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Evaluation of Daunorubicin as an adjuvant in Trabeculectomy

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Abstract
Purpose of the study is to evaluate the intraocular pressure (IOP) lowering effect and ocular side effects of Daunorubicin (DNR) in drug modulated trabeculectomy.
Method: *A prospective study was conducted on 50 eyes of 49 patients. Only primary open angle cases were taken up for the study. These were randomly divided into equal groups. Group I underwent modified trabeculectomy with application of 0.2mg/ml of Daunorubicin (DNR) intra operatively. Group II underwent conventional trabeculectomy, patients were followed for six months. Parameter including visual acuity , IOP by NCT/ shiotz, slit lamp examination were performed on every visit. An IOP of 21mg Hg or less were taken as criteria for success.*
Results: *48% of the patients were males and 52% females. The visual acuity was maintained at preoperative levels for all cases except two in which it improved from 6/24 top 6/18 in group I and deteriorated from 6/9 to 6/18 in one patient in group II. The final mean IOP at 24 weeks was 14.23 + 4.94 mm Hg in group I and 16.2 + 5.07 mm Hg in group II. A success rate of 92% (IOP < 20mm Hg) was obtained in S/C Daunorubicin versus 84% in group II at 24 weeks.*
Conclusion: *These results indicate primary trabeculectomy with Daunorcubicin to be associated with 92% success rate and lower mean IOP levels as compared to those undergoing Primary trabeculectomy without adjuvant Daunorubicin.*
Keywords: *Trabeculectomy, Daunorubicin, Intraocular Pressure (IOP).*

Introduction

Glaucoma is a serious sight threatening disorder. India being the second most populous country in the world[1]. The most common type of glaucoma is primary open angle glaucoma (POAG) the other being narrow angle glaucoma and secondary glaucoma. In present study we have taken patients with POAG. In POAG, the eye drainage canals become blocked and the fluid accumulation causes pressure to build up within the eye. This pressure (IOP) can cause damage to the optic nerve. When medical and laser therapy fail to control IOP, glaucoma filtration surgery needs to be performed. Conventional trabeculecomy was first time introduced by Cairns[2] and is the most widely used glaucoma filtration surgery (G.F.S) in POAG. The most common cause of failure of GFS is the fibrosis at the conjuctival episcleral interface. Glaucoma surgery is unique in its success as it is linked to interruption of the wound

healing response in order to maintain patency of the new filtration pathway. The healing and scarring determine the percentage of patients achieving low final intraocular pressure (IOP) which is not associated with glaucoma progression.

The use of anti-fibrotic agents to inhibit scarring of trabeculectomy blebs is now a well established clinical practice. The advent of anti-fibrotic agents, such as Mitomycin- C and 5- Fluorouracil has vastly prolonged the longetivity of the bleb but concerns remain regarding the potential increase in post operative complications. Newer pharmacological compounds and materials have been developed in recent years of the many anti proliferative drugs tested, Daunorubicin (DNR) appears to be one of the most potent [3] drug. DNR is an anthracycline anti tumor antibiotic produced by the fungus Streptomycis peucetius var. caesius. Like other antibiotic of its group, DNR has a tetracycline ring structure with an unusual sugar, daunosamine attached by the glycoside linkage. DNR is an anti metabolite that inhibits fibroblast proliferation invitro and invivo[4], the antifibroblastic action of DNR has been used to improve success rate of various ophthalmic surgeries, strabismus surgery[5], Pterygium surgery [6] and retinal detachment [7] surgery. DNR aided glaucoma filtration surgery has shown 87% success rate as reported by other surgeons [8].

Material and Methods

This study was conducted at Government Medical Collage, Jammu. It included patients with primary open angle glaucoma only. 50 eyes of 49 patients were included. An approval from research ethnical committee and an informed consent from every patients was obtained. Patients were randomly assigned to two groups. Group I and Group II. Group I underwent modified trabeculectomy with application of 0.2mg/ml of DNR for three minutes intra operatively. Group II underwent conventional trabeculectomy. Each vial containing 20mg DNR was diluted with 10ml of normal saline, i.e 2mg/ml. from this solution 0.1ml was withdrawn in a sterile tuberculin syringe. The cellulose sponge was soaked in 0.2mg/ml of DNR and applied for 3 minute at the proposed site of trabeculectomy before preparation of the partial thickness sclera flap.

Surgery was performed by standard surgical technique by one surgeon under peribulbar anesthesia and facial block. A 4x6 mm rectangular sclera flap was outlined and half thickness scleral flap raised. A 2x2mm block of inner sclerostomy was excised using vannas scissors and peripheral iridectomy done. Daunorubicin was applied intra operatively as 4x6mm soaked cellulose sponges soaked in 0.2 ml of 0.2mg/ml, Daunorubicin was applied under the conjunctiva for 3 minutes. Post operatively the patient received oral antibiotics and analgesics for 5 days and topical antibiotic steroid drops administered for 4-6 weeks. Patients were assessed on day 1, day 7 and subsequently every 2 weeks for a period of six months.

Criteria of success was defined as 10P < 20mm Hg by Shiotz/ N C T without anti glaucoma medication. Final IOP > 21 mm Hg with medication was regarded as a failure of the operative procedure.

Results

The patients of POAG were divided into two equal groups I and group II as discussed. The mean age of patients was 56 + 16.26 years (Range 24-80 years) in group I and 61.36 + 11.95 years in group II. There was no difference statistically in the distribution of males and females in two group.

Table I: Preoperative visual acuity

Visual acuity	Group I	Group II	Total
6/6—6/9	3	1	4
6/12—6/18	4	4	8
6/24—6/60	12	12	24
<6/60	6	8	14

p value >0.1 (Non Significant)

The visual acuity distribution of two groups was found to be statistically insignificant. Those with visual acuity <6/60 had a mean Cup Disc Ratio of 0.8 and 57.14% of them had associated cataract.

Preoperative Intraocular Pressure

It was recorded with Schiotz tonometter/ Non contact tonometer. Different level of IOP observed in the two groups are shown in table II

Table II: Preoperative intraocular Pressure

IOP (mm Hg)	Group I		Group II	
	No of eyes	% age	No of eyes	%age
20-30	10	(40%)	9	(36%)
31-40	13	(52%)	8	(32%)
41-50	2	(8%)	6	(24%)
51-60	~	~	2	(8%)
	Mean 30.14+5.6		**Mean 30.0+9.49**	

The preoperative IOP was recorded in both the groups with the use of antiglaucoma medications. The mean IOP of the group I was 30.14+5.6 mm Hg (range 23—43.4 mm Hg). The mean IOP of group II was 30.0+9.49 (range 21—50 mm Hg).

Cup – Disc Ratio (Ophthalmoscopy)

It was possible only in those patients where media was sufficiently clear to enable adequate visualization. The main cause of inadequate visualization was advanced lenticular changes or corneal edema. There was 6 such eyes in group I and 4 in group II. The details of the cup disc ratio are summarized in Table III.

Table III: Cup-Disc ratio

Cup Disc Ratio	Group I	Group II	Total
0.3—0.4	0	0	0
0.5—0.6	6	10	16
0.7—0.8	8	8	16
>0.8	5	3	8
No. of patients	19	21	40

Cataract

Cataract was present in 68% of the cases (34 out of 50).

Table IV: Presence of cataractous changes

Cataract	Group I	Group II	Total
Present	21 (84%)	13 (52%)	34 (68%)
Absent	4 (16%)	12 (48%)	16 (32%)

Gonioscopy:

It was possible only on 19 eyes in group I and 21 eyes in group II.

Table V: Gonioscopic Findings

Gonioscoic findings	Group I		Group II	
	(No of eyes)	(%age)	(No of eyes)	(%age)
Gonioscopy possible	19	76%	21	84%
Not possible	6	24%	4	16%
Grade of Angle in cases where Gonioscopy was possible				
Grade Iv	5	20%	5	20%
Grade III	14	56%	16	64%
Grade II	~	~	~	~
Grade I	~	~	~	~
Grade 0	~	~	~	~
Pseudoexfoliation	6	24%	4	16%
Neovascularisation of angle	~		~	

Visual fields: The visual filed could not be assessed in 20 patient due to poor visual acuity. (Humphrey- Galucoma Hemified test 30—2 full threshold test was used) In group I, 6 patient showed generalised depression, 4 showed paracentral scotoma/nasal step, 5 showed Arcuate/double Arcuate scotoma and tubular field/temporal island of vision in 3 patients. Similarly in group II- 4 patient showed generalised depression, 6 showed paracentral scotoma/nasal step and 2 showed Arcuate/double Arcuate scotoma.

Post operative data

Post operative visual acuity: The visual acuity of the patients belonging to group I and group II eyes at the end of 24 weeks in shown in the Table V.

Table V: Postoperative visual acuity at 24 weeks

Visual acuity	Group I	Group II	Total
6/6—6/9	3	0	3
6/12—6/18	6	4	10
6/24—6/60	10	13	23
<6/60	6	8	14

The best corrected visual acuity was maintained at the preoperative level in all patients at the end of follow up except two. It improved in these two patients from 6/24 to 6/18 in group I. it deteriorated in one patient in group II from 6/9 to 6/18.

Intraocular pressure post operative: The variation of the post operative intraocular pressure with time in summarized in Table VI.

Table VI: post operative intraocular pressure

Follow up (in weeks)	Group – I (IOP in mm Hg)					Group II (IOP in mm Hg)				
	< =6	7-10	11-15	16-21	21-30	<=6	7-10	11-15	16-21	21-30
1	4	3	8	8	2	1	6	10	4	4
2	0	4	12	7	2	0	3	13	5	4
6	0	2	16	5	2	0	2	13	6	4
12	0	4	17	2	2	0	2	13	6	4
24	0	4	18	1	2	0	2	13	6	4

The preoperative and post operative intraocular pressure recordings were compared statistically and a significant difference (p value < 0.01) was observed for both the group till the end of follow up. Additional medications were added as and when needed for control of IOP in cases where IOP was >21 mm Hg. Mean post operative and initial IOP in group I and II eyes was compared (Table VII and II). The average post operative IOP at the end of follow up of 24 weeks was 14.23 + 4.94 mm Hg, in the group I, and 16.2+ 5.07 mm Hg in group II. Average fall in the post operative intraocular pressure was 15.94 + 7.61 mm Hg (52.89%) in the group I and 10.88 + 3.62 mm Hg in the group II (32%)

Table VII: Mean post operative IOP in group I and II

No of weeks weeks	Mean post operative IOP	
	Group I	Group II
1	13.28	14.88
2	14.27	15.61
6	14.48	16.82
12	14.97	16.12
24	14.23	21.8

p value ('t' test < 0.01) (significant)

Average fall in post operative IOP was 52.89% in group I and 32% in group II. Comparison of the mean IOP during pre operative and post operative periods in the two groups is shown in Table VIII.

Table VIII: comparison between pre-operative and post operative IOP

IOP	Group I	Group II
Pre- operative	30.14 + 5.6	34.0+ 9.49
Post- operative	14.23+ 4.94	6.2 + 5.07

p value < 0.001 (HS) p value <0.005 (S)

The fall in IOP in group II is found to be significant but in group I the fall in IOP is highly significant.

Bleb characteristic: There was a characteristic diffuse, elevated vascular bleb in majority of patients (80%) in group I. In group II the bleb was thin and localized (48%) and thick in (36%), (16%) showed flat vascular blebs.

Complications: - Hypotony is this study was taken to be an IOP less than 6 mm Hg. The incidence of hypotony was 16% in group II. It is a notable that in group I, all the four cases developed hypotony on day 1 which resolved by day 7. Post operative Hyphaema was present in 4% of group I eyes which resolved spontaneously within one week. No cases of hyphaema were there in group II eyes. Sub conjunctival haemorrhage was seen in 12% cases (3 eyes) in the group I. No such complication was observed in group-II. No corneal changes like corneal edema/epithelial changes were observed in either of the groups.

Discussion

The aim of a successful glaucoma filtration Surgery is to control and maintain IOP, which stops the progression of the disease. It should also be safe for the ocular tissue, the major cause of failure of GFS is the bleb scarring. Many Pharmacological agent like Mitomycin C, 5 FU having anitfibroblastic action have been used in modulated trabeculectomies[10,11] . Although these antimetabolites have successful in enhancing IOP control in humans, their use have been associated with side effects such as corneal erosions, leaking blebs, cataract formation, late endophthalmitis and hypotony leading to maculopathy[12,13]

In glaucoma, anitfibroblastic action of DNR has been evaluated experimentally and clinically by many researchers like Morales et al.[10], Rabowsky et al[16] who have worked on rabbits as a model.

Dermailley et al[16] used DNR during trabeculectomy in human eyes. He compared the results of subconjunctival 5 FU and subconjuntival DNR injections before filtering surgery. The success rate was 79% with 5 FU & 68% with DNR they noted the complication Such as flat anterior chamber choroidal detachments, Corneal ulcers are less in cases with DNR modulated surgery. Dadeya et al [5.6] has evaluated DNR in strabismus and pterygium surgery he reported less of recurrence rate of pterygium when using DNR. In strabismus surgery the alignment and motility of the ocular muscles was better with DNR. Kumar et al[15] has used DNR vitreoretinal surgery, he encluded that DNR seemed to be effective to suppress proliferation.

In this study, and attempt has been made to evaluate the IOP lowering effect and safety of DNR, an anti fibroblastic adjunct. In this study patients had a mean age of 56 + 16.26 years 48% were males and 52 were females. The visual acuity was maintained at preoperative level, similar results were seen by D.Verma et al[15], and Agarwal[8] . Percentage fall of IOP following DNR modulated trabeculectomy in our study (52%) was similar to Agarwal et al[8], (59.57%), D Verma et al [15] (59%) at the end of six months follow up. In the study group I, one person developed shallow anterior chamber on first way which resolved spontaneously without treatment as also reported by D Verma et al[15]. Hypotony was observed in 4 cases in group I and one case in group II and resolved by day seven. This finding is in concurrence with D Verma et al[15].

Conclusion

The intra- operative adjuvant use of Daunorubicin in primary open angle glaucoma produces highly significant pressure lowering effect compared to standard trabeculectony. It is found to be a safe anti metabolite with almost no side effect. However larger study with considerable number of years will eventually demonstrated its safety and efficiency.

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