ORIGINAL ARTICLE

COMPARISON OF CYCLOCRYOTHERAPY COMBINED WITH RETROBULBAR CHLORPROMAZINE VERSUS CYCLOCRYOTHERAPY ALONE IN REDUCING THE INTRAOCULAR PRESSURE AND PAIN IN END-STAGE GLAUCOMA

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ABSTRACT

***Introduction**: Patients with end-stage glaucoma often came with a painful blind eye. One of the managements is cyclocryotherapy (CCT) or retrobulbar chlorpromazine (CPZ). In this study, we aimed to evaluate the combined use of cyclocryotherapy and retrobulbar chlorpromazine versus cyclocryotherapy alone in reducing the intraocular pressure (IOP) and Visual Analog Scale (VAS) pain scores in end-stage glaucoma patients.*

***Methods**: Samples were taken from patients who enrolled in the Ophthalmology Clinic of Dr. Sardjito General Hospital from October 2021 to March 2022. Samples were then divided into 2 groups, the CCT+CPZ group received the combination of cyclocryotherapy and retrobulbar chlorpromazine and the CCT group received only cyclocryotherapy. IOP and VAS pain scores pre-operation and 30th-day post-operation were examined.*

***Results**: Thirty-three patients were included in the CCT+CPZ group and 17 patients were included in the CCT group. The mean IOP and VAS pain scores 30th-day post-operation in the CCT+CPZ group were 22.6±10.3 mmHg and 1.6±1.3 vs pre-operation 44.9±19.5 mmHg and 7.9±1.7 (p=0.000). Patients in the CCT group also show a significant reduction in both mean IOP and VAS pain scores 31.4±16 mmHg and 2.6±2.3 vs pre-operation 54.4±7.4 mmHg and 8.4±2.1 (p=0.001). Both IOP and VAS pain scores at 30th-day post-operation were significantly lower in the CCT+CPZ group compared to the CCT group (p=0.030 and p=0.013, respectively).*

***Conclusion**: There were statistically significant differences between patients who received a combination of cyclocryotherapy and retrobulbar chlorpromazine in reducing the IOP and VAS pain score compared with patients who received only cyclocryotherapy.*

***Keywords**: cyclocryotherapy, retrobulbar chlorpromazine, end-stage glaucoma*

INTRODUCTION

End-stage glaucoma or absolute stage glaucoma is the final stage of all types of glaucoma in which increased intraocular pressure (IOP) results in permanent vision loss or blindness. Adequate data for the prevalence of absolute/end-stage glaucoma in the general or glaucomatous population is tend to be scarce. According to a clinic-based study in the United Kingdom, 38% of newly diagnosed glaucoma patients were in the advanced stage.[1]

When in its initial stage, glaucoma does not show any symptoms or specific signs. Until the moment of vision loss occurs, this condition often goes unnoticed by the patients. The

patient often complains of the following symptoms in the absolute/end-stage glaucoma, such as tearing, severe eye pain, photophobia, the stone-like appearance of the eye, lost pupillary reflex, and no pupillary response.

The vision cannot be regained once lost, so to keep the patient in stable condition, the focus should be on maintaining vision in the fellow eye, psychological and other support, helping the patients to manage the affected eye comfortably, and giving a reasonable cosmetic appearance to the patients.[2] If conservative measures do not result in improved comfort for the patient, then pain can be relieved with retrobulbar injection of chlorpromazine (CPZ)[3] or absolute alcohol.[4] Another option is cyclocryotherapy (CCT).[5] If this is not effective, or there is a cosmetic concern, then evisceration or enucleation can be considered with subsequent restoration with ocular prosthesis.[6]

An alternative technique appeared in the early 1950s consisting of a retrobulbar injection of CPZ, a neuroleptic with antiemetic action, the action mechanism of which is not fully understood but it has been related to membrane stabilization in the ciliary ganglion, produced significant analgesia with good tolerance and fewer side effects.[7]

The utilization of retrobulbar CPZ injection combined with CCT as a therapeutic alternative in absolute/end-stage glaucoma patients is not very well known. This study assessed the results of retrobulbar CPZ injection in standard concentration (25mg/2ml) combined with CCT for the treatment of absolute/end-stage glaucoma, evaluating its effect on pain and IOP compared with patients who only got CCT for the treatment.

METHODS

A cross-sectional study was conducted to evaluate the combined use of CCT and retrobulbar CPZ injection versus CCT alone in reducing the IOP and Visual Analog Scale (VAS) pain scores. The study was conducted from October 2021 to March 2022. Samples were taken from patients who enrolled in the ophthalmology clinic of Dr. Sardjito General Hospital Yogyakarta.

Of the 50 participants, 33 received retrobulbar CPZ+CCT, and 17 received CCT only. IOP and VAS pain Scores pre-operation and 30th-day post-operation were examined. IOP was measured with a non-contact tonometer or Schiotz tonometer. We defined the normal IOP as <21mmHg. Pain intensity was measured using a VAS pain score. The total score ranged from 0 (no pain) to 10 (severe pain).

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All patients with a blind painful eye and absolute/end-stage glaucoma, regardless of previous treatments to the eye, were included. All patients had to be able to communicate the level of pain to the examiner.

Patients were excluded if they had ocular tumors requiring treatment, were pregnant, had active infections, or had cosmetically unacceptable eyes in which enucleation or evisceration had been planned. Patients with a known sensitivity to CPZ were excluded.

The procedure was performed in the operating room with under proper asepsis. After instilling topical anesthetic drops (Tetracaine 0.5%) in the inferior fornix, a 25-gauge retrobulbar needle was then passed into the retrobulbar space and a mixture of 2ml 2% lidocaine and 2ml CPZ (25mg/2ml) was injected for CCT+CPZ group. For CCT only group, 25-gauge retrobulbar needle was passed into the retrobulbar space and a mixture of 2ml 2% lidocaine and 2ml 0.75% bupivacaine was injected. After an interval of five minutes, the anesthetic effect was clinically visible. Then twelve equidistant cryo-applications were applied over the ciliary body region, starting 2 mm behind the limbus over 360 degrees with a size of 2.5 mm. For all cases, retinal detachment cryo-probe was utilized. Each application was a 60s freezing cycle to -80 degrees Celsius.

Statistical analysis using IBM SPSS software version 23.0. Baseline characteristics are presented using percentages in the study population. A level of significance of $p<0.05$ was accepted for this study. The data were analyzed using change scores of IOP and VAS pain scores from pre to post-operation with intragroup and between-group comparison. The Wilcoxon test was used for intragroup comparison, and The Mann- Whitney U test for between-group comparison.

RESULTS

A total of 50 patients were enrolled in this study. The CCT+CPZ group contained 33 patients. The CCT group contained 17 patients. The median age of all patients was 60 ± 12.3 years. The baseline characteristics of the subject in this study are shown in **Table 1**.

After the intervention, both groups showed statistically significant improvement in IOP scores ($p=0.03$) and VAS pain scores ($p=0.013$). Improvement was evidenced by the intragroup comparison of IOP and VAS pain scores from pre-and 30th-day post-operation which are described in **Table 2**.

Table 1. Baseline characteristics of study subjects

	Total (n=5)	**CCT+CPZ (n=33)**	**CCT (n=17)**	**P Value**
Age (years), median (IQR)	60 (12.3)	59 (12.5)	62 (17.5)	0.758
Sex				
Male	21 (42%)	11 (33.3%)	10 (58.8%)	0.258
Female	29 (58%)	22 (66.7%)	7 (41.2%)	

Table 2. IOP and VAS pain scores at baseline and 30th-day post-operation

	CCT+CPZ		**P value**	**CCT**		**P value**
	Pre	**Post**		**Pre**	**Post**	
IOP	44.9±19.5	22.6±10.3	<0.001	54.4±7.4	31.4±16	0.001
VAS	7.9±1.7	1.6±1.3	<0.001	8.4±2.1	2.6±2.3	0.001

All values are shown as the mean ± SD. P value represents intragroup differences

DISCUSSION

There are several challenges for ophthalmologists to manage patients with absolute/end-stage glaucoma.[8] Both CCT and retrobulbar CPZ injection are simple and efficient methods to control pain. CPZ exerts its effect by destroying the nerve fibers by coagulative necrosis.[6] The technique must be performed with accuracy, the CPZ must be injected close to the nerve fibers. A dampening of the nerve fiber conduction is achieved but the pain can recur again with time. Retrobulbar CPZ injection at the standard dose (25mg in 1 or 2ml) has been demonstrated to be an effective treatment for pain in patients with blind eyes of different etiology.[7]

CCT leads to pain management, because of the lowering effect on the IOP. The technique is widely used and many studies research the effect of CCT but the results have been conflicting. A stable decrease in IOP has been reported with various success rates ranging from between 0% - 80%.[9] Such variation in the results is probably due to individual differences in ciliary body anatomy and sensitivity of the eye tissues to low temperatures.

The results of this study demonstrate effective pain control in 75.8% and IOP reduction of <21mmHg in 63.6% of the 33 cases in the CCT+CPZ group. In CCT only group, the study demonstrates effective pain control in 35.3% and IOP reduction of <21mmHg in 35.3% of the 17 cases. Pain control in the CCT+CPZ group showed the effectiveness above generally reported for retrobulbar absolute alcohol, which in the literature varies between 20% to 87%.[6]

The high percentage achieved in this study is similar to other studies with CPZ such as Fiore et al., who reported pain control in 82.5% of 63 cases with an average follow-up time of

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2.6 years.[10] However, Fiore et al. research only used retrobulbar CPZ injection, meanwhile in this study we combined retrobulbar CPZ injection with CCT but with only a 1-month post-operation follow-up time.

Marinov et al. studied 35 patients with absolute/end-stage glaucoma and treated them with a combined technique of CCT and retrobulbar alcohol 96% 1ml injection. VAS pain scores were used to evaluate the pain and all of the patients (100%) were pain-free 12 months after the procedure. No significant long-term complications were observed.[6] In this study, 25 of 33 patients (75.8%) were pain-free 1 month after the procedure.

As regards the IOP, this study found a reduction of approximately 63.6% (21 of 33 cases) in the CCT+CPZ group and 35.3% (6 of 17) cases in CCT only group. This was similar in comparison with similar studies for the CCT+CPZ group but lower in comparison with similar studies for CCT only group.[7] Galindo-Ferreiro et al. found that retrobulbar injection of alcohol or CPZ decreased IOP and reduced pain in approximately two-thirds (66.7%) of blind painful eyes with few postoperative complications. However, 33% of patients required further intervention to manage pain.[7]

In this study, we combined the CCT with a retrobulbar injection of CPZ and demonstrate a notable improvement in pain and reducing the IOP compared with CCT only group. To our knowledge, there is no similar study that evaluates the combination of CCT and retrobulbar CPZ injection in reducing the IOP and pain. This method appears to be efficient, safe, and suitable as a last-resort treatment for eyes without useful vision and significant pain syndrome.

This study has two limitations. The first is the small number of samples size. Second, the short follow-up time only 1-month post-operation was another limitation of this study. Further studies including more samples and with longer follow-up period time may be useful for the management of patients with absolute/end-stage glaucoma.

CONCLUSION

This study concluded that patients with absolute/end-stage glaucoma had a significant improvement in IOP and pain intensity using VAS pain score after treatment with a combination of CCT and retrobulbar CPZ injection compared with patients who only got CCT for treatment.

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