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COMPARISON OF THE EFFICACY OF DIODE LASER CYCLOPHOTOCOAGULATION, ALONE OR IN CONJUNCTION WITH AVASTIN IN THE TREATMENT OF NEOVASCULAR GLAUCOMA

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Purpose: *To assess the efficacy of Avastin as an adjunct to Diode Laser cyclophotocoagulation in the treatment of Neovascular Glaucoma.*

Design: *Prospective, comparative interventional case series.*

Method: *The patients were randomly assigned into two groups: Group A was treated with Diode laser cyclophotocoagulation alone (30 laser shots over 270 degrees of the circumference of the limbus). For our study we used the Iris Diode laser machine, the G-probe and we adjusted the settings for 2500 millisecond duration and the 3000 milli-joule and reduced the power progressively until just below the energy level that produced a pop, whereas group B received intravitreal Avastin (One milligram = 0.04 mL of 25 mg/mL) in conjunction with the Diode Laser. The preoperative Data included Etiology, mean age; follow up period, and a full ophthalmological examination with emphasis on mean IOP, iris neovascularization, pain and corneal edema.*

Results: *There was a significant IOP reduction in both groups $p < 0,05$, also there was significant reduction of pain in both groups with $p = 0.023$ and 0,004 respectively, group B showed significant reduction in iris neovascularization $p = 0.001$. There were no notable complications in our sample of patients.*

Conclusion: *Avastin is a useful adjunct in the treatment of Neovascular Glaucoma, the use of which should be further evaluated.*

Key words: Neovascular glaucoma, diode laser, cyclophotocoagulation, intravitreal Avastin.

INTRODUCTION. Neovascular glaucoma (NVG) is a form of secondary glaucoma in with pathologic fibrovascular tissue grows on the iris and angle structures including the trabecular meshwork. Contraction of this leads to progressive angle closure, elevation of intraocular pressure (IOP) eventually leading to a glaucoma which is poorly responsive to conventional treatment and as poor visual prognosis [1]. Ischemic retinal disorders are the most prevalent conditions leading to Neovascular Glaucoma, however, other pathophysiologic mechanisms such as inflammation, retinal detachment, tumors, and irradiation may also leas to this condition [2]. Currently, management of NVG is directed toward the underlying disease process, mostly by some form of retinal ablation to reduce the neovascular stimuli, and IOP reduction by means of various forms of medical and surgical therapy [1, 2]. It is now evident that several mediators are involved in the process of neovascularization, the most important and well studied of which is the vascular endothelial growth factor type A (VEGF-A) [1, 3]. Regarding the pivotal role of VEGF-A in ocular neovascularization, inhibition of this mediator seems to have a strong biologic basis for treatment of NVG [1, 3]. The aim of this study is to assess the efficacy of Avastin as an adjunct to Diode Laser cyclophutocoagulation in the treatment of Neovascular Glaucoma.

PATIENTS AND METHODS. Prospective, comparative interventional case series. Sixteen eyes of sixteen patients were included in the study. All cases had Neovascular glaucoma. The etiology of which is variable, eleven eyes were caused by proliferative diabetic retinopathy (68.75%), four eyes were secondary to ischemic central retinal vein occlusion (25%) and one eye had iris neovascularization secondary to carotid ischemia (6.25%). Patients were randomly assigned into either of 2 groups. Group A consists of 6 eyes of six patients (3 males and 3 females) three eyes were pseudophakic, they underwent diode laser cyclophotocoagulation. Group B consists of 10 eyes of 10 patients (6 females and 4 males) five eyes were pseudophakic, underwent diode laser cyclophotocoagulation in conjunction with intravitreal Bevacizumab (Avastin, Genentech) injection. Our routine workup involved visual acuity testing, measuring the IOP, documenting anterior chamber reaction if any. We also examined the iris under the high magnification of the slitlamp. We noted the extent of neovascularization as the number of clock hours involved. If the media clarity allowed; gonioscopy was performed to assess the state of the angle. Status of the cornea was documented pre and post operative as regards corneal edema and presence of bullous keratopathy or presence of corneal ulcers secondary to ruptured bullae. Fundus examination was performed to note the cause of neovascularization. All patients has undergone heavy pan retinal photocoagulation as a primary management for their retinal condition. The patients were all seeking a method to relieve their pain. Their pain was assessed pre and post operative, and it was graded according to the following scoring system (0 = no pain. 1 = mild discomfort and or foreign body sensation, 2 = pain that is not present all time and is tolerable and responds to analgesics (NSAID) 3 = severe pain not responding to analgesics and affecting patients' sleep).

The operative procedure involved retro-bulbar anesthesia, draping the patient in an aseptic manner, introduction of an eye speculum, 30 laser shots over 270 degrees of the circumference of the limbus. For our study we used the Iris Diode laser machine, the G-probe and we adjusted the settings for 2500 millisecond duration and the 3000 milli-joule and reduced the power progressively until just below the energy level that produced a pop. We gave an intravenous non steroidal anti inflammatory (NSAID) to reduce postoperative pain.

In Group B patients, in whom we were going to inject Bevacizumab (Avastin, Genentech) we proceeded as above, then after applying the laser, we performed a paracentesis with a 27 gauge needle to soften the globe, followed by intravitreal injection of the Avastin from a site 3.5 millimeter posterior to the limbus. The dose we administered was one milligram of bevacizumab (0.04 mL of 25 mg/mL).

We used topical Prednisolone acetate, tobramycin combination eye drops 3 times daily, combined with Atropine sulphate eye drops 3 times daily.

We examined the patient one day, one week, one month and 3 and 6 month postoperatively. During each follow up visit the following was performed; IOP measurement, extent of iris neovascularization, corneal condition, and assessment of pain score.

After the cornea cleared we performed gonoiscopy when possible. All of those patients showed synhecial angle closure.

STATISTICAL ANALYSIS: Data were described as arithmetic mean ± SD or number and percentages when appropriate. Comparisons of quantitative variables were done using (Wilcoxon signed ranks test, Mann Whitney, Student t test, and paired sample t test). Comparison of categorical variable was done using the Fisher exact test. All test were two tailed a probability value (p. value) < 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science: SPSS Inc, Chicago, IL, USA).

RESULTS: Mean follow-up period for group A in 13. 4 ± 1.8 month, and group B is 8.0 ± 3.7 months p = 0.001 indicating significant statistical difference. Mean age for group A is 63.8 ± 6.4, and group B is 49.7 ± 14.9 years (p = 0.047) which indicates significant statistical difference between the two groups. The difference in age between both groups, is perhaps skewed by the small sample size and the presence of a single 14 year old Type I diabetic with renal failure. Mean preoperative IOP in group A is 57.33 ± 3.93 mmHg, group B is 53.0 ± 9.14 mmHg. There is no statistical difference between the 2 groups. Mean post-operative IOP in group A is 24.50 ± 2.25 mmHg, group B is 21.9 ± 2.64 mmHg. There is no statistical difference between the 2 groups. However there was a statistically significant difference between pre and post operative IOP measurement in both groups $p < 0.05$.

As regards pain, pain scoring in group A had a preoperative median of 3 (minimum = 2, maximum = 3) and post operative of 0.5 (minimum = 0, maximum = 1), this was a significant difference with p = 0.023, group B had a preoperative median of 3 (minimum = 2, maximum = 3) and post operative of 1 (minimum = 0, maximum = 2), this was a significant difference with p = 0.004, however there were no difference between group A and B as regards the post-operative pain relief as $p > 0.05$. Regarding the regression of the iris neovessels, group B showed significant association with the use of intravitreal injection of Avastin (bevacizumab), p = 0.001. Corneal epithelial edema and bullae improved in all cases of both groups this may add to the relief of their ocular discomfort. There were no significant difference between pre and post operative visual acuity in either of the two groups or between the two groups $p > 0.05$.

No cases were complicated by hyphema or hemophthalmia. There were no systemic complications related to the use of Avastin in our series. All patients stopped using systemic carbonic anhydrase inhibitors (CAI). In Group A and B all patient continued on topical beta blockers, steroids and atropine eye drops.

DISCUSSION. Vascular endothelial growth factor (VEGF) is recognized to be a key regulator of pathological ocular neovascularization. Significantly raised levels of VEGF have been demonstrated in patients with rubeosis and neovascular glaucoma as well as the other ocular neovascular diseases [4]. Recently preparations that inhibit the effects of VEGF have become available. Bevacizumab (Avastin, Genentech) is a recombinant, full-length, anti-VEGF monoclonal antibody that binds to all forms of VEGF-A, is Food and Drug Administration-approved for the treatment of colorectal cancer [5]. Recently, several case series have been published regarding the off-label use of intravitreal bevacizumab (IVB) for the treatment of cystoid macular edema [6], neovascular age-related macular degeneration [7, 8], and two single cases of neovascular glaucoma (NVG) [9, 10]. These studies suggest that IVB effectively reduces neovascular activity and vascular permeability in ocular tissues.

The mechanism by which IOP may be reduced by bevacizumab or any other anti-VEGF-A agent is a matter of speculation. In eyes with partially open drainage angles one may explain this effect by improvement in filtration; however, in eyes with extensive peripheral anterior synechiae formation this pressure reducing effect may be more difficult to explain. One possibility includes a reversible anatomic closure in angles not yet completely and permanently compromised by the abnormal tissue; with regression of the neovascular membrane the angle may be partially relieved from the pretrabecular obstruction. On the other hand, what we observe and report as «synechial closure» may be a gross view of the drainage angle; functional trabecular tissue may exist at a microscopic level the performance of which improves after regression of new vessels [11]. Safety remains an important consideration in the use of VEGF inhibitors. Although VEGF plays a role in pathological neovascularization, it is also involved in a number of homeostatic mechanisms including normal wound healing [12]. In a study by Chilov et al. [13] one of their patients developed infectious keratitis 2 weeks after administration of bevacizumab. Although his compromised cornea placed him at an increased risk of infection, potential interference with the neurotrophic actions of VEGF and inhibition of its wound healing role may have been a contributory factor [14]. Breakdown of the blood ocular barrier is common in the ocular neovascular diseases. Animal studies have demonstrated the intravitreal administration of VEGF inhibitors results in systemic exposure [12]. Systemic

administration of bevacizumab has been associated with an excess of thromboembolic arterial events [15]. The largest study of intravitreal bevacizumab (266 eyes), for age-related macular degeneration, which was prospective but non-randomized, did not demonstrate an excess of arterial thromboembolic events at 3 months [16].

Anti-VEGF agents might be particularly suited to the management of neovascular glaucoma. Given the rapid reported resolution of the iris neovascularization, a single administration in conjunction with retinal ablative procedures may be sufficient. Fewer administrations might be anticipated to correlate with less potential for adverse outcomes, as opposed to neovascular age-related macular degeneration where more frequent administrations may be required. For the purposes of neovascular glaucoma where the role of the anti-VEGF agent is an a temporizing measure, to cause regression and prevent angle closure, the longer half life of bevacizumab, as compared with ranibizumab, may prove beneficial [13].

In our series, although we could not show a statistical difference in the IOP reduction between the two groups, there was a statistical difference in the regression of the iris neovascularization, denoting a possibility of a more stable long term control of the IOP in patients treated with Avastin. Although there is a theoretical advantage for the use of Avastin, this was not evident in our series, perhaps due to the fact that our sample of patients included end stage pathology with established angle closure. However, we would expect that should the injection have been carried at an earlier stage, prior to the synchial angle closure set in, there would have been a window of opportunity for the effect of the Avastin.

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СРАВНЕНИЕ ЭФФЕКТИВНОСТИ ЛАЗЕРНОЙ ЦИКЛОФОТОКОАГУЛЯЦИИ В СОЧЕТАНИИ С АВАСТИНОМ В ЛЕЧЕНИИ НЕОВАСКУЛЯРНОЙ ГЛАУКОМЫ

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Статья посвящена лечению больных неоваскулярной глаукомой.

Проанализированы результаты лечения 16 больных (16 глаз). Пациентам группы А (6 человек, 6 глаз) проведена лазерная циклофотокоагуляция.

Пациенты группы Б (10 человек, 10 глаз) в дополнение к этому получали препарат Авастин в виде интравитреальных инъекций.

Результатом лечения в обеих группах больных явилось значительное снижение уровня внутриглазного давления ($p < 0,05$) и снижение болевых ощущений ($p = 0,023$ и $0,004$ — соответственно). Однако у пациентов группы Б наблюдалось также значительное уменьшение степени неоваскуляризации в радужке ($p = 0,001$). Осложнений лечения не отмечено.

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УЛЬТРАСОНОГРАФИЧЕСКИЙ КОНТРОЛЬ ПОЛОЖЕНИЯ ГЛАУКОМНОГО КЛАПАННОГО ДРЕНАЖА

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Можливості ультрасонографічного та біомікроскопічного дослідження положення глаукомного клапанного дренажу вивчалися на 8 очах (8 пацієнтів) після імплантації клапана за допомогою апарату «Vu Max II» (Sonomed). Показано, що застосування ультразвукової біомікроскопії дозволяє встановити положення силіконової трубки під склеральним клаптем та у передній камері, а також діагностувати порушення її позиції навіть в умовах недостатньої прозорості рогівки та судити про «герметичність» її імплантації в передню камеру.

Проведення ультрасонографії в режимі В-сканування дозволяє також встановити причини порушення положення імплантату, що сприяє визначенню тактики лікування та запобігає розвитку тяжких ускладнень.

Ключевые слова: глаукома, клапанный дренаж, ультрасонография.

Ключові слова: глаукома, клапанний дренаж, ультрасоногрфія.

Имплантационная хирургия глаукомы за свою почти полувековую историю прошла путь от введения в переднюю камеру капиллярной трубки Epstein E. [15] до создания клапанных дренажей [8, 18], однако вопросы предупреждения возможных осложнений остаются очень актуальными и на сегодняшний день [1].

Осложнения, возникающие у пациентов после имплантации глаукомных дренажных устройств, можно условно разделить на две группы. К первой следует отнести осложнения, относительно «специфические» для имплантации дренажей, ко второй — общие для всех антиглаукоматозных операций.

Наиболее частыми осложнениями имплантационной хирургии глаукомы являются гипотония [5, 8, 13, 14, 17], цилиохориоидальная отслойка [5, 8, 13, 17], гифема [5], прогрессирование катаракты [5], а также осложнения, приводящие к «отказу» в работе дренажного устройства — формирование фиброзной капсулы вокруг дренажа [5, 8, 17, 22], блокада или закупорка силиконовой трубки [5, 8]. К значительно менее частым, но очень грозным, зачастую требующим повторных вмешательств, относятся такие осложнения, как контакт силиконовой трубки с роговицей [8, 17], смещение дренажного устройства [6, 17], воспалительные и инфекционные осложнения [4, 12].