequently occur with these therapies, prompting investigation into alternative drugs for managing post-operative failure[1,2].

Therapies that have been investigated in an attempt to minimize the adverse effects of using MMC and 5-FU include the administration of bevacizumab [monoclonal antibody directed to vascular endothelial growth factor (VEGF); Avastin® Genentech, San Francisco, California, USA][4] and methylcellulose[5] into the subconjunctival spa-

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ce. Bevacizumab may enhance the outcomes of glaucoma filtration surgery because VEGF is not only involved in angiogenesis but has been shown to display direct activity on fibroblast-related healing processes[6]. As a potential way to improve surgical success, prolonging the bioavailability of bevacizumab using slow delivery systems could result in improved outcomes compared with isolated bevacizumab eye injections. We have recently shown that using implants containing bevacizumab in an experimental glaucoma surgery is feasible, and has promising results[7]. Based on the promising findings of using bevacizumab and methylcellulose compounds in glaucoma surgery, we evaluated the safety and feasibility of a bevacizumab-methylcellulose mixture (BMM) as an adjunct therapy to DS.

METHODS

This prospective non-randomized interventional case series followed the principles outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee (process # 5159/2009). Ten patients diagnosed with primary open-angle glaucoma (POAG) and indicated for glaucoma surgical treatment were included, and observed at the University Hospital of Ribeirão Preto Medical School.

The following diagnostic criteria were used to diagnose POAG: intraocular pressure (IOP) greater than 21 mmHg irrespective of medical treatment, typical glaucomatous changes in the optic disc, and reliable visual field defects compatible with glaucoma in the achromatic perimetry.

All patients who underwent surgery met the following inclusion criteria: age between 18 and 80 years, POAG diagnosis, confirmed evidence of the progression of glaucoma damage, and two IOP measurements higher than the individualized target IOP. Patients were excluded if they had other forms of glaucoma, previous glaucoma filtration surgery, rubeosis iridis, other severe retinal or corneal diseases, well-known history of adverse effects to bevacizumab, or were pregnant or breast feeding women. All patients underwent typical DS, with stripping of the external wall of Schlemm's canal on the same day[7]. At the end of the surgery, the patients received a 0.3 mL subconjunctival injection of BMM (bevacizumab 3.75 mg incorporated into 4% methylcellulose) at the surgical site by the same surgeon (MJLS). BMM was prepared by ultracentrifugation 24 h prior to surgery, in a local compounding pharmacy.

In order to detect free bevacizumab, five 0.5 ml samples of BMM were evaluated by size-exclusion high performance liquid chromatography (HPLC) using 50 µL of BMM with a flow rate of 1.0 mL/min, at 72 h (Waters BioSuite 250, 5 µm, HR SEC - 7.8 × 300 mm, pH 7.4, absorbance at 279 nm)[8]. A HPLC column was used in which the mobile phase comprised PBS at a pH of 7.4. An ultraviolet detector (model 2487, Waters, USA) was used at a wavelength of 279 nm, and the area under peak was used to determine the quantity of the drug in the test solution.

The following clinical outcomes were evaluated 6 months following surgery: IOP reduction (variation from pre- to post-operative average of three Goldmann tonometry readings taken between 08:00 h and 10:00 h), bleb's morphology (using the Moorfields bleb grading system)[9], visual acuity (using charts with the logarithm of the minimum angle of resolution notations, logMAR), corneal endothelial cell count (CECC; using specular microscopy, ROBO NSP-9900, Konan, Japan), and complications. Data was presented as median with 25th to 75th interquartile range (IR) for scores, and mean with standard deviation (SD) for numerical data. The paired Friedman test was used to compare the results (Prism 5.0a; GraphPad Software Inc., CA, USA), and a p-value of <0.05 was defined as significant.

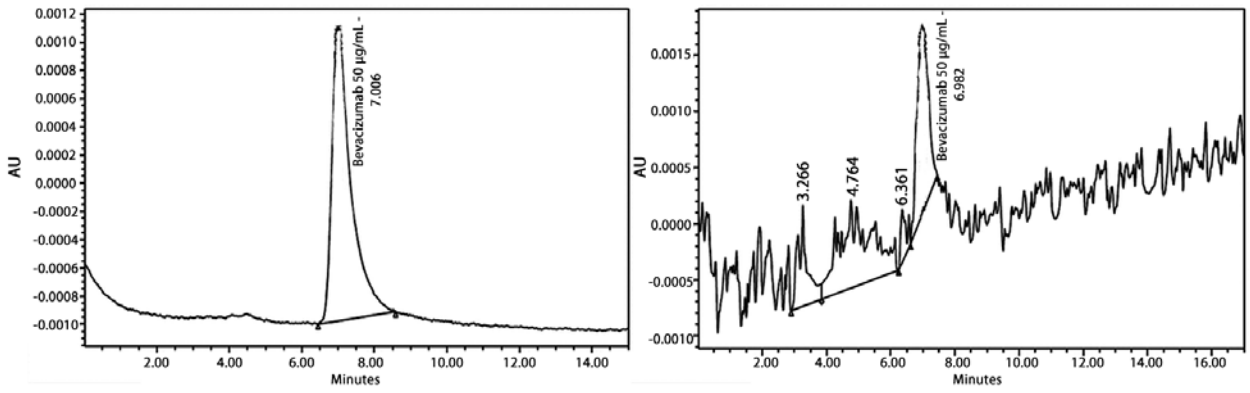
RESULTS

Ten caucasian patients (six males and four females, with a mean age of 56.4 ± 12.7 years) completed the procedure and 6 month follow-up. At the end of the follow-up, a significant IOP reduction was observed (20.7 ± 5.5 mmHg pre-operative vs 10.4 ± 2.5 mmHg post-operative; -10.3 ± 5.4 mmHg, P<0.001), and all patients exhibited diffuse blebs with low degrees of vascularity [median scores, with IR in parentheses - central area: 3.0 (3.0 to 3.75); maximal area: 3.5 (3.0 to 4.0); height: 2.0 (2.0 to 2.75); and vascularity: 2.0 (2.0 to 3.0)]. No significant difference was observed between the mean best-corrected pre-operative visual acuity score and that evaluated at the last visit (0.10 ± 0.02 and 0.15 ± 0.03, respectively). CECC was 7.4% lower 6 months after surgery (2529 ± 464 cells vs 2341 ± 432 cells, P=0.008). No complications were observed throughout the duration of the study.

HPLC detected bevacizumab in BMM at a mean retention time of 6.98 min across the five samples evaluated at 72 h (mean of 75.1% of free drug), close to the well-defined peak of free bevacizumab at 7.01 min (Figure 1)[5] BMM could be observed in the bleb areas of all patients during the first week (Figure 2). The blebs remained expanded with the hyaline material, but the liquid interface of aqueous humor could not be visualized during the slit-lamp examination.

DISCUSSION

Here, we show that BMM is a safe, feasible system for the delivery of bevacizumab during the early post-operative period following DS. Our results suggest that bevacizumab is available at the surgical site for a longer period of time than that following simple subconjunctival



AU= Absorbance unit (279 nm) × 10^4.

Figure 1. Size-exclusion high performance liquid chromatograms of 50 µL of bevacizumab (left) and one sample of BMM (right), at a flow rate of 1.0 mL/min (Waters BioSuite 250, 5 µm, HR SEC – 7.8 × 300 mm, 72 h).

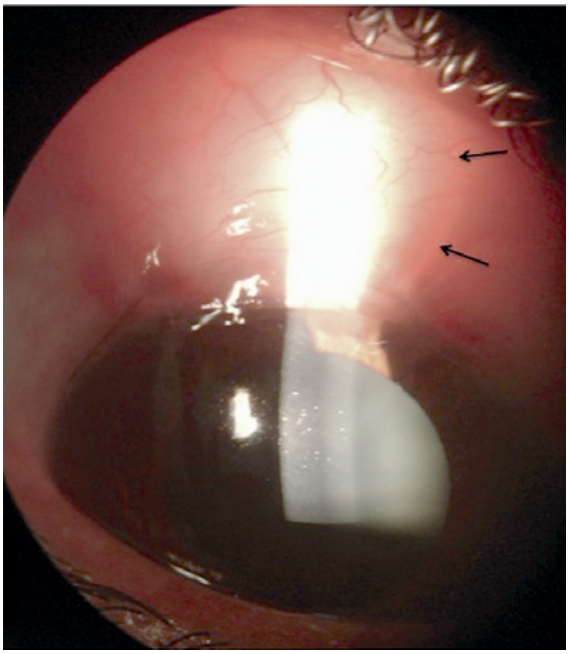


Figure 2. Slit-lamp photograph of the surgical site on the seventh day following deep sclerectomy augmented with BMM (patient #5). Note the elevated bleb with the subconjunctival hyaline material (arrows).

injection of the antibody. Moreover, both bevacizumab and methylcellulose have previously shown benefits in terms of enhancing the healing process following glaucoma surgery[4,5]; thus, delivering both compounds may increase the therapeutic effect.

We could not determine whether there was a synergistic effect between bevacizumab and methylcellulose in this study, but we believe that BMM may act as a slow delivery system for bevacizumab to the subconjunctival space, particularly during the first week post-surgery. The artificial expansion of bleb volume with this viscoelastic product may also contribute additional benefits, primarily in the first phase of the healing process[7].

Although CECC was significantly lower after surgery than before, this reduction was proportional to those reported in previous TRAB and DS studies[3,10]. We speculate that the non-penetrating procedure performed in our cases may help in limiting permeation of BMM into the anterior chamber, and may explain the reduction observed in CECC.

The limitations of this study, which include the absence of a control group, a small number of patients, and a short post-surgery evaluation period, should be addressed by future long-term follow-up randomized controlled trials. Moreover, use of BMM may result in higher costs related to the surgical procedure, and could add potential unforeseen complications related to both bevacizumab and methylcellulose administration. However, all patients enrolled in this study displayed good surgical results, and no complications were observed. Thus, efficacy and cost-effectiveness of BMM should be further verified prior to establishing it as an adjunctive therapy to DS, or other penetrating glaucoma surgeries.

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Association between visual impairment and depression in the elderly: a systematic review

Associação entre deficiência visual e depressão em idosos: uma revisão sistemática

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ABSTRACT

A systematic review was conducted to investigate the relationship between visual impairment and depression in the elderly. We searched electronic databases (LILACS, SciELO, MEDLINE, and Cochrane Central Register of Controlled Trials) from inception to August 2014 and researched the described references. The search strategy used the following terms: (visual impairment or blindness) and (elderly) and (depression). Of the 641 electronics, 42 works were selected in full and another 20 were identified as being possibly relevant. Ten studies were included. The studies ranged in sample size from 31 to 21,995 participants. Depression was associated with visual impairment in all studies; however, without standardization of diagnostic tests, we could not conduct a meta-analysis or establish a relationship between visual impairment and depression in the elderly.

Keywords: Visual impairment; Depression; Aging; Blindness; Vision loss

RESUMO

A revisão sistemática foi realizada para investigar a correlação entre deficiência visual e depressão em idosos. Foram pesquisados nas bases eletrônicas (LILACS, SCIELO, MEDLINE e Cochrane Central Register of Controlled Trials) do início até agosto de 2014 e pesquisas de referências descritas. A estratégia de busca utilizou os termos: (deficiência visual ou cegueira) e (idosos) e (depressão). Dos 641 eletrônicos, 42 trabalhos na íntegra foram selecionados e mais 20 trabalhos foram identificados como possivelmente relevantes da lista destes. Do total de estudos, 10 foram incluidos. Os estudos variaram entre 31 e 21.995 participantes. A depressão foi relacionada com deficiência visual em todos os estudos, mas sem padronização de testes diagnósticos não foi possível realizar a metanálise, nem estabelecer relação entre deficiência visual e depressão em idosos.

Descritores: *Deficiência visual; Depressão; Idoso; Cegueira; Perda visual*

INTRODUCTION

Visual impairment (VI) is becoming a major public health concern with the aging of the population. It is the third most prevalent physical impairment among older adults[1]. Visual impairment affects one-third of elderly subjects, with the prevalence of mild or severe VI ranging from 4% to 12%[2,3]. Ultimately, untreated eye disorders can contribute to avoidance of social situations, resulting in social isolation or leading to substantial physical decline, which may ultimately require a transition into an assisted living arrangement[4]. A number of studies suggest that disability may contribute to depression[5]; depression is the most common psychiatric disorder and carries a high burden in terms of treatment costs, effect on families and carers, as well as loss of workplace productivity[6]. The World Health Organization (WHO) currently ranks it as the third most prevalent moderate and severe disabling condition globally. It may become a chronic disorder with ongoing disability, particularly if inadequately treated, contributing to the global burden of disease[7]. Results from a number of population-based[8-12] and hospital-based studies[13,14] indicate that VI is associated with higher rates of depression.

This review aimed to verify whether there is an association between VI and depression in the elderly.

METHODS

The PRISMA guidelines[15] were followed for this review, and the sections below are set out according to these guidelines.

Articles that reported depression, as analyzed by the Geriatric Depression Score (GDS) or another specific scale, in adults aged 65 years and older with VI (visual acuity worse or equal to 20/70 or 0.55 in logMAR) or mild VI (visual acuity worse than 20/40 or 0.3 in logMAR) were included[16]. Cross-sectional, cohort studies, or case-control studies were also included. Any setting was permitted (primary care, secondary care, or general population), although the search was limited to articles in English or Portuguese. Review studies, unpublished articles, abstracts, theses, dissertations, and book chapters were not included. Articles regarding dual sensory loss (hearing and VI) were excluded, as were studies about a single ocular disease and those not reporting about VI as the primary objective.

The primary outcomes associated with the aim of this review were depression, most frequently evaluated using GDS[17] or the Center for Epidemiologic Studies-Depression scale (CES-D)[18] and visual acuity. Secondary outcomes analyzed included sociodemographic variables (age, gender, marital status, ethnicity, years of education, living alone or not, social activities), visual function (VF questionnaires), visual field, disability [analyzed by the Community Disability Score (CD-30) or Activities of Daily Living (ADL)], chronic disease, mortality, anxiety [measured using the State-Trait Anxiety Index (STAI-6) or General Health Questionnaire Score (GHQ-28)], physical activity, quality of life [measured using Short-Form Health Surveys (SF)], number of antidepressive medications, previous history of depression, duration of institutionalization if present, and duration of VI.

To gather as many studies as possible on the issue, the strategy for data collection aimed to identify articles that presented the de-

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finition of VI and depression in the elderly. The following electronic databases [LILACS, SciELO, MEDLINE (via PUBMED), and Cochrane Central Register of Controlled Trials (CENTRAL)] were searched, from inception to August 2014. Two independent reviewers conducted the search using the same keywords. The search strategy used the following terms: (visual impairment OR blindness) and (elderly) and (depression). Cited references were also evaluated.

Abstracts thought to be relevant were retrieved for closer inspection. If meeting the inclusion criteria, the full text of the article was located. The reference lists of all full-text articles identified during the electronic search were scanned for further articles that may be relevant. In addition, we scanned all related references of the full-text articles meeting the inclusion criteria. Data were independently extracted by two reviewers to ensure accuracy using a standard data table extraction that includes details about the studies such as name, author, year, periodical and database, country, number of participants, study design, variables, limitations, and main results. All included studies were subjected to methodological critical appraisal using the Cochrane Collaboration of risk of bias: the Newcastle-Ottawa Scale, adapted version[19]. The original Newcastle-Ottawa Scale[20] is used to analyze quality in observational studies. It has eight questions that access three dimensions: selection, comparability, and results (in cohort studies) or exposition (case-control studies). For each question, there are several options, and each option that is associated with the best quality is scored with a star; the more stars a study has, the better is its quality.

In this review, the questions were adapted to investigate exposition and outcome (depression), and the risk of bias was classified as low, unknown, and high risks; each star represents a low risk of bias. Two independent reviewers assessed the quality of studies.

For dichotomous outcomes, we intended to use the odds ratio (OR) and 95% confidence interval (CI) calculated using a random-effect model (REM). When the effect is absent, the risk difference (RD) and 95% CI is calculated using REM. For continuous outcomes, the mean and standard deviation are used to generate the mean difference (MD) and 95% CI using REM. BioEstat version 5.3 was used to conduct meta-analyses. Statistical heterogeneity (I^2) was assessed using heterogeneity tests, i.e., the standard chi-square test (p value <0.10 or <10%) and the I^2 test (I^2 >50% was considered statistically significant).

RESULTS

Study selection

Of the 641 search results, 42 full-text articles were retrieved. The reference lists of each of these articles were scanned, and further 20 articles were identified as being possibly relevant. Of the total studies identified, 10 were considered relevant and have been evaluated (Figure 1).

Study characteristics

A summary of the main results of the review is presented in table 1. Of the 10 studies included, the number of participants ranged from 31 to 21,995); two were conducted in the United States, two in Canada, one in New Zealand, one in France, two in China, one in Malaysia, and one in England. Five of the articles reported cohort studies and five others were cross-sectional studies. According to the Newcastle-Ottawa Scale, most articles had a low bias risk (Table 2).

Measures of depression

Depression was measured using a number of different tools, the most popular being GDS-15, used in eight studies. GDS-15is a self-administered questionnaire consisting of 15 items that are related to depression. It was specifically developed for older people and places less emphasis on somatic symptoms than other generic depression scales. It asks respondents to answer "yes" or "no" to 15 questions about how they have felt in the past week. GDS-15 is a screening tool for depression rather than an assessment scale providing a clinical diagnosis of depression; the level of depressive symptomatology is related to the level of depression. In these studies, the cut-off for depression ranged into four or more[21], five or more[22,23], six or more[24-26], and 11 or more[27]. Another questionnaire that was used was CES-D, used in two studies[4,12]. CES-D records the frequency and severity of depressive symptoms over the preceding week via a 20-item questionnaire. Each item is scored on a scale from 0 (less than 2 days duration) to 3 (5-7 days, both days inclusive), and a score of 16 or more indicates major depression. One of the studies[28] used depression diagnosis based on the International Diseases Code (ICD-10). Because of this heterogeneity, meta-analysis was not possible with this variable.

Measures of visual acuity

Visual acuity was presented as logMAR, decimal, or fraction standards and was measured using the Snellen chart (seven studies), Glasgow acuity chart (one study), ETDRS chart (one study), or subjective vision (one study). One study considered as VI a visual acuity less than 20/80 and analyzed visual function with the VF-14 score, which records the degree of deficiency in vision affecting-daily activities, and visual acuity to high and low contrast[21]. Another study analyzed three groups: one with no VI (visual acuity of 6/6 or better), one with

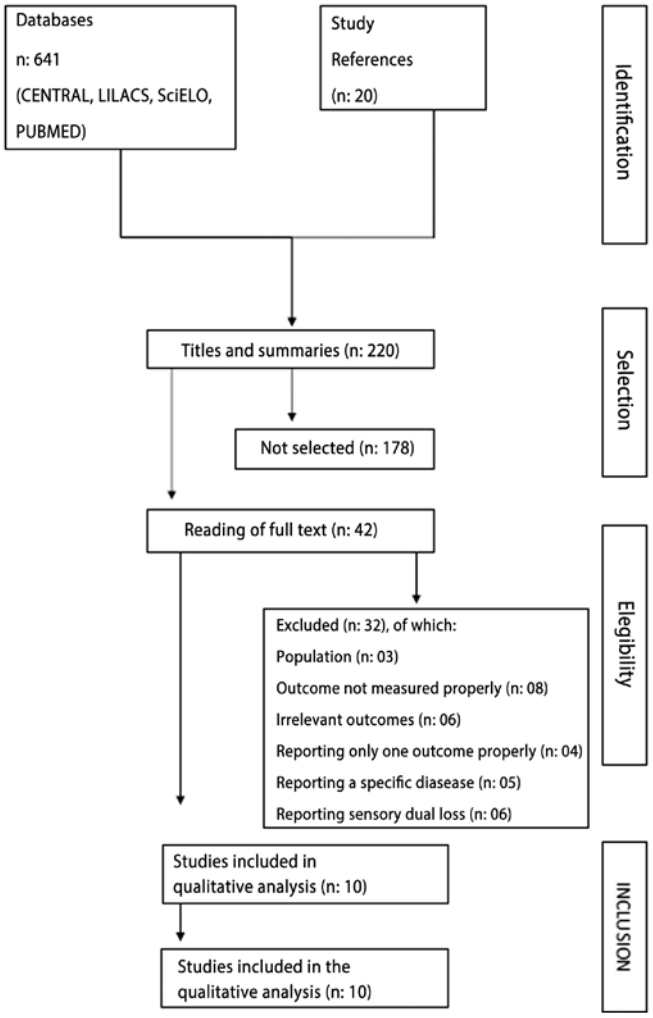

Figure 1. Flow diagram summarizing the process for selecting original articles for review.

Table 1. Factors associated with depression in the elderly according to observational studies

Author, year	Study design	Continuous outcomes	Categorical outcomes	Associated to depression	Not associated to depression	Study limitations
Rovner, 1996[27]	Panel study (2 year follow-up)	Age, education, diseases, time of VI, depression, disability	Depression (GDS), disability (CD score)	VI, disability	Neither of other variables had association	Small sample; only analyses distant VA, no specific disability scale, cross-sectional
Rovner, 1998[12]	Transversal	Age, gender, education, race, VI, limitations in daily activities	Depression	Disability	Education	Cross-sectional small sample
Ip, 2000[4]	Transversal	Age, time of institutionalization, duration of VI, disability	Depression	Severity of VI	Duration of blindness	Not described
Tsai, 2003[23]	Population-based survey	Age, education,	Cardiovascular diseases, gender, VI, stroke, DM	Age, gender, cardiovascular disease, stroke	Education	Lack of specialized psychiatric avaliation; other diseases and medications not analyzed
Haymann, 2007[21]	Cross-sectional	Age, gender, education, race, VI, instrumental activities of daily living	Depression (mCES-D)	Physical function, visual function, anxiety	Age, gender, living situation, ethnicity, antidepressant	Cross sectional; not enough participants, over reported disability
Evans, 2007[24]	Cross sectional	Age, VA	Depression, anxiety	VI	Anxiety	Cross sectional
Tournier, 2008[28]	Retrospective fixed cohort study	Age, chronic disease	Depression mortality	VI, previous history of depression	Severity of vision loss	Use of databases, Cohort based on the date of diagnosis, VI may have started before, patients not followed regularly
Noran, 2009[25]	Transversal	Age, gender, ethnic group, education, marital status, VI, duration of VI	Depression (GDS)	Severity of VI,	Don't describe	Cross-sectional
Popescu, 2012[22]	Cohort	Age, binocular VA, visual field, mini mental score, life space assessment	Depression	ARMD, glaucoma, and Fuchs distrophy	Mean age, ethnicity	Not longitudinal, depression limit in GDS was 5.0
Carrière, 2013[26]	Cohort	VI, socio-demographic, and clinical variables	Depression	Baseline loss	2-year decrease in distance VA	Functional vision was poorly measured

VI= visual impairment; VA= visual acuity; DM= diabetes mellitus.

Table 2. Avaliation of bias risk using the adapted Newcastle-Ottawa Scale[20]

Article (year)	Acessing independent variables	Is depression avaliation adequate?	Sample representivity	Participants selection	Definition of control group or cohort*
Rovner (1996)[17]	H	L	H	H	U
Rovner (1998)[12]	H	I	L	L	-
Ip (2000)[4]	L	L	U	H	-
Tsai (2003)[23]	L	U	L	L	I
Haymann (2007)[21]	H	L	H	H	-
Evans (2007)[24]	L	L	L	L	-
Tournier (2008)[28]	L	U	L	L	L
Noran (2009)[25]	L	L	L	H	-
Popescu (2012)[22]	L	L	H	H	U
Carrière (2013)[26]	L	U	L	L	L

L= low risk of bias; U= uncertain risk of bias; H= high risk of bias.
*= only for longitudinal studies.

moderate VI (6/6 to 6/18), and one with worse VI (worse than 6/18 or 20/60)[24]. Some studies considered visual acuity less than 20/70 (based on ICD-9 and -10) as VI[4,23,25]; however, only one study measured near and distant visual acuities[4]. Two studies considered VI as visual acuity less than 20/40 or visual field defects[22,23]. One study analyzed blindness (visual acuity of 20/400 or worse)[26] and another analyzed visual loss with a subjective questionnaire of self-reported activities that the person can or cannot answer because of his vision[12]; it was not possible to perform meta-analysis with this variable because visual acuity was measured using different methods in each article.

Depression and visual impairment

Despite heterogeneity between the groups of visually impaired subjects and the group of depressed subjects, it was not possible to perform statistical analysis.

Anxiety and depression

Anxiety was just analyzed in two studies. In one study, it was recorded using STAI-6 and was associated with VI and depression[21]. Another study used GHQ-28[24] to analyze anxiety, and it was not possible to perform meta-analysis.

Quality of life and depression

Quality of life was analyzed in one study[21] by the SF-36 score and had an association with depression with regard to a low quality-of-life score. SF-36 generates a Mental Component Summary (MCS) and a Physical Component Summary (PCS) score. SF-36 can also be considered a disability measure because the questions are worded to reflect limitation in ability related to health issues.

Limitation in daily activities and depression

A limitation in daily activities and depression was measured using the Nottingham Extended Activities of Daily Living Index (NEADL) in one study[21]. In this scale, a low score suggests that the person is dependent in his activities. In another study, ADL was used[12].

Physical activity and depression

This variable was measured in only one study[21] using the Human Activity Profile (HAP), which records the respondent's highest level of energy expenditure and generates the maximum activity score.

Disability and depression

Mobility in one study was measured using the Life Space assessment (LS-C-120), a questionnaire that records the frequency of going to different level spaces at home and outside in a month[22]. Disability was also analyzed in one study[27] using CDS-30 and in another using the Oregon Administrative Rules (OAR) instrument[12]. It was impossible to perform meta-analysis for this factor.

Mortality and depression

Mortality and depression was analyzed only in one study[28], because of this, it was not possible to perform meta-analysis.

Chronic diseases and other comorbidities in depression

Two studies reported an association between chronic diseases and depression, measured using CDS; another study just analyzed specific diseases such as diabetes, cardiovascular diseases, and stroke[23,28] using two different methods; therefore, it was not possible perform statistical analysis.

Ocular diseases and depression

One study compared three ocular diseases as the cause of VI[22]. Age-related macular degeneration (ARMD) was compared in two other studies to the prevalence of other ocular diseases (ARMD 61.4%, cataract 31.4%, glaucoma 21.4%, diabetic retinopathy 15.7%, and others 5.7%) in visually impaired participants[21,27]. Therefore, it was not possible to compare these different data.

Risk of bias in the articles

Most articles had L and U (low and uncertain risk) in the major items of the quality scale used. The risk of bias in the studies included is summarized in table 2.

DISCUSSION

Depression is a major public health concern among the elderly. It causes suffering, family disruption, disability, worsening of the outcome of many medical illnesses, and increased mortality[29]. The prevalence of depression among the elderly varies. Almost 3% of the general elderly population suffers from major depression; 8%-16% of the elderly have clinically significant depressive symptoms[30].

Rates of VI in the elderly increase with age and are associated with functional loss, mortality as well as psychological distress, sense of loneliness, and depression. Given that depression is treatable and some ocular diseases that cause visual loss are reversible, early identification and treatment of persons most at a risk could have an important impact in the well-being of the elderly[26].

The studies included in this review were observational, with half of them being cross-sectional, and these study designs do not show causality. Therefore, it is difficult to confirm a temporal relationship between depression and VI. The limitations of this review were the inadequate definition of outcomes and lack of responses by some authors regarding missing data.

The sociodemographic variables were not associated with depression in most articles. In one study, men were more depressed than women[28]. In another, women had a higher incidence of depression than men[23]. Another study showed that a low level of education is associated with greater symptoms of depression[25].

The outcome depression was analyzed using GDS-15 in six studies[4,21,24,25,27,28]; nevertheless, the cut-off for depression varied in these studies, limiting the comparison between heterogeneous groups.

Only one study analyzed a previous history of depression or the use of antidepressant medicine, which is, by itself, a risk factor for depression[28].

Depression was related to VI in all studies (prevalence ranged from 8.8% to 45.2%).

Visual acuity was accessed using different methods (Snellen, Glasgow, and ETDRS), and only one study[21] evaluated the Visual Function Score (VF-14), and this variable was associated with depression. The same study also assessed high- and low-contrast visual acuity, and both were related to more depression. Only one article assessed near and far visual acuity[26] and found that only far visual acuity was associated with depression.

Most articles used the best-corrected visual acuity; nevertheless, just one article[23] related that refraction was done when visual acuity was low, considering that refractive errors are reversible VI[31].

The criteria to determine VI varied between the studies. One study used ICD-9[28], while another used ICD-10[25]. Most articles did not establish standard criteria to diagnose VI. Consequently, there was a high heterogeneity between the VI groups, ranging between worse than 20/40[23,24] and worse than 20/70[25].

The relationship between severity of VI and depression was just reported by two studies[4,25]. One study found that the severity of visual loss does not matter and that VI was a risk factor for depression only in participants without a previous history of depression, and this study found that a 2-year history of depression is the most important risk indicator of depression[28]. The other study found that there is a positive association of more severe visual loss with depression[25].

One study used a questionnaire with subjective questions about the vision of the participant and what the participant was and was not able to do because of the visual loss. This type of questionnaire could be a risk because there is no objective method to measure the real visual acuity in these cases[27].

Only two authors evaluated baseline and follow-up visual acuities, and they found that the follow-up visual loss was associated with depression[26,27]. The two studies that analyzed the time of visual loss and depression found different results[4,25].

Anxiety was analyzed by two authors, and one found a relationship between anxiety and depression and VI; however, the other did not described such an association[21,24].

Other variables (quality of life, limitation of diary activities, physical activities, and disability) that were previously considered as very important in the association between VI and depression were correlated with depression; nevertheless, they were analyzed in only few studies[21]. When advanced age is coupled with low vision, a person's level of activity is narrowed further than with either age or VI alone. Furthermore, although older people can normally adjust well to environmental challenges, when the demands on their body are increased, such as when vision is disrupted, physical limitations may become problematic and affect quality of life[21].

The limitation of daily activities was analyzed in two studies, measured using different methods, and it was associated with depression in both[21,27].

In one study[24], the author reported that a high limitation in daily activities is associated with an eight times greater VI and 12 times more depressed people.

One study[26] reported that the time of institutionalization, when it occurs, is not related with depression. In addition, one study related that living alone is not associated with an increase in depression rates[21].

Disability is already well known in the literature as an important risk factor for VI and depression[2], and it is a major public health issue for the elderly. Age is associated with decreased physical competence and increased prevalence of chronic illness[21]. VI is an important, but not life threatening, chronic illness and cause of disability[32] and has been associated with depression in three studies[12,22,27]. Different indices were used to assess disability. Low functional ability was associated with depression in one study, as measured using the Barthel index[25].

Mortality and chronic diseases were described in one and two studies, respectively[23,28]; both associated this factor with depression, and these factors are also described in the literature as being important to depression and VI[33,34]. VI causes impaired psychosocial functioning with impaired ADL, loss of independence, reduced social interaction, and depression, and it is known to be related to mortality. In addition, patients may be exposed to shared risk factors for mortality and VI, such as aging, diabetes, vascular pathology, high blood pressure, or smoking[28].

Chronic diseases were assessed by the CDC score in one study and were associated with depression and VI; another study reported that stroke and cardiovascular diseases are related to depression[23,28], and there is a strong association in the literature with these risk factors[18].

The causes of VI were described in one study[22], which demonstrated that diseases that cause central visual loss are more associated with depression than those that present with peripheral visual loss. Another study just reported the prevalence of the diseases[27] without specifying whether any of them is associated with depression. None of the articles classified ocular disease as being reversible or permanent, which could have been important in determining whether a person with an irreversible disease had more or less depression than one with a reversible cause.

The implication with regard to clinical practice is that because there is no established link between standardized VI measurements and depression, physicians would have to rely on knowledge and clinical experience to decide when to investigate and treat a depressed visually impaired patient.

This review shows that new research is necessary to analyze each important variable because most studies did not include the full range of common risk factors for both VI and depression, making it impossible to establish a linear correlation between them. In addition, it is important to use standard criteria to classify depression and VI, such as the GDS scale with a standard cut-off to depression and VI criteria following just IDC or WHO.

CONCLUSIONS

After a literature research, we could not definitely establish an association between VI and depression in the elderly. The reasons include a lack of standardized measures of VI and depression to allow comparability of the studies and the potential bias created by several other variables.

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A review of "approach of Turkish ophthalmologists to micronutrition in age-related macular degeneration"

Um comentário para abordagem dos oftalmologistas turcos em relação a micronutrição na degeneração macular relacionada à idade

Dear Editor:

We read with interest the article "Approach of Turkish ophthalmologists to micronutrition in age-related macular degeneration" by Şahın et al.[1] They aimed to evaluate the knowledge and behavior of ophthalmologists in Turkey with regard to micronutrition support in patients with age-related macular degeneration (ARMD). We congratulate the authors on their well-designed study. We would, however, like to make some contributions and report some inconsistencies in the article.

Different risk factors were defined for ARMD such as older age, ultraviolet light, genetic predisposition, smoking, and nutrient deficiency[2]. Many studies have investigated the use of vitamins and antioxidants, such as lutein, omega-3, zeaxanthin, zinc, vitamin E, and vitamin C, in the treatment of ARMD; the best known studies include the Age-related Eye Disease Study (AREDS) and AREDS2[3-5]. AREDS revealed a significant effect of zinc and antioxidants on the development of advanced age-related macular degeneration (AMD) in patients with early signs of the disease and recommended their use in at-risk patients (categories 3 and 4). AREDS2 further examined the effects of carotenoids and omega-3 long-chain fatty acids in patients at risk of ARMD[4].

The present study by Sahin et al. shows that the results of the aforementioned valuable studies have not been accurately understood and analyzed by most ophthalmologists, even by retina and uvea specialists[1]. The authors report that micronutrients are mostly prescribed by general ophthalmologists. However, 56,3 % of the ophthalmologists stated that they did not use the AREDS criteria, and 10,1% and 1,7% used micronutrients for grade 1-2 and grade 5 patients with AMD, respectively. This means that several ophthalmologists prescribe these expensive drugs in spite of scientific facts, and many patients use these drugs although not beneficial to them.

We believe that another explanation as to why retina and uvea specialists prescribe micronutrients less than general ophthalmologists is that these specialists see more patients with neovascular ARMD than general ophthalmologists, and these patients make up an important part of their patient cohort. However, the use of micronutrients is not effective for these patients, so retina and uvea specialists may be less prone to prescribing these drugs than general ophthalmologists. Indeed, the mean number of patients seen per month and patients with ARMD seen per month are also important factors.

Additionally, the authors asked the participants about the frequency of prescribing micronutrients, and the reply options were "always," "frequently," "occasionally," and "never." We think that these options are quite subjective and that the meaning of always, frequently, occasionally, and never may be differently perceived by each participant. Instead of this, a scale ranging from 0 to 10 showing the number of micronutrient prescriptions for each of 10 AMD patients would be a more scientific approach (mean number of micronutrient prescription/10 AMD patients: 0/10, 1/10,…, 9/10, 10/10).

We would also wish to report that the number of participants indicated in the article is inconsistent, and we believe that this error was made by mistake. In the results section, the authors mentioned that the number of participants was 249, with 158 being males and 85 being females. However, the sum of 158 and 85 is 243. Additionally, the total number of participants is given as 243 and 240 in table 1, 247 in table 2, and 246 in table 3.

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INSTRUCTIONS TO AUTHORS

- Scope and policy
- Methods
- Types of Manuscripts
- Editorial Process
- Manuscript Preparation

ABO-ARQUIVOS BRASILEIROS DE OFTALMOLOGIA (ABO, ISSN 0004-2749 - printed version and ISSN 1678-2925 - online version) is the official bimonthly publication of the Brazilian Council of Ophthalmology (Conselho Brasileiro de Oftalmologia - CBO). The purpose of the journal is to publish scientific studies in Ophthalmology, Visual Sciences, and Public Health, encouraging research, as well as qualification and updating of the professionals involved in this field.

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Original manuscripts are accepted only in English. Manuscripts are grouped into one of the following categories, based on the methodology used:

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Approval of the Institutional Review Board (IRB). All retrospective, cross-sectional, or prospective studies involving primary data collection or clinical and surgical reports should include the project number and name of the institution that provided the approval of the IRB on the title page. Studies involving humans should be compliant with the Declaration of Helsinki, whereas studies involving animals should be in accordance with the principles suggested by the Association for Research in Vision and Ophthalmology (ARVO).

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Books

Bicas HEA. Oftalmologia: fundamentos. São Paulo: Contexto; 1991.

Book Chapters

Gómez de Liaño F, Gómez de Liaño P, Gómez de Liaño R. Exploración del niño estrábico. In: Horta-Barbosa P, editor. Estrabismo. Rio de Janeiro: Cultura Médica; 1997. p. 47-72.

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- ☐ No figures and tables are included in the main document of the manuscript.
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- ☐ Author Contribution Statement completed and saved as a digital file to be sent as a supplementary document.
- ☐ Form for Disclosure of Potential Conflicts of Interest of all authors completed and saved as digital files to be sent as supplementary documents.
- ☐ Digital version of the report provided by the Institutional Review Board containing the approval of the project to be sent as a supplementary document.

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Authors' Participation Form
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http://www.wma.net/en/30publications/10policies/b3/index.html

Principles of the Association for Research in Vision and Ophthalmology (ARVO)
http://www.arvo.org/About_ARVO/Policies/Statement_for_the_Use_of_Animals_in_Ophthalmic_and_Visual_Research/

World Association of Medical Editors: Conflict of interest in peer-reviewed medical journals
http://www.wame.org/about/wame-editorial-on-coi

Form for Disclosure of Potential Conflicts of Interest
http://www.icmje.org/coi_disclosure.pdf

U.S. National Institutes of Health
http://www.clinicaltrials.gov

Australian and New Zealand Clinical Trials Registry
http://www.anzctr.org.au

International Standard Randomised Controlled Trial Number - ISRCTN
http://isrctn.org/

University Hospital Medical Information Network Clinical Trials Registry - UMIN CTR
http://www.umin.ac.jp/ctr/index.htm

Nederlands Trial Register
http://www.trialregister.nl/trialreg/index.asp

Registros Brasileiros de Ensaios Clínicos
http://www.ensaiosclinicos.gov.br/

MeSH - Medical Subject Headings
http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh&term=

DeCS - Health Sciences Keywords in Portuguese
http://decs.bvs.br/

Format suggested by the International Committee of Medical Journal Editors (ICMJE)
http://www.nlm.nih.gov/bsd/uniform_requirements.html

List of Journal Indexed in Index Medicus
http://www.ncbi.nlm.nih.gov/journals

AMA Manual of Style 10th edition
http://www.amamanualofstyle.com/

Protocols of the International Committee of Medical Journal Editors (ICMJE)
http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/scientific-misconduct-expressions-of-concern-and-retraction.html

Protocols of the Committee on Publication Ethics (COPE)
http://publicationethics.org/resources/flowcharts

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