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Intravitreal triamcinolone and retrobulbar chlorpromazine as alternative to blind painful eye management

Triancinolona intra-vítrea e clorpromazina retrobulbar como alternativas ao manejo do olho cego doloroso

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ABSTRACT

Objective: *The objective of this study was to evaluate the efficacy of intravitreal triamcinolone and retrobulbar chlorpromazine as alternatives in the management of ocular pain in blind eyes.* ***Methods:*** *This was a non-randomized interventional prospective study of patients with painful blind eye unresponsive to topical treatment and without indication of evisceration treated at the Hospital Governador Celso Ramos Ophthalmology Service in 2010. After ocular examination and ocular B mode ultrasound, patients were divided into two groups. Group 1 patients had intractable glaucoma and received retrobulbar injection of chlorpromazine 2.5ml, and Group 2 patients had phthisics eyes with inflammatory component and received intravitreal triamcinolone injection 0.3ml. Evaluations were performed at 1, 3 and 6 months after the procedure and quantified pain subjectively on a scale from 0 to 10 (no pain and maximum pain, respectively).* ***Results:*** *38 eyes were included, 15 in Group 1 and 21 in Group 2. There was a predominance of males with a mean age of 54 years. The most prevalent cause of painful blind eye was the neovascular glaucoma. Any retrobulbar injection of chlorpromazine as the intravitreal triamcinolone shown to be effective in the control of ocular pain in the eye blind study period (p <0.001). There was a 77.1% reduction in eye drops (p <0.01) after application of medication.* ***Conclusion:*** *Both the retrobulbar injection chlorpromazine as the intravitreal triamcinolone showed significant results in the control of ocular pain in blind eyes, and a reduction in the use of eye drops. Chlorpromazine is a low cost product, with a better adverse effect profile and showed slightly better results compared to triamcinolone. Potential bias identified in the study are the time and selection.*

Keywords: *Ocular pain; Injections;Iintravitreal injections; Triamcinolone; Chlorpromazine*

RESUMO

Objetivo: O objetivo desde estudo foi avaliar a efetividade da triancinolona intra-vítrea e da clorpromazina retrobulbar como alternativas no manejo da dor ocular em olhos cegos. **Métodos:** Este foi um estudo prospectivo intervencionista não-randomizado de pacientes com olho cego doloroso não responsivo ao tratamento tópico e sem indicação de evisceração atendidos no Serviço de Oftalmologia do Hospital Governador Celso Ramos no ano de 2010. Após exame oftalmológico e ultrassonografia ocular modo B, os pacientes foram divididos em dois grupos. Pacientes do Grupo 1 possuíam glaucoma intratável e receberam injeção retrobulbar de clorpromazina 2,5ml, e pacientes do Grupo 2 possuíam olhos phthisicos com componente inflamatório e receberam injeção intra-vítrea de triancinolona 0,3ml. Foram realizadas avaliações com 1, 3 e 6 meses após o procedimento e a dor quantificada de forma subjetiva em uma escala de 0 a 10 (sem dor e com o máximo de dor, respectivamente). **Resultados:** Foram incluídos 38 olhos, sendo 15 no Grupo 1 e 21 no Grupo 2. Houve predomínio do sexo masculino e idade média de 54 anos. A causa mais prevalente de olho cego doloroso foi o glaucoma neovascular. Tanto a injeção de clorpromazina retrobulbar quanto a de triancinolona intra-vítrea mostraram-se eficazes no controle da dor ocular em olhos cegos no período do estudo (p<0,001). Ocorreu uma redução de 77,1% no uso de colírios (p<0,01) após a aplicação das medicações. **Conclusão:** Tanto a injeção de clorpromazina retrobulbar quanto a de triancinolona intra-vítrea mostraram resultados significativos no controle da dor ocular em olhos cegos, além de uma redução no uso de colírios. A clorpromazina é um medicamento de baixo custo, com melhor perfil de efeitos adversos e mostrou resultados discretamente melhores relação à triancinolona. Possíveis viéses identificados no estudo são o de tempo e seleção.

Descritores: Dor ocular; Injeções; Injeções intravítreas; Triancinolona; Clorpromazina

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Introduction

The management of chronic ocular pain is a constant challenge to Ophthalmology.[1]Treatment varies according to the intensity of pain, and the topical use of anti-inflammatory, hypotensive and cycloplegic eyedrops and contact lens therapy are effective in many patients. In refractory cases without vision, surgical removal of the eye by evisceration or enucleation is considered a classical therapy. As a less invasive alternative, there is the injection of neurolitic drugs in order to promote analgesia for an extended period.[2]

Among the causes of chronic pain is the ocular trauma, followed by retinal detachment, neovascular, open-angle, chronic glaucoma, phthisis bulbi, intraocular inflammation and corneal decompensation.[2]

Since the beginning of the 20th century the retrobulbar injection of absolute alcohol has been used as an alternative treatment to surgery in cases of blind and painful eyes, especially in cosmetically normal eyes.[2] This procedure reduces the pain in 20% to 80% of the patients for at least one month.[3] It is believed that the alcohol infiltrates around the sensory nerve fibers, promotes damage to them but not their complete destruction, with recurrent pain and regeneration of the peripheral portion.[2] Como complicações estão descritas dor intensa durante a injeção, edema palpebral, ptose, quemose conjuntival e paralisia temporária da musculatura extra-ocular.[4]

In the 80s, Fiore suggested the injection of retrobulbar chlorpromazine and noted a reduction of 83% of pain in the patients. Although the neurotrophic effects of chlorpromazine may cause irreversible changes in the ciliary ganglion and decrease pain, the exact mechanism of action is unknown.[1,5] Chlorpromazine is a typical antipsychotic substance, and acts by inhibiting mesolimbic dopamine post-synaptic receptors in the brain, with a strong alpha-adrenergic blocking effect.[1,5] The most frequent complications are eyelid edema and chemosis, both transient and treated spontaneously.[1]

The use of triamcinolone for the management of pain in blind eyes is not routine, however there are publications to support this purpose. [5,6]

The objective of this study was to evaluate the efficacy of intravitreal triamcinolone and retrobulbar chlorpromazine as alternatives to control ocular pain in blind eyes, as well as raise the epidemiological data of the patients.

Methods

It is a non-randomized interventional prospective study in patients with blind and painful eye, unresponsive to topical treatment with eyedrops and with no indication of evisceration, attended at the Ophthalmology Service of Hospital Governador Celso Ramos (HGCR) in 2010. We included patients with the above-mentioned characteristics, who wished to be part of the protocol and signed an informed consent. Patients whose follow-up period was less than 3 months were excluded.

The patients included were previously submitted to an ocular B-mode ultrasound to rule out the presence of ocular tumor as a primary cause of pain, as well as a complete eye exam including corrected visual acuity, biomicroscopy, intraocular pressure (IOP) with Goldmann applanation tonometer and fundoscopy.

Two groups were created according to the clinical conditions and treatment that each patient would receive. Group 1 comprised patients with ocular pain due to intractable glaucoma retrobulbar, and received retrobulbar injection of chlorpromazine. IOP was measured during the study to assess the relationship between IOP and pain in this group. Group 2 comprised patients with painful phthisic eyes with an inflammatory component, such as those with previous eye surgeries and trauma, and received intravitreal injection of triamcinolone.

For the procedure, the patient was positioned in supine position, received topical anesthetic with anesthetic eyedrops and lidocaine gel during 5 minutes, and intravitreal triamcinolone injection 0.3 ml (12.5 mg) or retrobulbar chlorpromazine 2.5 ml (40 mg/ml), according to the group they belonged. Patients were followed monthly for at least 3 months to assess the ocular pain after injection. It was quantified in a subjective scale of 0 to 10, with 0 being the absence of pain and 10 maximum pain felt by the patient.

The study was designed according to the Guidelines and Regulating Norms of Research Involving Human Beings (Resolutions 196/96 and 251/97 of the National Health Council), and the study design was previously submitted and approved by the Committee for Ethics in Research on Human Beings of HGCR, being registered under the number 2010/0043, on August 18, 2010.

The statistical analysis used the "Student's t-test" for the calculation of different means with independent samples to compare scales and pain scores in both groups in each of the different moments in time, and for the analysis of variance to compare the development of the pain scale in different moments in time. For comparison of proportions, we used the "Chi Square test". A 95% confidence index (5% CI) was established for the significance tests.

Results

We assessed 36 patients and 38 eyes (two patients received bilateral medication). Sixteen eyes received retrobulbar injection of chlorpromazine (Group 1), and 22 received intravitreal injection of triamcinolone (Group 2). The study excluded two patients, the first one belonging to Group 1 for corneal ulcer developing to drilling and subsequent evisceration, and the second belonging to Group 2 for loss of follow-up, with a total of 15 eyes in Group 1 and 21 in Group 2.

Regarding gender, there was a male predominance of 61.1%, and the average age was 54 years old. (Table 1) The visual acuity (VA) of all patients was "absence of light perception" in the eye who received the medication.

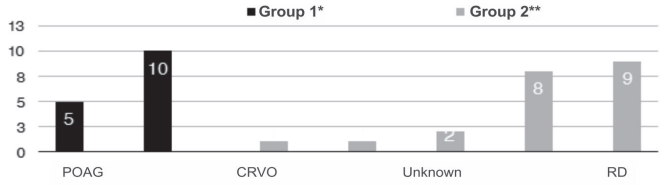
Table 1

Frequency of patients with painful blind eye regarding gender, age and medication received

	Group 1* No.(%)	Group 2** No.(%)	Total
Male	6 (40)	16 (76.2)	22
Female	9 (60)	5 (23.8)	14
Total	15	21	36
Average age	59.6 (±13.9)	49.9 (±11.1)	

*Chlorpromazine; **Triamcinolone

The main cause of painful blind eye in Group 1 was the neovascular glaucoma, and in Group 2 was retinal detachment, as shown in Figure 1. Among patients with retinal detachment, 5 had proliferative diabetic retinopathy as the base cause.



*Chlorpromazine; **Triamcinolone; POAG = primary open-angle glaucoma; NG = neovascular Glaucoma; CRVO = central retinal vein occlusion; RD = retinal detachment.

Figure 1: Frequency of patients with painful blind eye regarding the cause of the pain.

All patients made use of topical medication for pain relief before the treatment proposed, including hypotensive eyedrops, ocular lubricant, corticosteroid associated to antibiotic and atropine. Afterwards, there was a total reduction of 77.1% in the use of eyedrops (p<0.001) at the time of the last assessment. The use of eyedrops remained in 5 patients of Group 1 and 3 patients of Group 2. (Table 2)

	Use of eyedrops			
	Yes No.(%)	**No** No.(%)	**P value**	**Q²**
Group 1*	5 (33.3)	10 (66.7)	<0.001	15
Group 2**	3 (15)	17 (85)	<0.001	29.57
Total	8	27	<0.001	45.82

*Chlorpromazine; **Triamcinolone

The IOP was initially measured in all patients, and also at the end of the follow-up in patients with neovascular glaucoma and primary open-angle glaucoma (Group 1). These patients achieved an IOP reduction of 12% after treatment, but that was not statistically significant (p>0.05). (Table 3)

IOP mmHg	Group 1*		
	n	**Average**	**CI 95%**
Initial IOP	15	40.73 (±15.15)	(32.34 - 49.12)
Final IOP	11	35.72 (±12.43)	(27.37 - 44.08)

*Chlorpromazine. *p*>0.05

There was a significant reduction of pain on injection in relation to any subsequent follow-up time in both groups (p<0.01), but there was no linearity, with an increase in the 6th month of follow-up in relation to the 3rd month in Group 2. (Figure 2) (Table 4) When we compare the difference in pain score between Groups 1 and 2, there was no statistically significant difference both in injection and with 1, 3 and 6 months of follow-up. No patient received a second dose of medication during follow-up. There were no complications associated to injections in the patients studied, and all of them reported little discomfort with the procedure, in both intravitreal and retrobulbar injection.

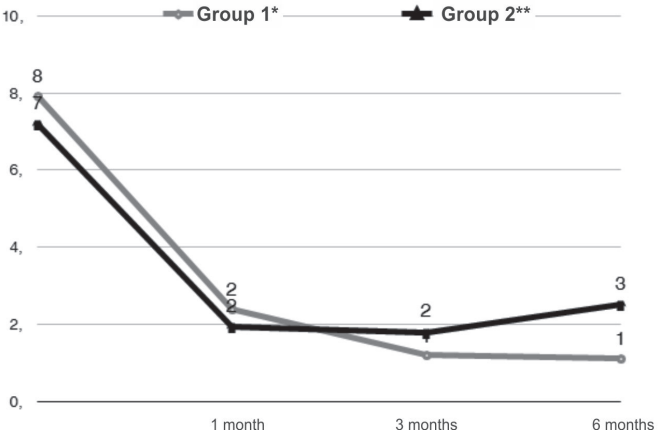


Figure 2: Average pain score at the time of injection, 1, 3 and 6 months after treatment with chlorpromazine (Group 1*) and triamcinolone (Group 2**). p<0.01

Table 4

Frequency of patients with painful blind eye who have received injection of chlorpromazine and triamcinolone in relation to ocular pain.

	Group 1*		Group 2**	
	n	**Average**	**n**	**Average**
At the time	15	7.93 (±1.98)	21	7.19 (±2.01)
1 month	15	2.40 (±2.52)	21	1.95 (±2.29)
3 months	15	1.20 (±1.37)	21	1.80 (±2.04)
6 months	8	1.12 (±1.80)	19	2.52 (±3.06)

*Chlorpromazine; **Triamcinolone

The minimum time of follow-up was 4 months (in 7 patients of Group 1 - 46.6%; and 2 patients of Group 2 - 9.5%), and the maximum time was 6 months. In relation to Group 1, only 1 patient reported pain score e" 5 in the 6th month of follow-up. Among those who were followed up for 4 months, none referred pain e" 3. In Group 2, 7 patients (33.3%) reported pain score e" 5 at the end of the sixth month. Both patients who were followed up for only 4 months denied pain.

Discussion

This study proposes the use of chlorpromazine and triamcinolone for the control of pain in painful blind eyes. The search for alternatives to surgical treatment, such as evisceration and enucleation, has been reported in the literature since 1900 for the cases where surgery is not possible or desired.[2] The absolute alcohol is widely used for this purpose among ophthalmologists, however with a variable and transitory result of pain relief. [2,3]

Fiore et al. and Bastrikov et al. were the first to report the use of chlorpromazine for the control of chronic ocular pain, and subsequent studies emphasized its advantages in relation to alcohol, such as little pain during the procedure, better efficiency and greater durability.[1,5-7] All the reports refer to the use of the drug mainly in cases of blind eyes due to glaucoma in terminal stage. The use of intravitreal triamcinolone for the management of ocular pain was reported by Rodríguez et al. in 2003 with important improvement of pain and ocular inflammation in phthisic eyes.[8]

This study showed a statistically significant reduction of pain in all patients in both groups, when compared to the pain score at the time of injection with the subsequent assessments in 1, 3 and 6 months. The patients receiving chlorpromazine (Group 1, n=15) had a reduction of approximately 70% in 1 month (pain score of 7.93 to 2.40), which kept falling until the sixth month of follow-up, reaching 86% of relief (score 1.12). These data corroborate the ones found in the literature. Fiore et al. obtained a reduction of pain of 83% in their set of 63 eyes; Bastrikov et al. reported a reduction of 83.8% in 53 patients; Estafanous et al. obtained a rate of reduction of 77% in 9 patients; and Chen et al. obtained 80% in 20 patients. [1,5-7]

The patients receiving triamcinolone (Group 2, n=21) achieved a reduction of pain in the first month of approximately 73% (score of 7.19 to 1.95), the most important reduction compared to Group 1, but with no statistical significance. The pain continued decreasing until the 3rd month, when it reached its maximum reduction (75% - score1.80), and in the sixth month of follow-up it showed a discrete increase (score 2.52), however with a still statistically significant score of pain reduction if compared to the time of injection. Rodriguez et al. also obtained significant relief of pain for at least 2 months with the use of intravitreal triamcinolone.[8]

Pharmacokinetic studies showed that a single injection of 4mg of intravitreal triamcinolone maintains detectable levels for up to 3 months.[9] Thus, we could expect a sustained effect of pain reduction for approximately 9 months in the patients followed up, which doesn't match the increase of the pain score in the sixth month. We would need more follow-up time to understand whether it was an isolated elevation of pain scores or if that would happen in a linear way until the full return of the pain.

The first researchers to use chlorpromazine to control ocular pain believed that the mechanism was connected to the reduction of IOP, which was evidenced after the procedure.[6] In subsequent studies, however, no correlation was found between the reduction of IOP and the reduction of pain. [1,6,7] Estafanous et al. reported that the probable mechanism for the reduction of pain is related to stabilization of the membrane in the ciliary ganglion caused by chlorpromazine.[6] In the present study, no statistical correlation was found between the reduction of IOP and the reduction of pain in individuals of Group 2. It is important to report, however, that of the 5 patients who kept topic use of eyedrops, only 1 reduced the IOP, which raises doubt about the real contribution of chlorpromazine on IOP of other patients. There is no report in the literature about the reduction of IOP in patients with glaucoma who received absolute alcohol.[1]

All patients made use of eyedrops before the treatment proposed, including lubricants, antibiotic associated to corticosteroids, atropine and hypotensive. At the end of follow-up, a reduction of 77.1% was observed in the use of topical medication, a statistically significant decrease ($p<0.01$). It can be said that this data correlates positively with to the relief of pain and the improvement of quality of life of the patients.

In all studies published about retrobulbar injection of chlorpromazine, 1 to 4 ml of retrobulbar lidocaine (with or without a vasoconstrictor) was injected before chlorpromazine. [1,2,5-7] This study did not use anesthesia prior to the application of chlorpromazine, and all patients showed good tolerability. One patient had already received retrobulbar injection of absolute alcohol to try to control the pain, and reported significant difference in the comfort of the current procedure.

The complications with retrobulbar injection of chlorpromazine are not common. However, we can expect paralysis of eye muscles, transient or permanent ptosis, neuroparalytic keratitis, conjunctival chemosis, proptosis and retrobulbar hemorrhage.[1] There is a report in the literature of 3 cases of extensive ocular inflammation after the procedure, with proptosis preventing the eyelid closure (requiring temporary tarsorrhaphy) and extent of swelling to the contralateral side, with complete resolution in three weeks.[10] There were no complications in the present series, both in patients receiving chlorpromazine and those receiving intravitreal injection of triamcinolone.

Some of the limitations of this study are the small sample of patients and the short period of follow-up. The use of different medications in two non-randomized groups with the same diagnosis, but with distinct etiologies, can lead to a selection bias. We suggest that future studies make use of chlorpromazine for patients with phthisic eyes as well, and not just for eyes with glaucoma, since its effect apparently is not related to the reduction of the IOP, but to the stabilization of membranes in the ciliary ganglion. Chlorpromazine is a low cost medication which showed good results in reducing linear pain in relation to triamcinolone during the 6 months of follow-up.

Conclusion

Both the injection of retrobulbar chlorpromazine and intravitreal triamcinolone showed statistically significant results in the control of ocular pain in blind eyes in the 6-month period of the study, in addition to a reduction in the use of eyedrops after the treatment proposed.

We suggest that future studies make use of chlorpromazine for patients with phthisic eyes as well, and not just for eyes with glaucoma, since its effect apparently is not related to the reduction of the IOP, but to the stabilization of membranes in the ciliary ganglion. Chlorpromazine is a low cost medication with improved adverse event profile and which showed slightly better results in reducing linear pain in relation to triamcinolone during the 6 months of follow-up.

References

1. Chen TC, Ahn Yuen SJ, Sangalang MA, Fernando RE, Leuenberger EU. Retrobulbar chlorpromazine injections for the management of blind and seeing painful eyes. J Glaucoma. 2002;11(3):209-13.
2. Merbs SL. Management of blind painful eye. Ophthalmol Clin North Am. 2006;19(2):287-92.
3. al-Faran MF, al-Omar OM. Retrobulbar alcohol injection in blind painful eyes. Ann Ophthalmol. 1990;22(12):460-2.
4. Olurin O, Osuntokun O. Complications of retrobulbar alcohol injections. Ann Ophthalmol. 1978;10(4):474-6.
5. Fiore C, Lupidi G, Santoni G. [Retrobulbar injection of chlorpromazinein the absolute glaucoma]. J Fr Ophtalmol. 1980;3(6-7):397-9. French.

6. Estafanous MF1, Kaiser PK, Baerveldt G. Retrobulbar chlorpromazine in blind and seeing painful eyes. Retina. 2000;20(5):555-8.
7. Bastrikov NI. [Symptomatic treatment of terminal painful glaucoma by the retrobulbar administration of aminazine]. Vestn Oftalmol. 1989;105(5):47-9. Russian
8. Rodriguez ML, Juarez CP, Luna JD. Intravitreal triamcinolone acetonide injection in blind painful eyes. Intraocular steroids as a treatment for blind painful red eyes. Eur J Ophthalmol. 2003;13(3):292-7.
9. Conti SM, Kertes PJ. The use of intravitreal corticosteroids, evidence-based and otherwise.Curr Opin Ophthalmol. 2006;17(3):235-44.
10. McCulley TJ, Kersten RC. Periocular inflammation after retrobulbar chlorpromazine (thorazine) injection. Ophthal Plast Reconstr Surg. 2006;22(4):283-5.

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