A randomized clinical trial comparing retrobulbar injection of absolute alcohol and chlorpromazine in managing painful blind eyes, Menelik II Hospital, Addis Ababa, Ethiopia

Tadesse T[1], Abeba TG[1], Damji K[2]

[1]Menelik II Hospital, Department of Ophthalmology, College of Medicine, School of Health Sciences, Addis Ababa University, Ethiopia
[2]University of Alberta, Department of Ophthalmology, Alberta, Canada

Corresponding author: Dr. Tesfaye Tadesse, Department of Ophthalmology, Addis Ababa University, P.O. Box 22776, Addis Ababa, Ethiopia. Email: tesfatad2005@yahoo.com

ABSTRACT

Background: Many eye diseases may end up with a painful blind eye. Different management options have been used to alleviate the pain and maintain the globe. Topical medications are frequently used as conservative treatment. Retrobulbar injection of neurolytic agents like alcohol, chlorpromazine (CPZ) or phenol are other medical options that can be considered.
Objectives: Comparing the efficacy and safety of retrobulbar absolute alcohol with chlorpromazine injection in the treatment of painful blind eyes.
Methods: A double masked trial in which patients with painful blind eye, aged 18 years or above, were randomized to receive either a retrobulbar injection of 2ml of absolute alcohol (96%) or 2ml of CPZ (25mg/ml), both with 2ml of lidocaine (2%). Visual Analogue Scale (VAS) is used to objectively measure intensity of pain and level of pain relief after the intervention.
Results: A total of 84 eyes of 84 patients were injected with either absolute alcohol (n=43) or CPZ (n=41). Thirty nine from alcohol group and 35 participants from the CPZ group appeared for third month follow-up evaluation. Sixth month response was also evaluated in 30 and 26 participants from alcohol and CPZ groups, respectively. The mean and standard deviation in VAS pain reduction was 57.9 mm (±32.17) in the alcohol group and 55.4 mm (±31.26) in the CPZ group (P value= 0.734). Based on the improvement in pain intensity 30 patients (79.6%) from absolute alcohol group and 28 patients (80.0%) from CPZ group had significant pain relief after the 3rd month of injection. Statistically significant mean IOP reduction was noted in CPZ group compared to the alcohol group: mean IOP (in mm Hg) reduction at 3rd month was 13.0 vs 2.5 (P-value 0.009). Immediately after the injection complications like burning sensation (20 vs 8), ptosis (2 vs 0) and retrobulbar haemorrhage (0 vs 2) were noticed in alcohol and CPZ group respectively. Lid swelling, external ophthalmoplegia, ptosis, chemosis and skin necrosis were the type of complications observed later on. All the immediate and subsequent complications had resolved spontaneously.
Conclusions and recommendation: Efficacy of pain reduction with retrobulbar injection of absolute alcohol and chlorpromazine was comparable. The choice of retrobulbar injection between the two agents also needs to consider availability and cost. Further study is required to evaluate long term efficacy and safety.

Key words: Blind eye, Pain, Retrobulbar injection, Absolute alcohol, Chlorpromazine, Visual Analogue Scale

INTRODUCTION

Intractable ocular pain in blind eyes may arise from many eye diseases. It is usually difficult to manage adequately[1,2]. Topical medications like anti glaucoma, anti inflammatory, cycloplegics and lubricants are used to treat elevated Intra Ocular Pressure (IOP), inflammation, ciliary spasm or corneal edema[3]. Ablation of the ciliary body can also be utilized to bring down elevated IOP. Some eyes may remain painful despite these relatively conservative measures and require further intervention. Retrobulbar injection of neurolytic agents like alcohol[2], chlorpromazine (CPZ)[4] and phenol[5] have been utilized to control intractable ocular pain in such conditions before considering more definitive surgical management

with enucleation or evisceration, for patients with cosmetically acceptable eyes.

Retrobulbar neurolytic agents like phenol and alcohol of different concentration were in use for more than 100 years and proven to be safe[2,6]. Of these two agents alcohol is widely used and frequently reported in literature. The reported success rates range from 20-87% and the duration of pain relief may extend from 2 weeks to 2 years. Retrobulbar alcohol provides pain relief by coagulating the proteins of the sensory nerve fibers. Pain may recur from regeneration of the sensory nerve fibers if they are not directly exposed to the alcohol and based on the degree and extent of nerve destruction[6]. Burning sensation, blepharoptosis, external ophthalmoplegia, cellulitis, retrobulbar haemorrhage, neurotrophic keratopathy, eyelid edema and conjunctival chemosis have been reported as complications of retrobulbar alcohol injection[2,6-8].

Similarly phenothiazine derivatives like methylene blue were known to have an analgesic effect over a hundred years ago[4]. Fiore *et al*[7] and Bastrikov[8] demonstrated in the 1980's that retrobulbar chlorpromazine (CPZ), a phenothiazine derivative, may serve as an effective and safe option for intractable ocular pain. Since then, CPZ was reported in several studies to be an additional and probably a better alternative[4,7]. However, the mechanism of action of CPZ in control of ocular pain is not well understood. According to Estafanous *et al*[6], the most likely mechanism is the membrane-stabilizing effect which the medication has on the ciliary ganglion. Retrobulbar CPZ injection has been associated with complications that include eyelid edema and conjunctival chemosis, ptosis, phthisis bulbi, cellulitis, external ophthalmoplegia, hyphema, increased intraocular pressure, nausea and vomiting with brief loss of consciousness and fat necrosis. Some patients may also develop reduction in vision, if given to eyes with some residual vision[4,6-8].

Though Visual Analogue Scale (VAS) was not validated in Ethiopia, it has been repeatedly shown to be easy and adaptable to a broad range of populations and settings. It has been shown to be reliable, generalizable and internally consistent measure of clinical and experimental pain. In addition, and most importantly, it was validated as ratio scale capable of measuring change in pain intensity[9,10].

Multiple literatures, which were done under different conditions and on different populations, reported variations in efficacy and safety of retrobulbar alcohol injection[12-14]. In contrast, studies which measured the efficacy of retrobulbar CPZ under different settings on different population reported fairly consistent proportion of patients to achieve pain control. However, to our best knowledge, there is no study done that compared the efficacy and safety profile of CPZ and alcohol injection under similar conditions.

Retrobulbar alcohol for decades and CPZ since the last four years has been used, at the hospital where this trial was conducted, for management of painful blind eyes. The choice of dose, concentration and type of neurolytic agents has been dependent on the ophthalmologist's experience and preference. This trial was therefore set to compare the efficacy and associated complications of retrobulbar absolute alcohol with CPZ in managing intractable pain in blind eyes.

MATERIALS AND METHODS

A randomized, double masked clinical trial was conducted at Glaucoma Clinic of the Ophthalmology Department. Based on WHO visual acuity classification, visual acuity worse than 3/60 regarded as blind eye and considered for the trial. VAS of pain intensity is used in this clinical trial as a tool for measuring pain intensity and extent of reduction in pain after treatment. Patients graded the intensity of pain they had before and after injection on a 100 mm long horizontal line. The end points of the line were anchored by both extremes of pain intensity.

As studies of pain intensity scoring and pain relief measures showed, only those who reported ≥33% VAS reduction were considered to have significant pain relief. Those who reported reduction between 15% to 32% were considered to have some pain relief. Those with VAS reduction of < 15% were considered to have no pain relief[11].

Ethical consideration: The study was conducted after securing approval from Addis Ababa University, Faculty of Medicine, Department of Ophthalmology research and publication committee. Written consent was obtained by a trained nurse at Glaucoma Clinic after the purpose of the trial and treatment was explained to each involved patient. Either the nurse or their attendants would read the consent form for patients in cases they couldn't read. Privacy and confidentiality were assured. Those who were excluded from the study or who refused to participate were given a retrobulbar agent at the discretion of the principal investigator taking into account the will of patients.

Between June 2011 and May 2013, all ophthalmology clinics of the department were informed to refer patients above 18 years of age with painful blind eyes, who had not responded to conservative topical treatment for possible retrobulbar injection. These represented the inclusion criteria. Patients with conditions causing chronic pain in the fellow eye, dependent on analgesic for other systemic illnesses, those who had prior cycloablation and those who were not able to record scores on Visual Analogue Scale (VAS) of pain intensity were excluded from the trial.

On arrival to the glaucoma clinic, patients were assessed as to whether they fulfilled the eligibility criteria. All recruits received an explanation regarding their problem, treatment options and purpose of the study. Patients who were willing to participate in the trial and sign a written consent were assigned randomly to either of the treatment groups.

Sample size: Sample size calculation was based on the primary outcome measure of improvement in VAS-pain average at 3 months and a minimal relevant difference of 6 mm, σ^2= assumed not to exceed 50, 2-sided significance level of 0.05, and power of 95%. The sample size was estimated to comprise of 72 participants; allowing for a dropout of 15%, the total participants needed was estimated at 84 (42 in each group).

Randomization and masking: Patients were randomly assigned in a 1:1 ratio to receive either 2ml absolute alcohol (Alc. 96%) or 2ml CPZ (25mg/ml) (chlorpromazine HCL, Lab. Renaudine- France) retrobulbar injection. Randomization was done by tossing a coin every Monday morning to pick the treatment arm for patients of the week. Head or tail label randomization of the injections was at discretion of the nurse assigned who was oriented for the trial. Both study participants and evaluating ophthalmologists were masked to treatment allocation.

Procedure: Retrobulbar injection technique was similar for both agents. Prior to the injection, explanation was given to each patient on the purpose of the treatment, possible complications and how the injection would be administered**.** The nurse prepared 2ml of 2% lidocaine with adrenaline 1:100,000 and 2ml of either of the two retrobulbar agents in two different disposable syringes with needle size was 24G and $1^{1/2"}$ long for injection. The skin injection site of each patients was cleaned with an alcohol swab. While the patient was on supine position and looking in the primary position of gaze, the needle of the syringe with lidocaine was inserted perpendicular to skin at the lateral one-third of the lower lid just above the inferior rim of the orbit. The bevel faced the globe and once the needle passed the equator of the globe it was directed nasally and backwards towards the muscle cone, where the injection was delivered. The syringe was removed while the needle was kept in place and the assigned neurolytic agent was then delivered through the same needle after two minutes. Both the doctor and the patient were blinded about the type of neurolytic agent administered. Gentle pressure was applied to the eye for a few minutes and the eye was patched under pressure for 24 hrs.

Assessment of outcomes: Patients were evaluated on the same day before and immediately after the injection by the principal investigator. Post injection evaluations were undertaken by two senior consultants at the glaucoma clinic on day 1, day 10, and then at 3 and 6 months. The patients were asked to report their pain intensity on VAS on every visit. A Schiotz tonometer was used throughout the trial to measure IOP. Presence or absence of complications was recorded by senior consultants on each visit using a structured check lists.

Outcome measures: The primary end point was improvement in VAS pain intensity in each individual after three months. The pain intensity as perceived by the patient in the preceding 24 hours was scored by the patient on 100 mm VAS. The secondary end point was rate of associated complications for each group.

Statistical analysis: Outcomes of patients who completed follow up for at least three months were analyzed. Data analysis was performed on an intention-to-treat basis, using SPSS version 19.0. The Student independent and paired t-test were used to compare the mean of the continuous variable (pain intensity). X^2 tests were used to compare the proportions at baseline, 10^{th} day, 3^{rd} month and 6^{th} month.

RESULTS

A total of 101 patients were referred for the trial. Of them, 17 patients did not fulfill the inclusion criteria and were excluded. Two were bilaterally blind and couldn't measure the pain on VAS, four were unable to understand and score on VAS. Two refused to be involved in clinical trial. The remaining 9 refused to come back for follow-up after the injection for they were either too far away from the hospital or they couldn't get someone to accompany them to the hospital. A total of 84 eyes of 84 patients were subsequently recruited and randomized to the treatment groups. Forty three patients were allocated to absolute alcohol group and

41 patients were allocated to CPZ group. Thirty-nine patients of alcohol group and 35 patients of CPZ group completed the evaluation at the third month. Fifty six patients, 30 patients of alcohol and 26 patients of CPZ groups were available for evaluation after 6 months.

Table 1: Demographic and baseline clinical characteristics of treatment groups, Menelik II Hospital, Jan 2011 - Dec 2012 (n=84)

Variable	Group Alcohol (n =43)	Group CPZ (n =41)	p-value
Age(mean)	60.00	62.37	0.400
Sex			
Female	18(41.9%)	14(34.1)	0.507
Male	25(58.1%)	27(65.9)	
Eye			
OD	20(46.5%)	16(39%)	0.516
OS	23(53.5%)	25(61%)	
Vision			
NLP	40(93%)	40(97.6%)	
LP	2(4.7%)	1(2.4%)	0.526
HM	1(2.3%)	0(0%)	
Underlying cause			
Glaucoma	28(65.1%)	32(78.0%)	
Trauma	4(9.3%)	5(12.2%)	0.267
Others	11(25.6%)	4(9.8%)	
Mean IOP in mm Hg (SD)	43.76(17.96)	44.70(16.75)	0.808
Mean VAS (SD)	85.40(14.30)	84.71(12.70)	0.817

Demographic and clinical baseline characteristics of the study population are presented in Table 1. There were no significant baseline differences between the two groups. The mean age was 60 and 62.4 in the alcohol and CPZ groups respectively. The vision of 80 eyes (95.2%) was no light perception (40 eyes in each group). Glaucoma was the underlying cause for 60 (71.4%), of which, 7 had neovascular glaucoma (4 eyes from alcohol group and 3 eyes from CPZ group). The mean IOP prior to the injection was 43.8 mmHg and 44.7 mmHg in the alcohol and CPZ groups respectively.

Figure 1 shows their progress throughout the trial. Average and mean VAS, mean IOP and mean IOP reduction to the baseline at 10th day, 3 and 6 months are demonstrated in Table 2. Both groups demonstrated comparable improvement in VAS-pain intensity after treatment. The improvement in mean VAS-pain intensity three months after injection was 57.9 mm in the alcohol group and 55.4 mm in the CPZ group (p= 0.734); a similar improvement was observed after six months. Based on the >33% VAS reduction in pain intensity 30 patients (79.6%) from absolute alcohol group and 28 patients (80.0%) from CPZ group had significant pain relief at the 3rd month of intervention; this was similar at 6th month, in 24 patients (80.0%) and 21 patients (80.8%) in the respective groups. None of these patients needed further intervention.

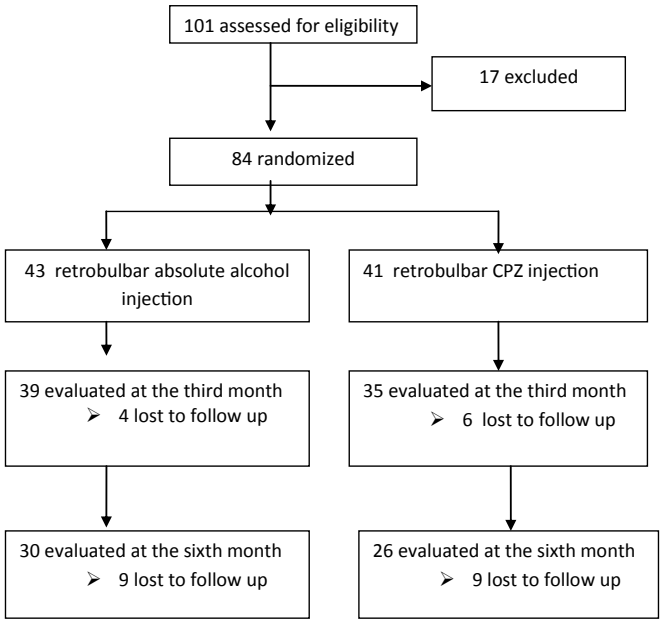

Figure 1: Profile of patients in comparative clinical trial, Menelik II Hospital, Jan 2011- Dec 2012 (n=101)

Eight patients, 5 from absolute alcohol group and 3 from CPZ group, had pain relief in VAS in the range of 20% to 30% after three months of injection and opted to wait for a while before considering further options as the pain was not considered by them to be very troublesome. The remaining 8 patients had <15% reduction in VAS of pain intensity. Of these eight patients, 2 from alcohol and 3 from CPZ groups required a 2nd retrobulbar injection in the first one month. One patient from CPZ group requested other mode of treatment after two months and cycloablation with diode laser was performed. The patient was pain free at last follow up visit (six months). The other 2 patients, from absolute alcohol group, refused repeated retrobulbar injection or other options despite persistent pain.

Table 2: Improvement in VAS and change in IOP after treatment, Menelik II Hospital, Jan 2011-Dec 2012 (n=84)

Variable	Alcohol Group	CPZ Group	P-value
10th day (n)	38	33	
VAS average in mm (SD)	26.5 (24.17)	21.9 (26.82)	0.45
Mean IOP in mmHg (SD)	41.3 (19.27)	30.3 (9.81)	0.006
Mean IOP reduction in mmHg (SD)	2.8 (9.21)	14.8 (15.50)	0.001
3rd month(n)	39	35	
VAS average in mm (SD)	28.9 (29.53)	28.3 (33.10)	0.927
Mean VAS reduction in mm (SD)	57.9 (32.17)	55.4 (31.26)	0.734
Patients with>33% VAS reduction	30 (76.90%)	28 (80.0%)	0.785
Mean IOP in (SD)	39.8 (19.42)	32.4 (13.86)	0.087
Mean IOP reduction (SD)	2.5 (10.27)	13.0 (18.57)	0.009
6th month (n)	30	26	
VAS average in mm (SD)	25.1 (31.85)	24.2 (34.68)	0.916
Mean VAS reduction in mm (SD)	61.6 (34.14)	60.0 (32.63)	0.859
>33% VAS reduction	24 (80.0%)	21 (80.8%)	1.000
Mean IOP (SD)	43.5 (20.75)	28.6 (12.94)	0.004
Mean IOP reduction (SD)	3.0 (9.53)	17.9 (18.36)	0.002

VAS = Visual Analogue Scale IOP = Intra Ocular Pressure CPZ = Chlorpromazine

There were four patients who had some residual vision. Two patients with vision of light perception and one with hand motion were in the alcohol group and the other one patient with vision of light perception was in CPZ group. The patient with vision of hand motion maintained vision until her last visit (9 months). Of the two people who had light perception and assigned to absolute alcohol group, one maintained her vision till her last visit (6 months), but the second patient developed phthitic bulbi and the vision became NLP at 6 months. The patient in CPZ group had vision improvement to hand motions and maintained this at the last visit (6th month).

Statistically significant mean IOP reduction was noticed in CPZ groups compared to those who had alcohol injection (Table 2). Mean IOP reduction at 10 days, 3 and 6 months for the CPZ vs absolute alcohol group was 14.8 vs 2.8, 13.0 vs 2.46 and 17.9 vs 3.0 (P-value 0.001, 0.009 and 0.002 respectively). Two patients were uncooperative and did not undergo IOP measure at baseline and all follow-up visits.

Table 3: Encountered complications after injection, Menelik II Hospital, Jan 2011- Dec 2012 (n=84)

Complications	Alcohol Group (n =39)	CPZ Group (n =35)	p-value
During injection			
Burning sensation	20 (51.3%)	8 (22.9%)	0.016
Ptosis	2 (5.1%)	0 (0.0%)	0.495
Retrobulbar haemorrhage	0 (0.0%)	2 (5.7%)	0.220
During follow-up			
Lid swelling	31 (79.5%)	29 (82.9%)	0.773
External ophthalmoplegia	10 (25.6%)	11 (31.4%)	0.615
Ptosis	13 (33.3%)	7 (20.0%)	0.295
Chemosis	14 (54.3%)	16 (45.7%)	0.390
Skin necrosis	4 (10.3%)	1 (2.9%)	0.361

Among the post injection complications (Table 3), burning sensation was the most frequently complaint immediately after injection in both groups, with significantly larger number of patients in the alcohol group [20 (51.3%) vs 8 (22.9%), p=0.016]. Ptosis was noted in two eyes from the alcohol group immediately after the injection. Retrobulbar haemorrhage occurred in two eyes from CPZ group right after the injection. All these immediate post injection complications were resolved in two weeks to three months time except, one ptotic eye with external ophthalmoplegia (alcohol group) that took more than 3 months to resolve completely.

Skin necrosis around the injection site was the other type of complication noticed in five eyes, 4 eyes in alcohol group, during follow-up time. The necrosis was noticed five to seven days after the injection and healed without scar in three weeks time. Lid swelling, ptosis, chemosis and external ophthalmoplegia were the remaining complications noticed in both groups during the follow-up time.

DISCUSSION

The study has identified comparable efficacy in pain relief in both retrobulbar absolute alcohol (76.9%) and CPZ (80.0%) groups. Moreover, no statistically significant difference was found in the type, rate and course of complications between the two agents, other than the burning sensation after injection, that was more common in the absolute alcohol groups.

In addition to the 30 patients (76.9%) that had significant relief of pain for at least three months with only single retrobulbar absolute alcohol injection, another 5 patients (12.8%) reported some improvement not requiring re-injection. This make overall rate of complete and partial relief of 89.7% that is comparable with finding of Olurin and Osuntokun from Nigeria[12]. They reported that 65 patients out of 75 (87%) achieved pain relief with single injection of 96% alcohol. Al-Faran *et al*[2] also reported similarly comparable efficacy of 82% in controlling pain for three months using absolute alcohol. On the other hand, some studies reported that the pain controlling effect of retrobulbar alcohol wears off sooner. Maumene[13] in one of the foremost reports of retrobulbar alcohol use; reported only 20% (3/15) of eyes managed to maintain pain relief for three months and longer. As pain controlling effect of alcohol depends on its local protein coagulation and lipid precipitation of peripheral nerves; using relatively lesser concentration of alcohol (80%-95%) might also have affected to the lower efficacy. Similarly Fejer[14] reported only 60% (3/5) of eyes which were given retrobulbar alcohol of 80% concentration, got pain relief adequate enough to avoid enucleation. Again use of less concentrated alcohol and the small sample size might have contributed for lower rate of efficacy.

Complete and partial pain relief was achieved in 86.6% in the CPZ group at 3 months in this trial, which is comparable with report of Fiore *et al*[7], in which, 83% (52/ 63) patients had complete and partial pain relief after retrobulbar CPZ injection for painful blind eye. Another larger study by Bastrikov[8] also reported 83.8% (47/56) of pain relief. A recent study by Chen *et al*[4] reported 88.6% (31/35) pain relief sufficient enough to avoid the need for further measures.

Most published studies tried to determine the efficacy of neurolytic retrobulbar agents by computing the proportion of study subjects with reduced pain intensity. Accordingly in this trial mean reduction in pain intensity was compared primarily.

No reported comparative study was found to compare with the current trial. The observed rates of clinically significant and some pain reduction after three months of injection were similar in patients who were given retrobulbar alcohol (76.9%, 12.8%) and those who were given CPZ (80.0%, 8.6%). Mean VAS average score and mean reductions of VAS were found to be similar as well. The similarity in efficacy was maintained even after six months. Of the 56 study patients, who came for evaluation after six months, 80% (24/30) of alcohol group and 80.8% (21/26) of CPZ group reported significant pain reduction. The difference in dropout rate at 6th month evaluation (32% for alcohol and 37% for CPZ) might have affected the results.

In the study by Chen *et al*[4] retrobulbar CPZ injection was noted to cause 36.6% reduction in average IOP after three months of injection. This rate is higher than the reduction noted in this trial (27.5%). The reduction in IOP was not found to be associated with reduction in VAS. The current trail and other studies found no IOP reduction with retrobulbar alcohol injection.

Eyelid edema and chemosis, ptosis, phthisis bulbi, sterile orbital cellulitis, external ophthalmoplegia, retrobulbar haemorrhage, neuroparalytic keratitis, increased intraocular pressure, nausea and vomiting and fat necrosis were reported with both agents. These complications, due to either of the agents, appeared to be temporary with inevitable spontaneous resolution[2,4,6,7,13,15]. Since most literatures on the subject was retrospective in design, non-comparative and most were case series with small sample size; the rate and course of complications of previous studies could not be compared with this study.

Significantly higher proportion of patients from alcohol group experienced burning sensation (51.3% vs 22.9%, p-0.016). This statistically significant difference might not have clinical significance as such because it merely lasts hours and might be avoided by allowing time for lidocaine to numb the nerves. Ptosis (Alcohol group) and retrobulbar haemorrhages (CPZ) were the remaining immediate complications observed, which occurred in 2 patients each, few for significance.

Lid swelling, conjunctival chemosis, ptosis, skin necrosis and external ophthalmoplegia were the kind of complications encountered in both groups during

the follow-up. Lid swelling and chemosis were the two most common side effects noticed for both alcohol and CPZ groups (79.5%, 54.3% and 82.9%, 45.7% respectively). This figure is higher than that reported by Fiore *et al*[7] (40%) and Indeikina[15] (47%). Unlike the other studies, in this trial no clamp was used to stabilize the needle during the injection. This might have resulted in unsteady injection and extravasation of the agents into periocular region to cause higher rate of lid edema and chemosis. However, there was no permanent complication noted in both treatment groups.

Literatures on impact of retrobulbar injection of neurolytic agents on vision are lacking. Only few observations were reported. Estafanous *et al*[6] reported visual reduction in two eyes out of five (40%) after being given retrobulbar CPZ. Chen *et al*[4] also reported one of the two eyes which had vision of light perception went to no light perception after retrobulbar CPZ injection. In this trial one of the three eyes with some remnant vision and assigned to alcohol group had gone from light perception to no light perception in six months. The other two patients (HM and LP) maintained their vision to their last visit. One eye which was injected CPZ showed improvement in vision from LP to HM. This improvement could be explained by resolved corneal edema as the IOP reduced markedly after the injection. These numbers are quite small and don't permit comparison between the two agents or between the studies.

CONCLUSIONS AND RECOMMENDATION

Efficacy of pain reduction with retrobulbar injection of absolute alcohol and chlorpromazine was comparable. Complication rates were also similar; however, chlorpromazine caused less burning sensation and was superior in IOP reduction. The choice of retrobulbar injection between the two agents will also need to consider local availability and cost. Further study is required to evaluate long term efficacy.

REFERENCES

1. Philip C, Chet R. Enucleation of blind, painful eyes. *Ophthalmol Plastic Recons Surg*. 2000; **16** (5):326–329.
2. Al-Faran MF, Al-Omar O. Retrobulbar alcohol injection in blind painful eyes. *Ann Ophthalmol.* 1990; **22**:460–462.
3. Custer L, Reistad E. Enucleation of blind, painful eyes. *Ophthalmol Plast Reconstr Surg*. 2000; **16**:326-344.
4. Chen TC, Ahn Yuen SJ, Sangalang MA, *et al.* Retrobulbar chlorpromazine injections for the management of blind and seeing painful eyes. *J Glaucoma.* 2002; **11** (3): 209-213.
5. Birch M, Strong N, Brittain P, *et al*. Retrobulbar phenol injection in blind painful eyes. *Ann Ophthalmol.* 1993; **25**: 267–270.
6. Estafanous MFG, Kaiser PK, Baerveldt G. Retrobulbar chlorpromazine in blind and seeing painful eyes. *Retina.* 2000; **20**: 555–558.
7. Fiore C, Lupidi G, Santoni G. Effet de l'injection retrobulbaire de chlorpromazine dans le glaucome absolu. *J Fr OphtHalmol.* 1980; **3**: 397–399.
8. Bastrikov NI. Symptomatic treatment of terminal painful glaucoma by the retrobulbar administration of aminazin. *Vestn Oftalmol.* 1989; **105**:47–49.
9. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain.* 1983; **17**: 45-56.
10. Price D, Harkins W. The combined use of visual analogue scales and experimental pain in providing standardized assessment of clinical pain. *Clin J Pain.* 1987; **3**: 3-11.
11. Mark P. Jensen, Connie Chen, and Andrew M. Brugger Interpretation of Visual Analog Scale Ratings and Change Scores. © 2003 by the American Pain Society.
12. Olurin O, Osuntokun O. Complications of retrobulbar alcohol injections. *Ann Ophthalmol.* 1978; **10**: 474–476.
13. Maumenee AE. Retrobulbar alcohol injections: relief of ocular pain in eyes with and without vision. *Am J Ophthalmol.* 1949; **32**: 1502–1508.
14. Fejer J. The treatment of painful absolute glaucoma and other eye diseases with retrobulbar injections of alcohol. *Am J Ophthalmol.* 1932; **15**:135–136.
15. Indeikina GV. Retrobulbar injections of aminazin during cupping in acute attacks of terminal glaucoma. *Oftalmol Zh*. 1987; **21**:122–123.