MEDICAL TREATMENT OF GLAUCOMA

A STUDY ON ONE DROP TOPICAL APPLICATIONS OF PILOCARPINE 2% AND LEVOBUNOLOL 0.5%

AND

THE NORMAL DIURNAL INTRAOCULAR PRESSURE VARIATION AT THE KENYATTA NATIONAL HOSPITAL

A DISSERTATION SUBMITTED AS PART FULLFILMENT FOR THE DEGREE OF MASTER OF MEDICINE (OPHTHALMOLOGY) OF THE UNIVERSITY OF NAIROBI

BY

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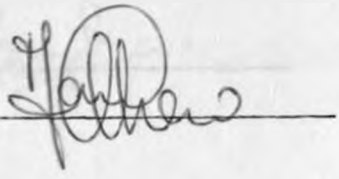
1988

DECLARATION

This dissertation is my original work and has not been presented for a degree at any other University.

SIGNED  DATE 21/6/88

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CONTENTS

I. INTRODUCTION

1. DEFINITION OF GLAUCOMA

Glaucoma is an eye disorder in which an intraocular pressure that is too high for the health of the eye causes the optic disc to be cupped and atrophic, and the visual field to develop characteristic nerve fibre bundle defects. (1).

Normal intraocular pressure (IOP) ranges from 10-21mmHg with an average of 15.5 mmHg. It is maintained by a balance in rate of aqueous production and outflow.

Glaucoma is variously classified according to age of onset (childhood vs. adult), aetiology (primary vs. secondary), and pathogenic mechanism (open angle vs. closed angle). (1)

Primary glaucoma in adults is that type for which no ocular cause is known, while secondary glaucoma is that which is secondary to a specific ocular or systemic disorder.

This study was carried out on patients with primary open angle glaucoma (PoAG), which is also called chronic open angle glaucoma (CoAG) or chronic simple glaucoma (CSG). This class of glaucoma is characterised by raised

resistance to aqueous outflow in the presence of an open anterior chamber angle.

2. EPIDEMIOLOGY OF GLAUCOMA

Glaucoma is one of the leading causes of blindness in the world accounting for approximately 20% of the worlds blindness. (2)

In Kenya glaucoma is the third commonest cause of blindness (14%) after cataracts (43%) and trachoma (16%). (3)

Primary open angle glaucoma is the most commonly diagnosed type of glaucoma at the Kenyatta National Hospital and indeed in Kenya as a whole.

3. AIMS OF THE STUDY

3.1 To determine the one drop intraocular pressure curves for two drugs commonly used in the medical treatment of glaucoma at the Kenyatta National Hospital, pilocarpine 2% and levobunolol 0.5% (a B-blocker) and hence compare the onset, magnitude and duration of response for both drugs used individually and in combination.

3.2 To determine what effect the topically applied drugs have on the cardiovascular system of the patients in terms of pulse and blood pressure (BP) changes.

3.3 To determine if the clinical state of the eye e.g. level of intraocular pressure has any correlation with the response to treatment.

3.4 To determine the diurnal intraocular pressure variation in normal subjects.

3.5 To compare the findings in this study to the findings in other studies carried out elsewhere in the world.

4. PHARMACOLOGY OF PILOCARPINE

Pilocarpine is the oldest ocular hypotensive drug and has been in use for well over one hundred years. It is a direct acting parasympathomimetic drug that lowers intraocular pressure by increasing facility of aqueous outflow. It accomplishes this by stimulating the contraction of the ciliary muscle which by its direct attachment to the scleral spur opens up the trabecular meshwork and schlemm's canal enhancing aqueous outflow. (4) Pilocarpine is also thought to lower intraocular pressure by reducing aqueous production since the reduction in pressure has been reported to exceed and outlast the improvement in outflow facility. (4) (5) Maximum intraocular pressure lowering effect occurs at 2 hours after instillation and lasts for 8 hours. (4) Standard pilocarpine, which is available in several concentrations, is generally given six hourly to insure adequate pressure control. Common ocular side effects are: iduced myopia due to ciliary muscle spasm and myosis. Systemic side effects are variable. (4)

5. PHARMACOLOGY OF LEVOBUNOLOL

Levobunolol, like other B-blockers, is relatively new in the market for glaucoma therapy. B-blockers lower the intraocular pressure by reducing aqueous formation, and this is accomplished by their direct action on the ciliary epithelium to block active transport and ultrafiltration by which aqueous humour is formed.

For normal ionic transport in the ciliary epithelium cyclic-AMP, whose synthesis is catalysed by the enzyme adenylate cyclase, is necessary. B-blockers reduce the activity of this enzyme by binding to the B-adrenergic receptors in the ciliary epithelium rendering them non responsive to catecholmaine stimulation. (4) (5)

The maximum pressure lowering effect of B-blockers occurs in 2-6 hours, and the pressure remains low for 24 hours. (4) The drugs are however applied 12 hourly to insure adequate pressure control. Unlike pilocarpine, B-blockers do not affect pupillary size or visual acuity and are relatively free from systemic side effects. They should however be prescribed cautiously for patients with known contraindications to systemic use of B-blockers e.g. obstructive pulmonary diseases like asthma, and heart failure. (6)

II SUMMARY

In this controlled study, one drop intraocular pressure curves were plotted for 50 patients over 6 hours. the patients were treated with levobunolol 0.5%, pilocarpine 2%, levobunolol/pilocarpine combined and placebo. It was found that levobunolol produced some effects on the cardiovascular system, lowering pulse rate and blood pressure to a statistically significant but clinically insignificant degree, while pilocapine had no such effects. The magnitude of response to treatment was larger with levobunolol than with pilocarpine and the two when used together had an additive effect.

Onset of action was more prompt with pilocarpine but its ocular hypotensive effect was short lived as the IOP started rising again after 4 hours, while levobunolol continued to lower the IOP upto the 6th hour. At 2 hours the IOP fall was 83.7% of the total fall for levobunolol while it was 100% for pilocarpine. Levobunolol produced a contralateral effect when topically applied to one eye while pilocarpine did not, and for both drugs the magnitude of response appeared to be directly proportional to the pre-treatment intraocular pressure level. As for the normal diurnal IOP variation, the mean amplitude of variation was found to be 4mmHg with the IOP being highest in the morning at 6 am and lowest in the the evening at 6 pm in the 40 eyes studied.

III MATERIALS AND METHODS

1. DRUGS:
   - Pilocarpine 2%
   - Levobunolol 0.5%
   - Placebo (Normal saline)

2. APPARATUS:
   - Snellens 6m visual acuity chart
   - Haag streit slit lamp, with
   - Goldmann applanation tonometer
   - Direct and indirect ophthalmoscopes
   - Local anaesthetic drops (Benoxinate HCL)
   - Fluorescein drops
   - Sphigmomanometer and stethoscope
   - Timer (watch)

3. PATIENTS

The patients who participated in the one drop intraocular pressure curve study were selected from among those attending the Kenyatta National Hospital eye clinic with chronic simple glaucoma. Both unoperated eyes and those operated but uncontrolled were included in the study. Excluded were those with corneal abnormalities preventing reliable tonometry, aphakia, ocular inflammation and patients with cardiovascualr or respiratory disorders. Altogether the one drop curves were plotted for 50 patients (100 eyes) divided into 4 groups thus:

a) levobunolol group - 15 patients (30 eyes)

b) pilocarpine group - 15 patients (30 eyes)

c) Combined pilocarpine/levobunolol group 10 patients (20 eyes)

d) placebo group - 10 patients (20 eyes)

For the normal diurnal intraocular pressure varation curve, the participants were chosen from 2 groups:-

a) well parents admitted to the eye wards to care for their sick children.

b) patients admitted to the eye wards who had at least one normal eye, i.e. eyes with no ocular pathology except for early senile lenticular changes - these normal eyes were used in the study.

Altogether 40 eyes from 18 patients were used of which 18 were of well parents, 16 were patients with one normal eye while 6 were of patients whose both eyeballs were normal. Patients whose one eyes were used had a variety of disorders in the fellow eyes that included: aphakia, trauma, tumors, dense cataracts and corneal ulcers, while those whose both eyes were used had lid plastic surgical problems with normal eyeballs.

4. METHODS

a) one drop IOP curves: - patients who had been on treatment prior to the study were subjected to 'wash-out' before entering the study. They were asked to discontinue medication as follows:-

pilocarpine - at least 2 days

diamox - at least 3 days

B-blockers - at least 2 weeks

These are the periods required for the effects of these drugs to completely ware off. (7) (8) Those admitted into the study then underwent a systematic assessment that included history and examination, both ocular and cardiovascular (ref. study form). the history included name, age, sex, symptoms and duration and previous treatment(s) Examination included - best visual acuity with pinhole, slit lamp examination, tonometry, fundoscopy, heart rate and blood pressure (BP). For each patient, one eye randomly chosen received a drop of the drug(s) while the fellow eye which acted as the control received a drop of normal saline, except for those in the placebo group in whom one eye received a drop of normal saline while the fellow (control) eye received nothing. Tonometry was carried out at 0, ½, 1,2,4 and 6 hours and recorded graphically. Pulse counted over one

minute, and blood pressure were recorded at the expected peak effect time for each drug i.e. 2 hours for the pilocarpive group and 6 hours for the levobunolol and combination groups. As for the placebo group this was arbitrarily done at 6 hours. The study was carried out in the eye clinic commencing in the mornings (8-10am) and ending in the afternoon (2-4pm) each patient being observed for six hours.

b. The normal diurnal intraocular pressure variation:- the baseline data included age, sex, visual acuity (with pinhole where necessary), disease of the sick eye (where present), slitlamp examination and fundoscopy to rule out any anomalies. Serial tonometry was done every three hours for 24 hours and recorded graphically. The study commenced at 9 am and ended at 9 am the following day.

To minimise the effects of ambulation and recumbency on intraocular pressure, the participants were asked to be seated quietly for at least five minutes prior to each measurement. There were no instructions given as to the participants fluid intake.

MEDICAL TREATMENT OF GLAUCOMA STUDY FORM

(ONE DROP IOP CURVES & THE NORMAL VARIATION CURVE)

HISTORY

GROUP _____ CASE NO. _____ DATE _____

NAME _____ SYMPTOMS & DURATION _____

AGE _____ _____

SEX _____ PREVIOUS TREATMENT(S) _____

IP/OP NO. _____ _____

EXAMINATION

	RE	LE
VA	_____	_____
TONOMETRY	_____	_____
ANT. SEGMENT	_____	_____
C/D RATIO	_____	_____
VESSELS NASAL SHIFT	_____	_____

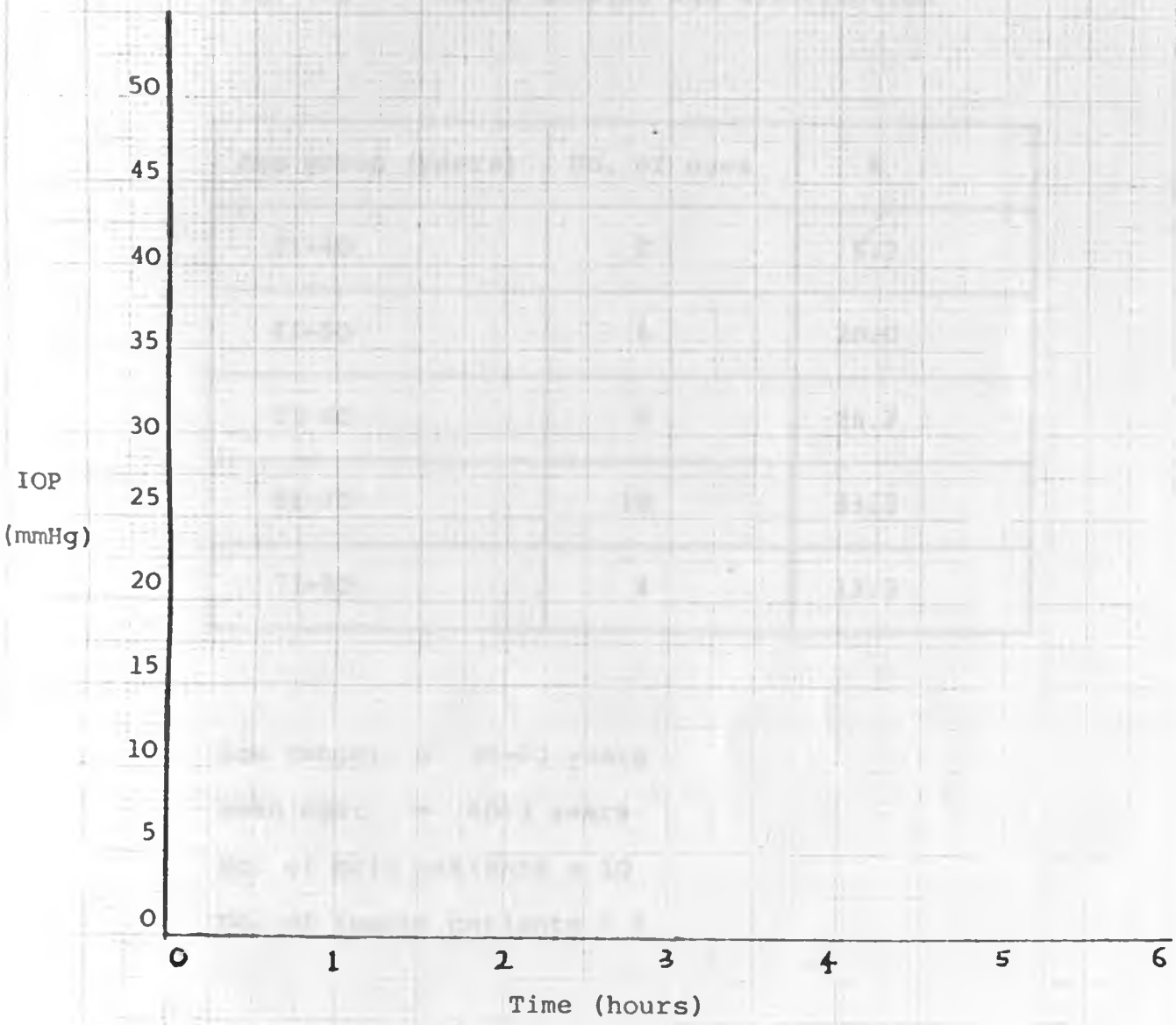
PULSE: INITIAL _____ 2 hours _____ 6 hours _____

BP: INITIAL _____ 2 hours _____ 6 hours _____

TREATMENT

RE _____ LE _____

TONOMETRY GRAPH



IV RESULTS

1. LEVOBUNOLOL GROUP

Fig. 1.1 - table showing age distribution

Age group (years)	No. of eyes	%
31-40	2	6.7
41-50	6	20.0
51-60	8	26.7
61-70	10	33.3
71-80	4	13.3

Age range: = 38-80 years

Mean age: = 60.3 years

No. of male patients = 10

No. of female patients = 5

Fig. 1.2 - table showing range of visual acuity

Visual Acuity	No. of Eyes	%
6/6	3	10.0
6/9	4	13.3
6/12	7	23.4
6/18	1	3.3
6/24	4	13.3
6/36	2	6.7
6/60	3	10.0
CF	4	13.3
HM	2	6.7
PL	-	-

Fig 1.3:- Table showing pulse changes on treatment with levobunolol 0.5%.

Patient	Baseline pulse	pulse at 6 hours	Change in pulse
1	76	74	-2
2	68	60	-8
3	64	60	-4
4	80	74	-6
5	86	84	-2
6	74	68	-6
7	74	80	+6
8	72	70	-2
9	80	76	-4
10	70	68	-2
11	60	60	0
12	80	76	-4
13	86	80	-6
14	72	72	0
15	80	68	-12

Mean baseline pulse = 74.8

Mean pulse at 6 hours = 71.3

Mean drop in pulse = -3.5 (i.e. 4.7%)

Fig 1.4:- Table showing blood pressure changes in treatment with levobunolol 0.5%.

Patient	Baseline BP	BP at 6 hours	Change in BP
1	120/70	110/70	-10/0
2	140/100	130/80	-10/-20
3	150/90	150/90	0/0
4	130/80	120/80	-10/0
5	130/80	120/75	-10/-5
6	130/80	120/70	-10/-10
7	110/70	100/60	-10/-10
8	140/80	140/80	0/0
9	140/90	130/80	-10/-10
10	150/100	140/90	-10/-10
11	120/80	120/80	0/0
12	180/100	180/100	0/0
13	110/70	110/70	0/0
14	160/100	170/100	+10/0
15	200/100	200/90	0/-10

Mean baseline BP = 140/86 mm Hg

Mean BP at 6 hours = 136/81 mm Hg

Mean drop in systolic BP = 4 mm Hg

Mean drop in diastolic BP = 5 mm Hg

Fig 1.5:- Table showing intraocular pressure changes with time in the levobunolol-treated eyes.

Patient	0 hr	½ hr	1 hr	2 hr	4 hr	6 hr	fall	%
1	30	22	18	16	15	14	16	53.3
2	26	20	19	18	16	16	10	38.5
3	28	24	20	18	16	16	12	42.9
4	34	28	24	20	18	16	18	52.9
5	34	30	25	21	19	18	16	47.1
6	26	24	21	18	16	16	10	38.5
7	29	26	24	22	21	21	8	27.6
8	31	28	25	22	21	20	11	35.5
9	34	31	26	23	22	21	13	38.2
10	26	25	23	21	20	20	6	23.0
11	43	40	34	30	29	28	15	34.9
12	24	21	19	17	16	16	8	33.3
13	22	20	17	16	16	15	7	31.8
14	25	22	20	19	18	18	7	28.0
15	50	42	30	26	24	23	27	54.0
MEAN	30.8	26.9	23.0	20.5	19.1	18.5	12.3	39.9

Mean baseline IOP = 30.8 mm Hg

Mean 10p at 6 hours IOP = 18.5 mm Hg

Mean drop in IOP at 6 hrs = 12.3 mm Hg (i.e. 39.9%)

Mean IOP at 2 hours = 20.5 mm Hg

Mean drop in IOP at 2 hrs = 10.3 mm Hg (33.4%)

Fig. 1.6: Bar graph showing magnitude of response in the levobunolol treated eyes after 6 hours.

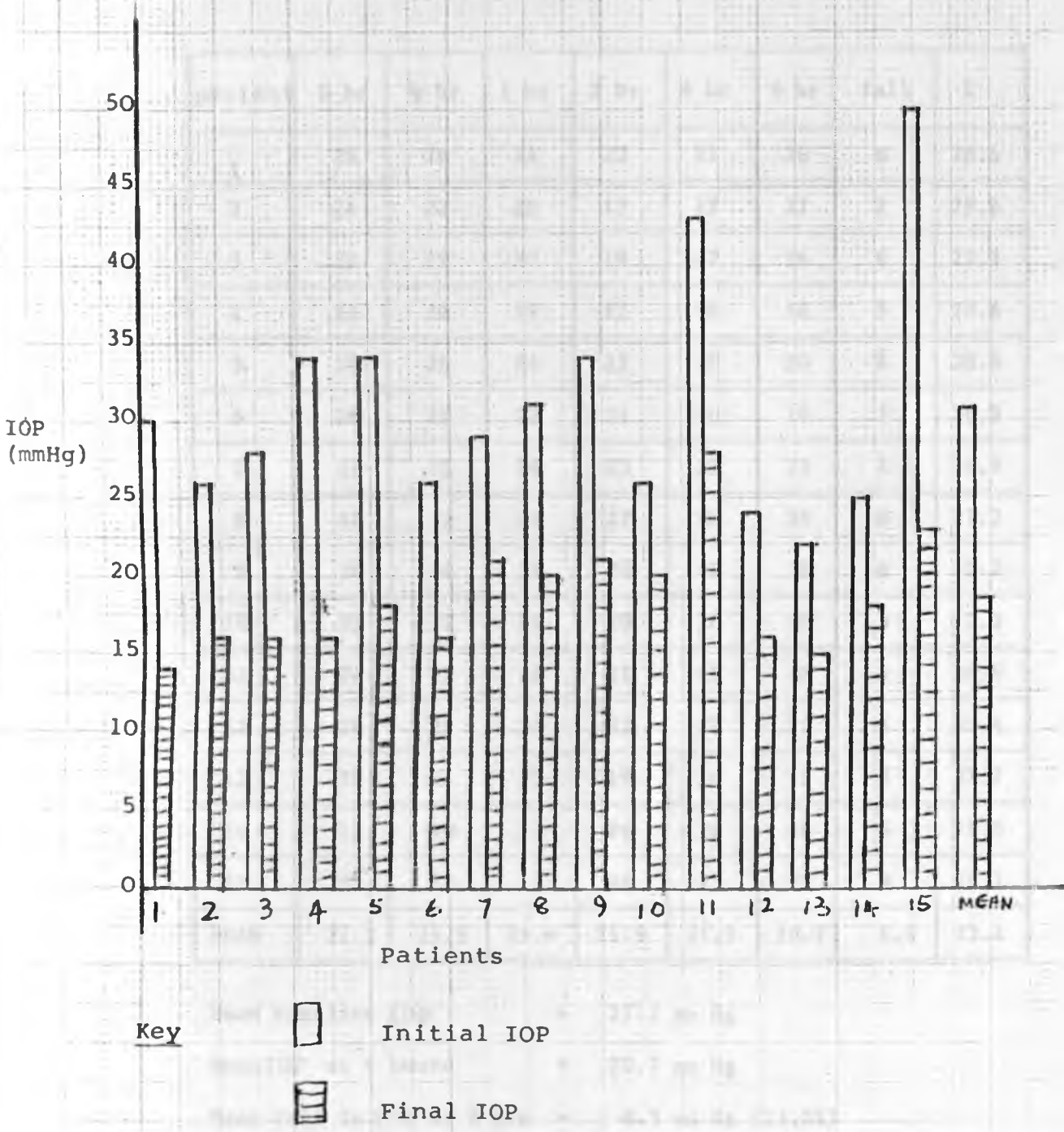


Fig 1.7:- Table showing intraocular pressure changes with time in the placebo treated eyes of the levobunolol group.

patient	0 hr	½ hr	1 hr	2 hr	4 hr	6 hr	fall	%
1	28	26	24	22	21	20	8	28.6
2	24	22	20	17	17	17	7	29.6
3	22	21	20	18	17	16	6	27.3
4	23	22	19	17	16	16	5	28.6
5	28	26	24	22	20	20	8	28.6
6	26	24	22	21	20	19	7	26.9
7	27	25	24	23	23	23	4	14.8
8	33	32	29	27	26	25	8	21.2
9	36	34	32	30	30	28	8	22.2
10	23	22	21	20	20	20	3	13.0
11	24	22	21	21	20	19	5	20.8
12	28	26	24	22	22	22	6	21.4
13	22	21	20	19	18	17	5	22.7
14	32	30	27	26	26	26	6	18.8
15	32	29	27	24	23	23	9	28.1
MEAN	27.2	25.5	23.6	21.9	21.3	20.7	6.3	23.2

Mean baseline IOP = 27.2 mm Hg

Mean IOP at 6 hours = 20.7 mm Hg

Mean fall in IOP at 6 hrs = 6.3 mm Hg (23.2%)

Mean IOP at 2 hours = 21.9 mm Hg

Mean fall in IOP at 2 hrs = 5.3 mm Hg (19.5%)

Fig. 1.8: Bar graph showing magnitude of IOP change in the placebo-treated eyes of the levobunolol group at 6 hours

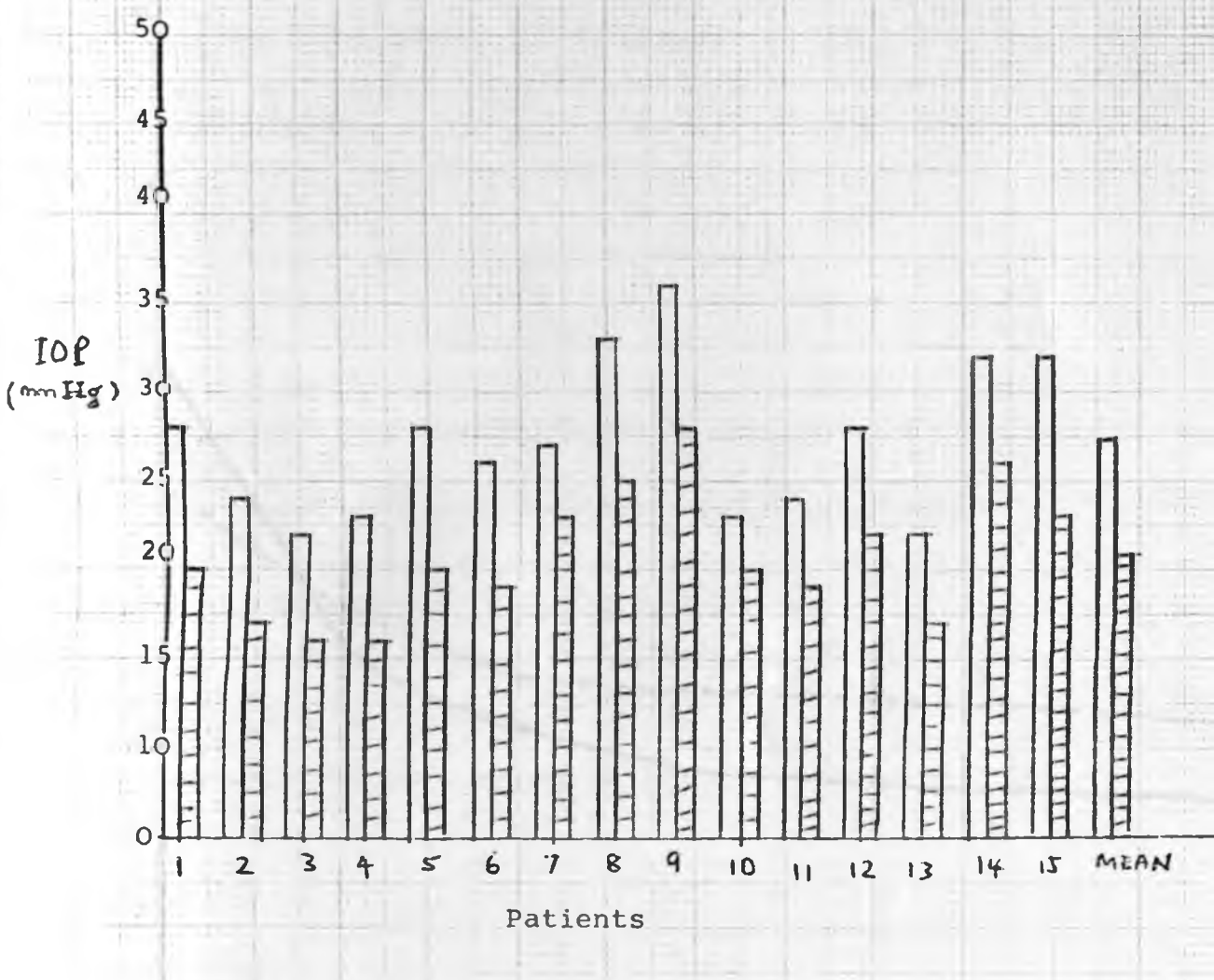
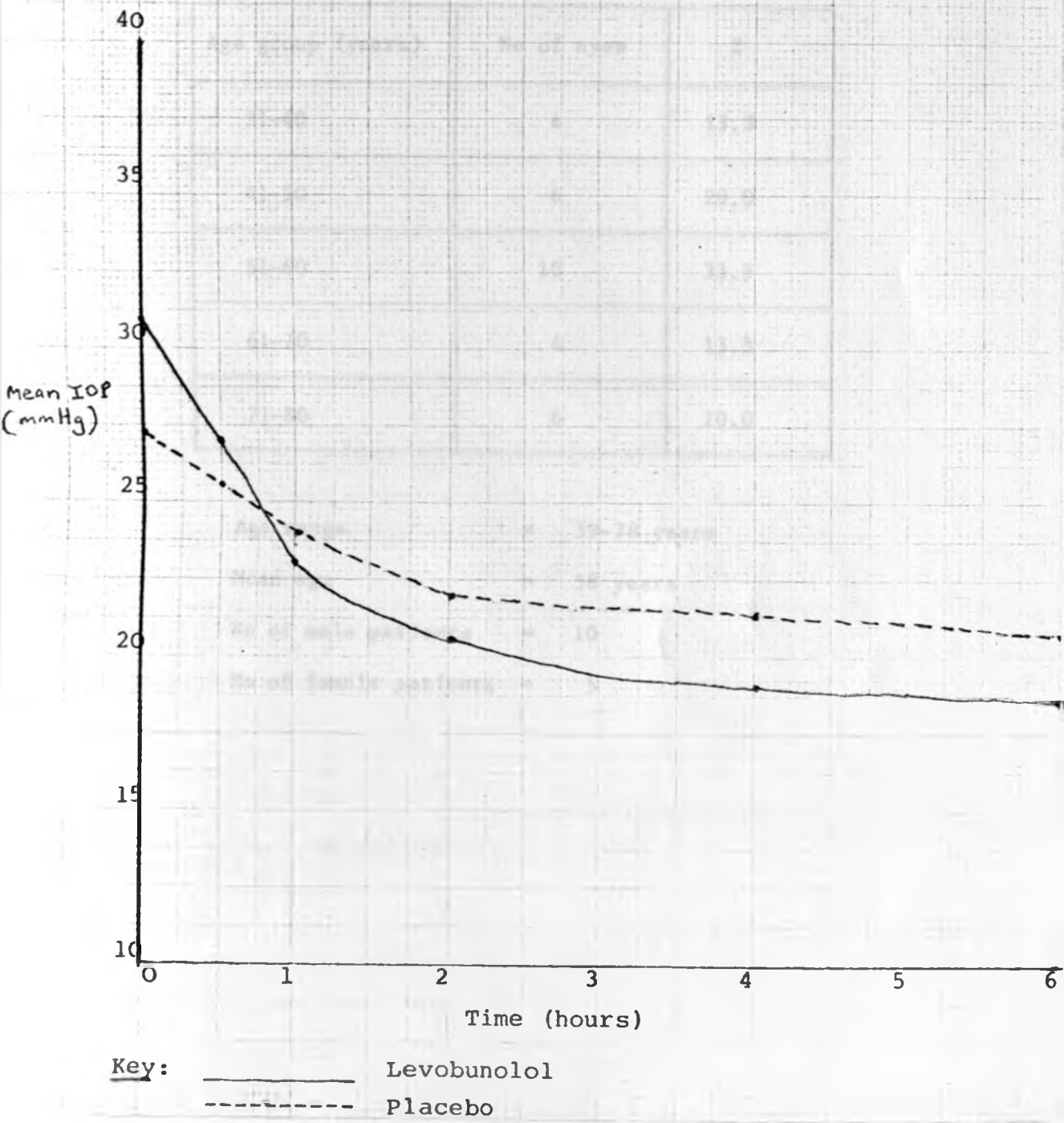


Fig. 1.9: graph showing mean IOP changes with time in both eyes.



2. PILOCARPINE GROUP

Fig 2.1:- Table showing age distribution

Age group (years)	No of eyes	%
31-40	4	13.3
41-50	6	20.0
51-60	10	33.3
61-70	4	13.3
71-80	6	20.0

Age range = 39-78 years

Mean age = 58 years

No of male patients = 10

No of female patients = 5

Fig 2.2:- Table showing range of visual acuity

Visual acuity	No. of eyes	%
6/6	1	3.3
6/9	6	20.0
6/12	4	13.3
6/18	2	6.7
6/24	3	10.0
6/36	1	3.3
6/60	3	10.0
CF	5	16.7
HM	3	10.0
PL	2	6.7

Fig 2.3:- Table showing pulse changes on treatment with pilocarpine 2%.

Patient	Baseline pulse	Pulse at 2 hours	Change in pulse
1	64	62	-2
2	72	72	0
3	78	78	0
4	66	68	+2
5	68	68	0
6	70	72	+2
7	80	76	-4
8	76	74	-2
9	72	72	0
10	80	78	-2
11	74	74	0
12	66	66	0
13	78	76	-2
14	70	70	0
15	68	66	-2

Mean baseline pulse = 72.1

Mean pulse at 2 hours = 71.5

Mean drop in pulse = -0.6 (i.e. 0.8%)

Fig 2.4:- Table showing blood pressure changes on treatment with pilocarpine 2%.

Patient	Baseline BP	BP at 2 hours	Change in BP
1	130/80	130/80	0/0
2	120/80	110/70	-10/-10
3	120/70	120/80	0/+10
4	150/90	140/90	-10/0
5	130/90	140/90	+10/0
6	110/80	110/80	0/0
7	140/80	130/70	-10/-10
8	120/70	120/80	0/+10
9	120/70	120/70	0/0
10	110/70	110/70	0/0
11	140/80	130/80	-10/0
12	140/100	130/90	-10/-10
13	130/80	130/90	0/+10
14	150/90	150/90	0/0
15	120/70	120/70	0/0

Mean baseline BP = 128/80 mm Hg

Mean BP at 2 hours = 126/80 mm Hg

Mean drop in systolic BP = -2 mm Hg

Mean drop in diastolic BP = 0 mm Hg

Fig 2.5:- Table showing intraocular pressure changes with time in the pilocarpine - treated eyes.

Patient	0 hr	½ hr	1 hr	2 hr	4 hr	6 hr	fall	%
1	32	26	20	20	21	24	12	37.5
2	28	26	24	20	22	23	8	28.6
3	24	20	17	13	20	22	11	45.8
4	28	26	22	19	22	24	9	32.1
5	32	28	22	22	24	26	10	31.3
6	28	23	20	20	21	23	8	28.6
7	30	27	23	22	25	25	8	26.7
8	24	22	20	20	21	21	4	16.7
9	46	40	33	20	22	23	26	56.5
10	36	33	30	24	24	26	12	33.3
11	36	34	28	27	27	27	9	25.0
12	26	23	21	20	21	23	6	23.1
13	25	23	20	17	17	19	8	32.0
14	26	22	20	17	19	23	9	34.6
15	38	32	25	20	20	24	18	47.4
MEAN	30.6	27.0	23.0	20.1	21.7	23.5	10.5	34.3

Mean baseline IOP = 30.6 mm Hg

Mean IOP at 2 hours = 20.1 mm Hg

Mean drop in IOP at 2 hrs = 10.5 mm hg (34.3%)

Fig. 2.6: Bar graph showing magnitude of response in the pilocarpine treated eyes after 2 hours

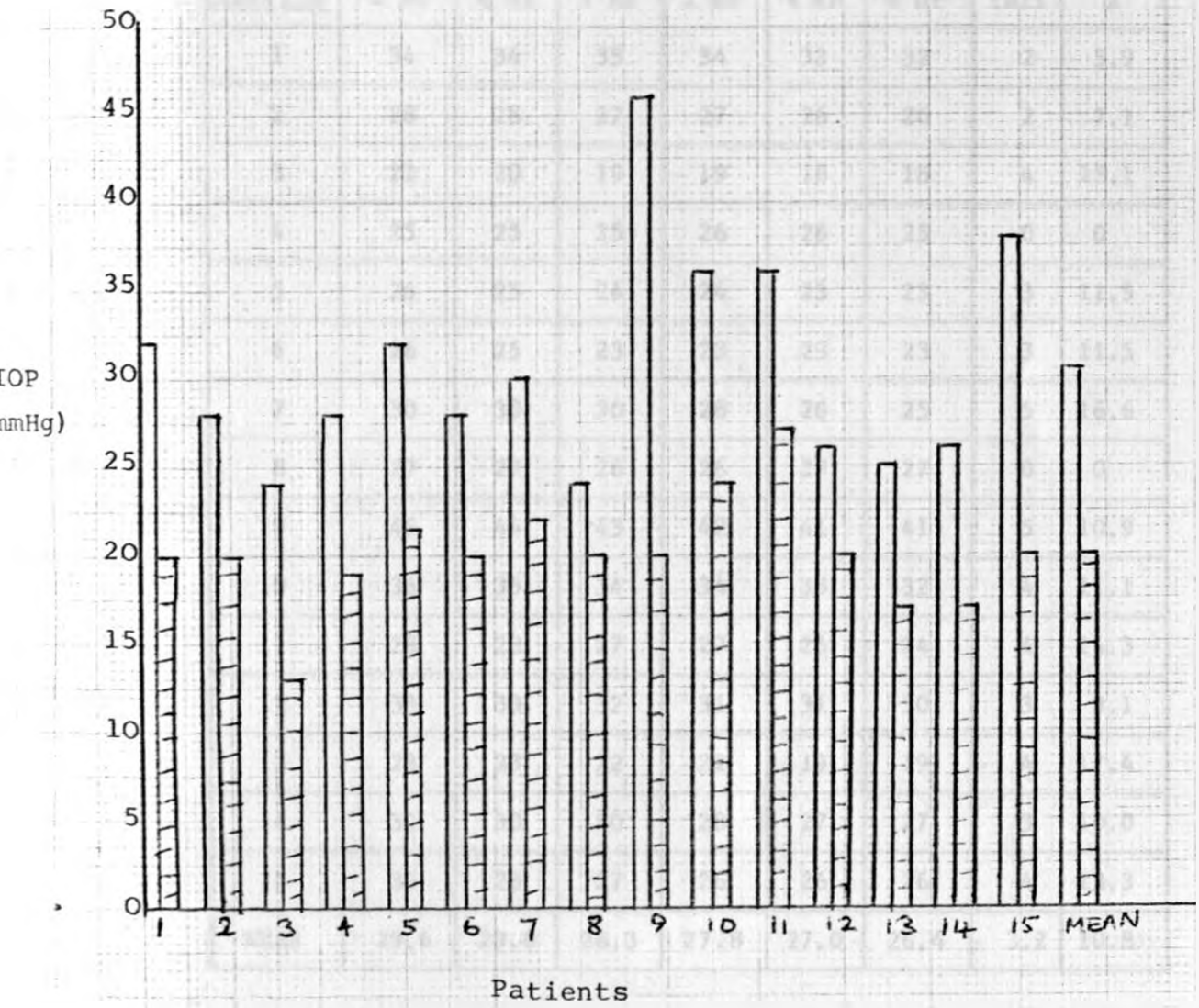


Fig 2.7:- Table showing intraocular pressure changes with time in the placebo treated eyes of the pilocarpine group.

Patient	0 hr	½ hr	1 hr	2 hr	4 hr	6 hr	fall	%
1	34	34	35	34	33	32	2	5.9
2	28	28	27	27	26	26	2	7.1
3	22	20	19	19	18	18	4	18.1
4	25	25	25	26	26	25	0	0
5	26	25	24	24	23	23	3	11.5
6	26	25	23	23	23	23	3	11.5
7	30	30	30	28	26	25	5	16.6
8	27	27	26	26	27	27	0	0
9	46	44	43	42	41	41	5	10.9
10	36	35	34	34	33	32	4	11.1
11	28	28	27	27	26	24	4	14.3
12	33	33	32	31	31	30	3	9.1
13	23	23	22	22	19	19	4	17.4
14	30	30	30	28	27	27	3	10.0
15	30	28	27	26	26	26	4	13.3
MEAN	29.6	29.0	28.3	27.8	27.0	26.4	3.2	10.8

Mean baseline IOP = 29.6 mm Hg

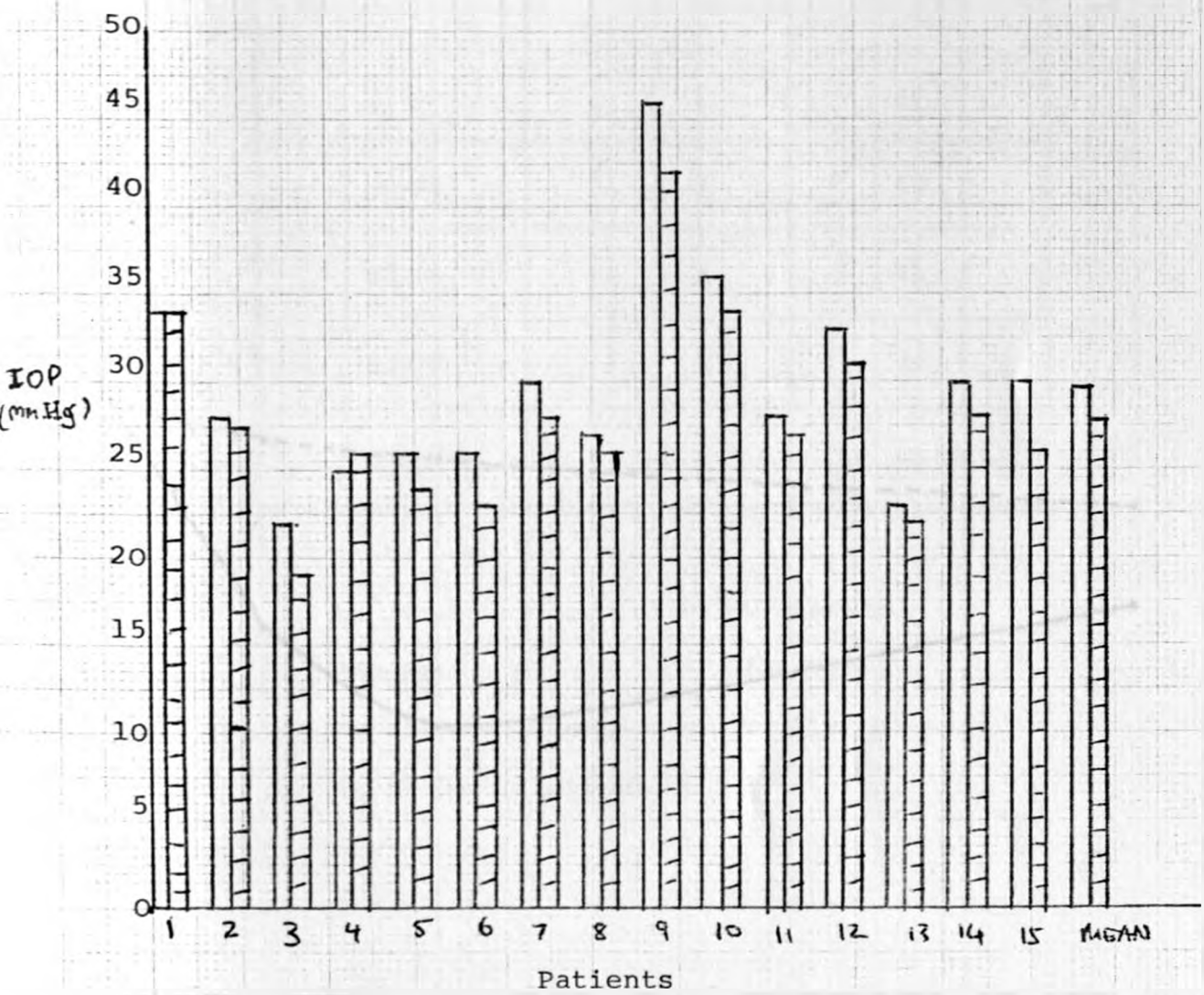
Mean IOP at 2 hours = 27.8 mm Hg

Mean IOP at 6 hours = 26.4 mm Hg

Mean IOP drop at 2 hrs = 1.8 mm Hg (6.1%)

Mean IOP drop at 6 hrs = 3.2 mm Hg (10.8%)

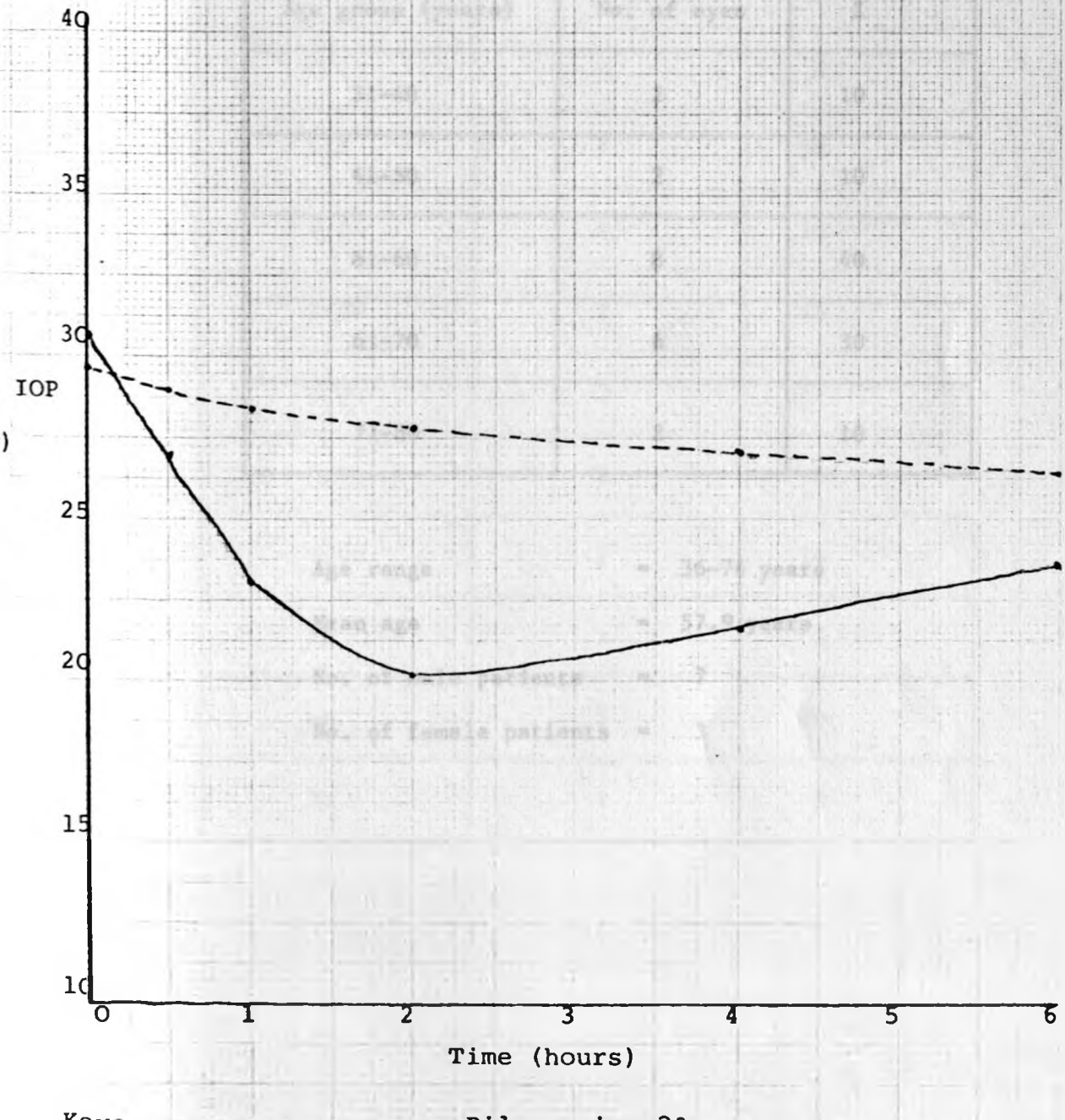
Fig. 2.8: Bar graph showing magnitude of IOP change in the placebo treated eyes of the pilocarpine group, after 2 hours.



Key: Initial IOP

Final IOP

Fig. 2.9: Graph showing IOP changes with time in both eyes.



3. COMBINED PILOCARPINE/LEVOBUNOLOL GROUP:

Fig 3.1:- Table showing age distribution

Age group (years)	No. of eyes	%
31-40	2	10
41-50	2	10
51-60	8	40
61-70	6	30
71-80	2	10

Age range = 36-76 years

Mean age = 57.9 years

No. of male patients = 7

No. of female patients = 3

Fig 3.2:- Table showing range of visual acuity.

Visual acuity	No. of eyes	%
6/6	0	0
6/9	4	20
6/12	2	10
6/18	2	10
6/24	5	25
6/36	1	5
6/60	2	10
CF	1	5
HM	2	10
PL	1	5

Fig 3.3:- Table showing pulse changes on treatment with combined pilocarpine/levobunolol.

Patient	Baseline pulse	pulse at 6 hours	Change in pulse
1	60	60	0
2	68	66	-2
3	76	72	-4
4	82	80	-2
5	68	64	-4
6	68	66	-2
7	80	76	-4
8	74	70	-4
9	80	76	-4
10	78	76	-2

Mean baseline pulse = 73.4

Mean pulse at 6 hours = 70.6

Mean drop in pulse = -2.8 (3.8%)

Fig 3.4:- Table showing blood pressure changes on treatment with combined pilocarpine/levobunolol.

Patient	Baseline BP	BP at 6 hours	Change in BP
1	150/100	130/100	-20/0
2	120/70	120/65	0/-5
3	135/60	140/60	+5/0
4	110/75	100/70	-10/-5
5	120/90	120/90	0/0
6	160/80	140/80	-20/0
7	130/90	120/80	-10/-10
8	110/70	110/65	0/-5
9	140/90	130/90	-10/0
10	130/80	120/80	-10/0

Mean baseline BP = 130/81 mm Hg

Mean BP at 6 hours = 123/78 mm Hg

Mean drop in systolic BP = -7 mm Hg

Mean drop in diastolic BP = -3 mm Hg

Fig 3.5 Table showing intraocular pressure changes with time in the combined levobunolol/pilocarpine treated eyes.

Patients	Ohr	½hr	1hr	2hr	4hr	6hr	fall	%
1	46	38	28	26	25	24	22	47.8
2	34	30	27	25	22	22	12	35.3
3	32	26	22	20	19	18	14	43.8
4	40	33	26	22	20	20	20	50.0
5	25	20	14	13	13	12	13	52.0
6	32	25	21	16	16	16	16	50.0
7	34	29	26	23	21	20	14	41.2
8	29	25	22	22	19	19	10	34.5
9	26	22	19	18	18	16	10	38.5
10	31	25	21	17	17	17	14	45.2
MEAN	32.9	27.3	22.7	20.2	18.9	18.5	14.4	43.8

Mean baseline IOP = 32.9mmHg
Mean IOP at 2 hours = 20.2mmHg
Mean IOP at 6 hours = 18.5mmHg
Mean drop in IOP at 2 hours = 12.7mmHg (38.6%)
Mean drop in IOP at 6 hours = 14.4mmHg (43.8%)

Fig. 3.6: Bar graph showing magnitude of response in the combined pilocarpine/Levobunolol treated eyes after 6 hours.

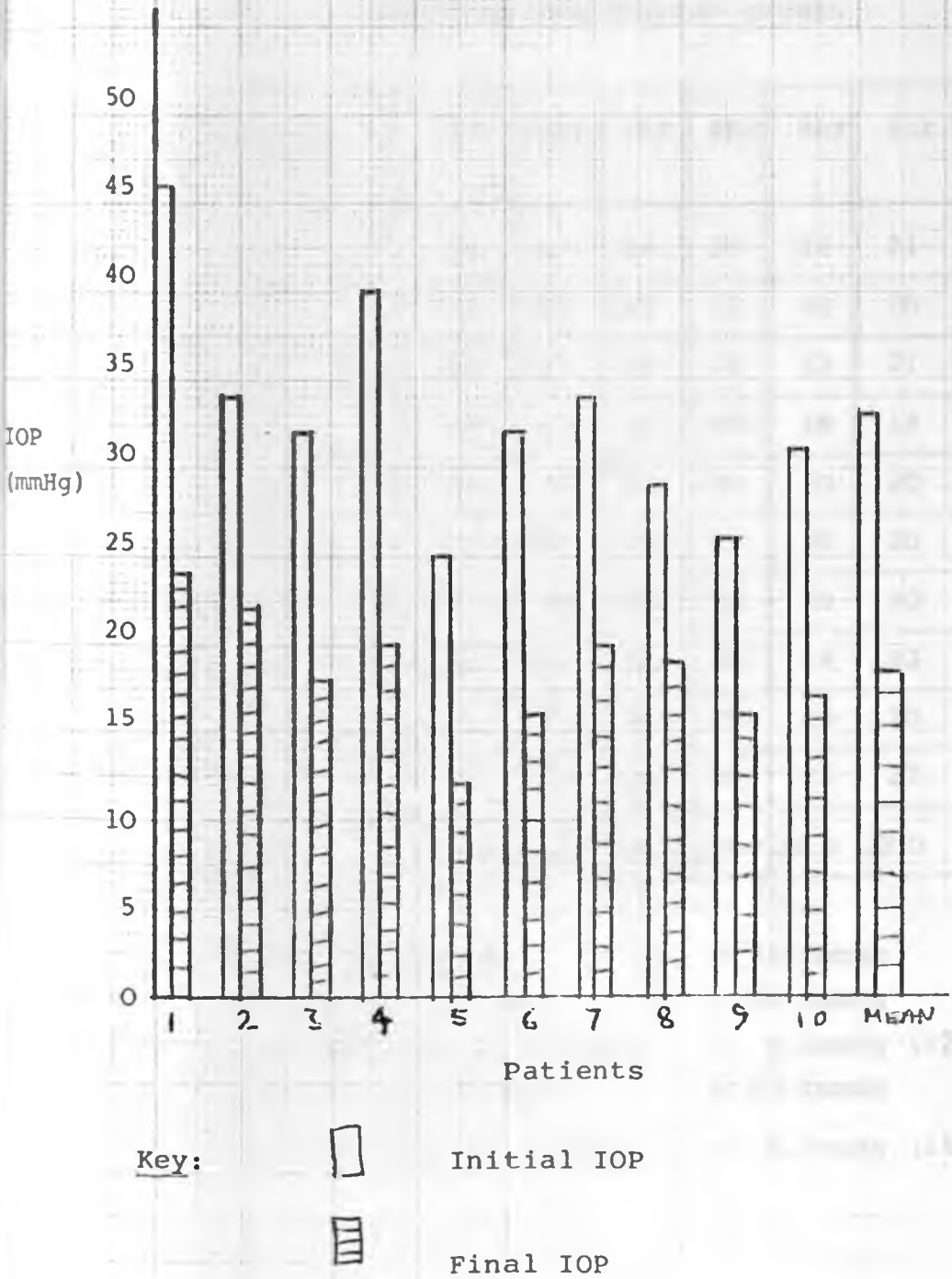


Fig 3.7 Table showing intraocular pressure changes with time in the placebo treated eyes of the drug combination group.

Patients	Ohr	½hr	1hr	2hr	4hr	6hr	Fall	%
1	28	26	24	23	22	21	7	25.0
2	25	23	22	21	20	20	5	20.5
3	28	26	23	21	21	21	7	25.0
4	24	22	20	19	18	18	6	25.0
5	27	25	21	20	20	20	7	25.9
6	26	24	23	19	20	20	6	23.1
7	37	35	33	32	30	30	7	18.9
8	29	27	26	25	24	23	6	20.7
9	24	22	21	21	20	20	4	16.7
10	35	33	30	29	28	27	8	22.9
MEAN	28.3	26.3	24.3	23.0	22.3	22.0	6.3	22.3

Mean baseline IOP = 28.3mmHg
Mean IOP at 6 hours = 22.0mmHg
Mean IOP drop at 6 hours = 6.3mmHg (22.3%)
Mean IOP at 2 hours = 23.0mmHg
Mean IOP drop at 2 hours = 5.3mmHg (18.7%)

Fig. 3.8: Bar graph showing magnitude of IOP change in the placebo treated eyes of the drug conbination group at 6 hours.

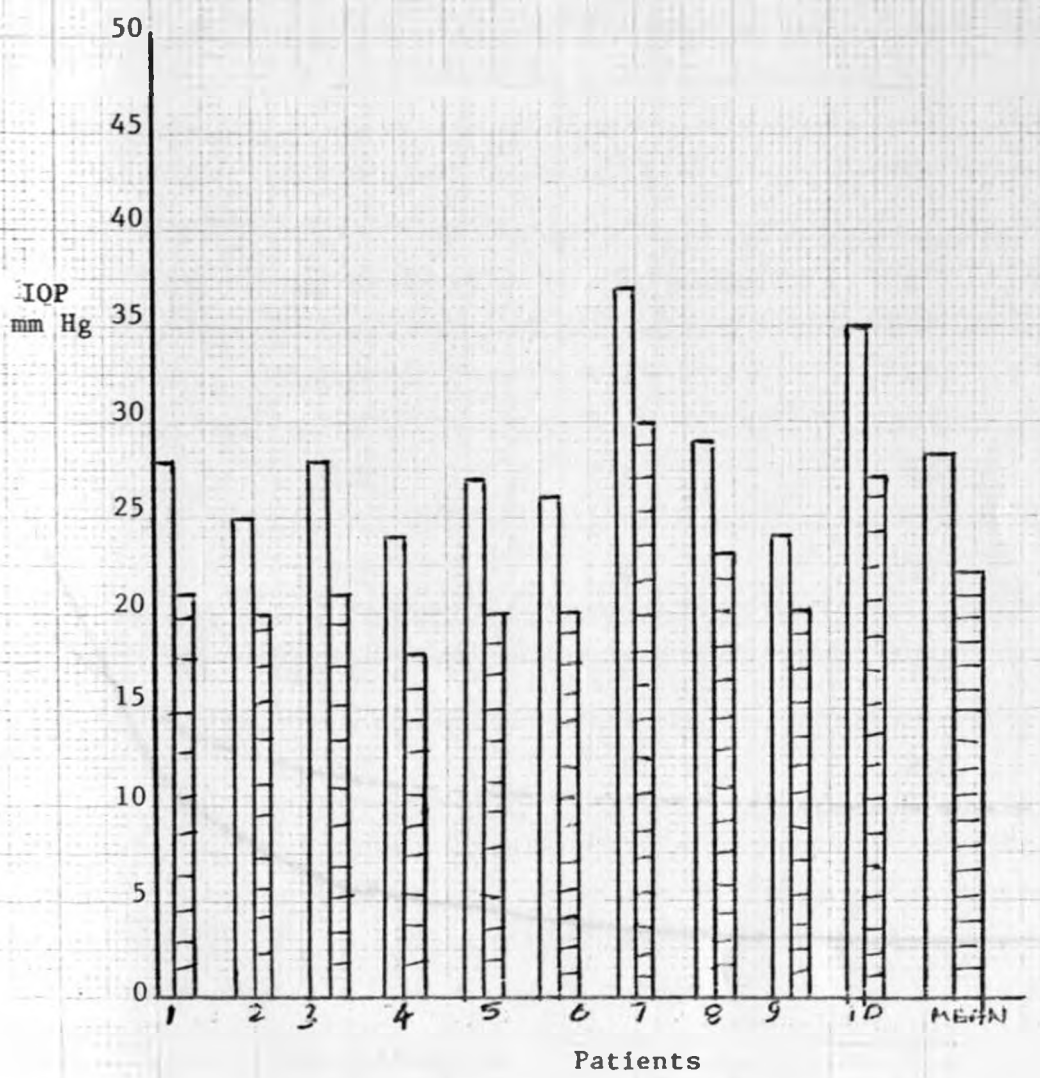
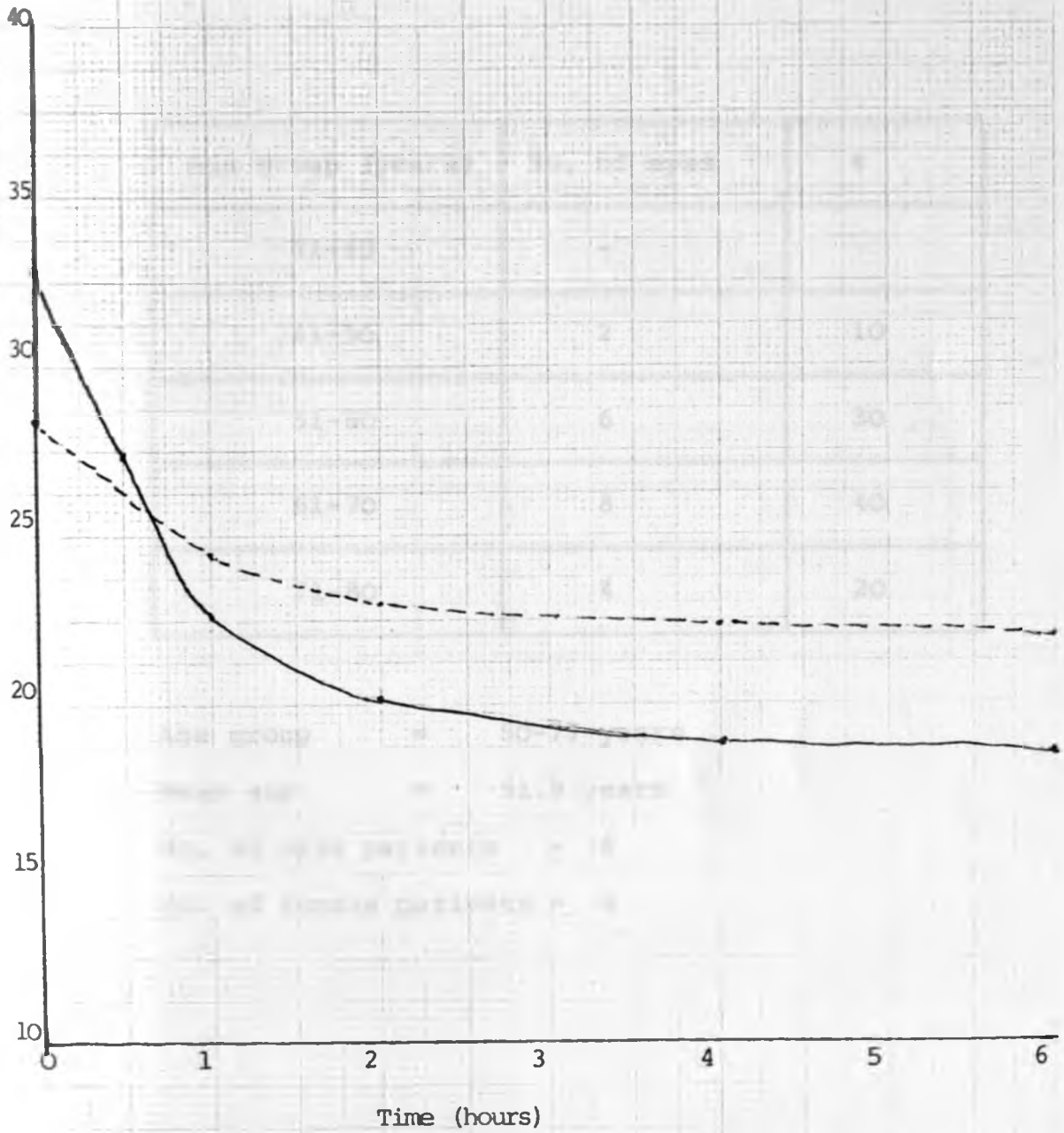


Fig. 3.9: Graph showing mean IOP changes with time in both eyes



Key: ———— Combined pilocarpine/levobunolol

4. PLACEBO GROUP

Fig. 4.1 Table showing age distribution

Age group (years)	No. of eyes	%
31-40	-	-
41-50	2	10
51-60	6	30
61-70	8	40
71-80	4	20

Age group = 50-77 years

Mean age = 61.9 years

No. of male patients = 6

No. of female patients = 4

Fig 4.2 Table showing range of visual acuity

Visual Acuity	No. of eyes	%
6/6	-	-
6/9	2	10
6/12	2	10
6/18	5	25
6/24	5	25
6/36	1	5
6/60	-	-
CF	1	5
HM	2	10
PL	2	10

Fig 4.3 Table showing pulse changes on treatment with placebo alone.

Patient	Baseline pulse	Pulse at 2hr	Pulse at 6hr
1	68	68	70
2	72	70	70
3	74	74	74
4	72	72	72
5	78	78	78
6	80	80	78
7	70	70	70
8	80	82	82
9	68	68	70
10	76	76	76

Mean baseline pulse = 73.8

Mean pulse at 2 hours = 73.8

Mean pulse at 6 hours = 74.0

Mean drop in pulse at 2 hours = 0

Mean change in pulse at 6 hours = +0.2

Fig. 4.4 Table showing blood pressure changes on treatment with placebo alone

Patient	Baseline BP	BP at 2 hrs	BP at 6 hours
1	135/90	130/90	130/90
2	120/80	120/80	130/80
3	130/90	120/80	120/80
4	120/80	120/90	120/90
5	130/80	120/80	120/80
6	140/90	150/90	150/90
7	110/70	110/70	110/70
8	125/80	120/80	120/80
9	130/80	130/80	130/90
10	150/90	150/90	140/90

Mean baseline BP = 129/83mmHg
Mean BP at 2 hours = 127/83mmHg
Mean systolic BP change at 2 hours = -2mmHg
Mean diastolic BP change at 2 hours = 0

Mean BP at 6 hours = 127/84
Mean systolic BP change at 6 hours =-2mmHg
Mean diastolic BP change at 6 hours = +1mmHg

Fig. 4.5 Table showing intraocular pressure changes with time in the placebo treated eyes of the placebo group

Patient	0hr	½hr	1hr	2hr	4hr	6hr	fall	%
1	28	28	28	28	27	26	2	7.1
2	30	30	29	29	28	27	3	10.0
3	30	29	29	29	28	27	3	10.0
4	34	34	33	32	31	30	4	11.7
5	31	31	31	30	30	28	3	9.7
6	34	33	33	32	32	30	4	11.8
7	28	28	28	28	27	26	2	7.1
8	34	34	33	33	32	30	4	11.8
9	36	35	35	34	33	31	5	13.9
10	33	33	33	32	31	30	3	9.1
Mean	31.8	31.5	31.2	30.7	29.9	28.5	3.3	10.4

Mean baseline IOP = 31.8mmHg
Mean IOP at 2 hours = 30.7mmHg
Mean drop in IOP at 2 hours = 1.1mmHg (35%)
Mean IOP at 6 hours = 28.5mmHg
Mean drop in IOP at 6 hours = 3.3mmHg (10.4%)

Fig. 4.6 Table showing intraocular pressure changes with time in the control eyes of the placebo group.

Patient	Ohr	½hr	1hr	2hr	4hr	6hr	fall	%
1	26	26	26	26	25	24	2	7.7
2	32	32	32	31	31	30	2	6.3
3	30	30	29	29	28	27	3	10.0
4	36	35	35	35	33	32	4	11.1
5	28	28	27	27	26	25	3	7.1
6	33	33	33	31	31	30	3	9.1
7	29	28	28	28	27	26	3	6.9
8	35	34	34	33	32	31	4	11.4
9	35	35	34	33	32	31	4	11.4
10	32	32	32	30	29	28	4	12.5
MEAN	31.6	31.3	31.0	30.3	29.4	28.4	3.2	10.1

Mean baseline IOP = 31.6mmHg

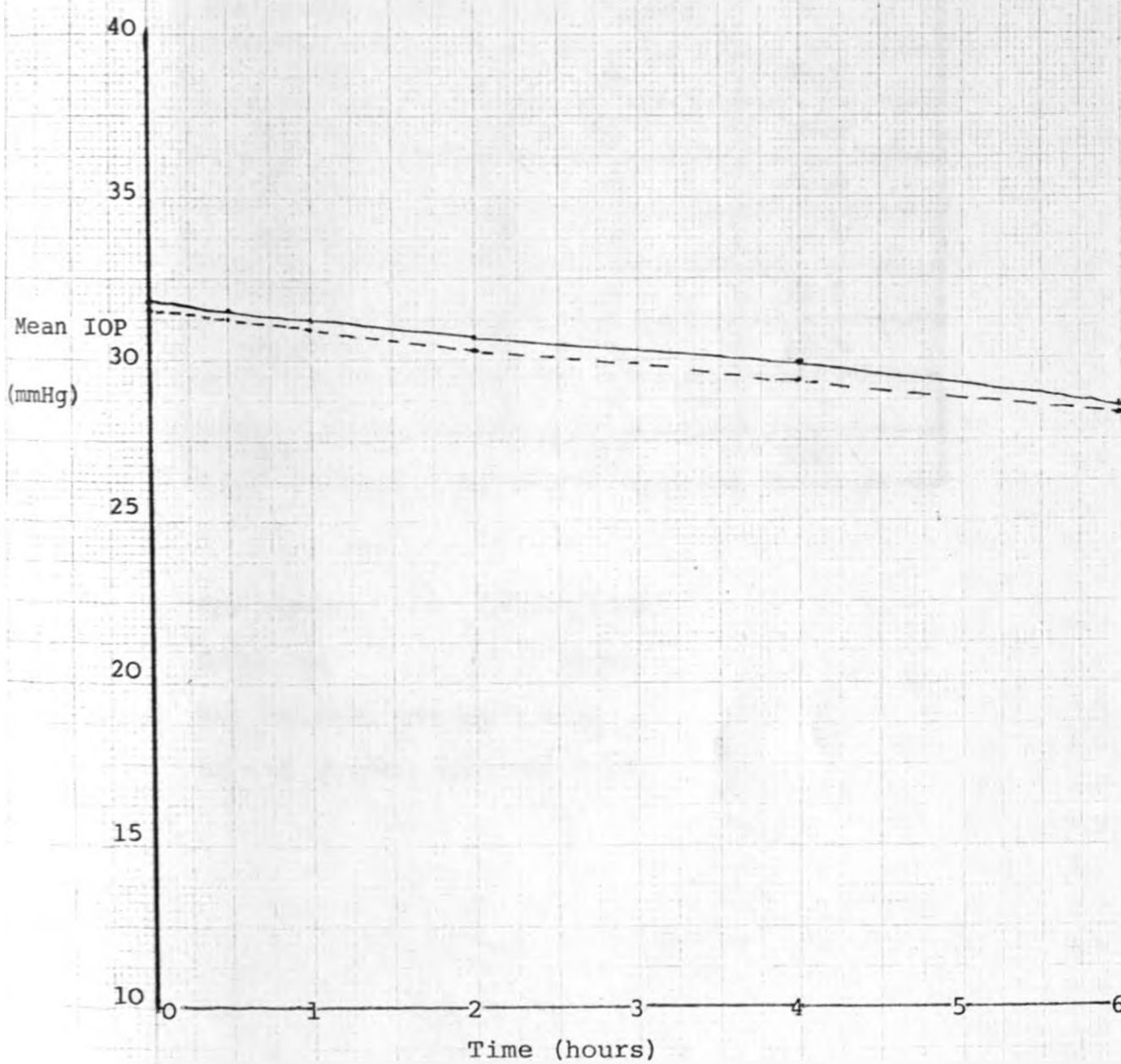
Mean IOP at 2 hours = 30.3mmHg

Mean drop in IOP at 2 hours = 1.3mmHg (4·1%)

Mean IOP at 6 hours = 28.4mmHg

Mean drop in IOP at 6 hours = 3.2mmHg (10.1%)

Fig. 4.7: Graph showing IOP changes with time in both eyes.



5. THE NORMAL DIURNAL INTRAOCULAR PRESSURE VARIATION

Fig. 5.1 Table showing age distribution

Age group (years)	No. of eyes	%
≤ 20	4	10.0
21-30	14	35.0
31-40	5	12.0
41-50	7	17.5
51-60	5	12.5
61-70	5	12.5
> 70	-	-
Total	40	100

Age range = 18-66 years

Mean age = 40.5 years

No. of male patients = 11

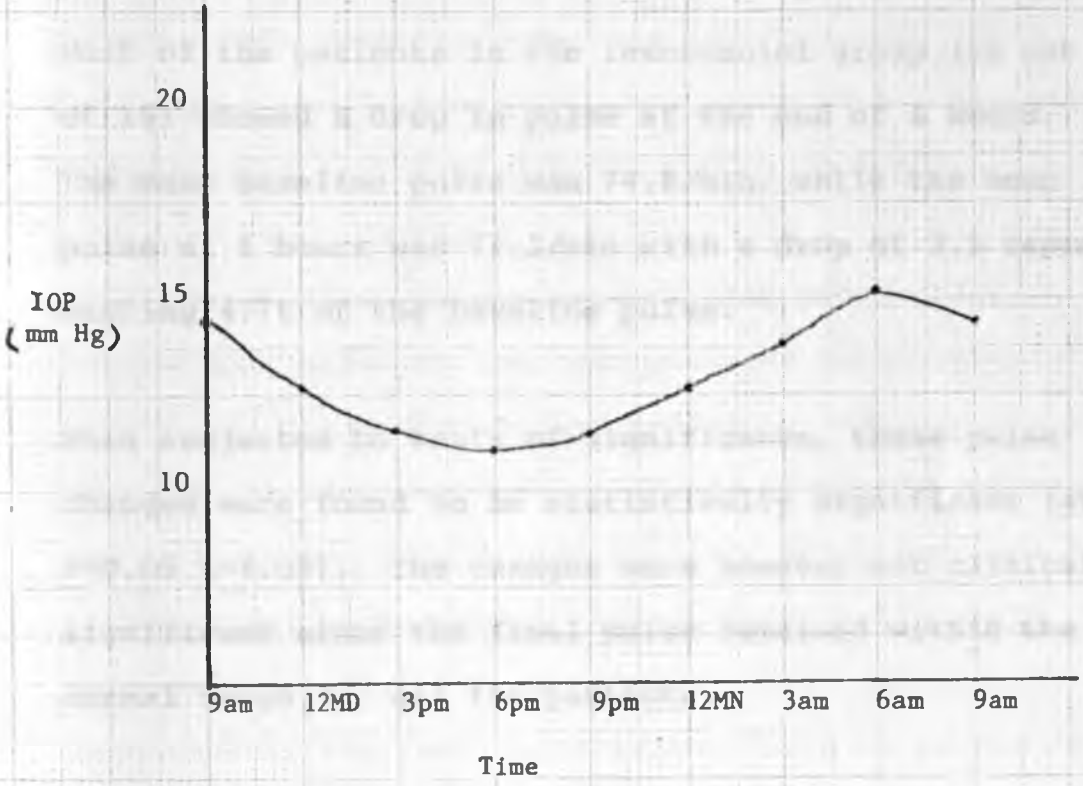
No. of female patients = 17

Fig 5.2:- Table showing mean intraocular pressure changes with time for each subject.

	9 AM	12 MD	3 PM	6 PM	9 PM	12 MN	3 AM	6 AM	9 AM	AMPLITUDE
1	13	12	11	10	10	11	12	13	12	3.0
2	14.5	12	11.5	11.5	11.5	12.5	13	15	14	3.5
3	12	10	9	8	8	11	12	13	12	5.0
4	13	11.5	11	10.5	11.5	12	12.5	13	13	2.5
5	20	19	18	16	15	15	17	20	19	5.0
6	13	12	11	11	10	11	12	14	13	4.0
7	10	8.5	8	8	8.5	10	10.5	11.5	11	3.5
8	15	13	12	11	10	11	13	16	15	6.0
9	14	13	11	11	12	13	14	15	14	4.0
10	18	16	14	15	15	17	18	20	19	6.0
11	15	13	12	11	11	12	13	16	14	5.0
12	17	14	14	13	15	15	16	17	16	4.0
13	15	14	12	12	12	14	16	16	14	4.0
14	12.5	10.5	10	10	10.5	12	13	13.5	12.5	3.5
15	14.5	13.5	13	12	12	13.5	14	15.5	13.5	3.5
16	19	16.5	15	13.5	14	15.5	17.5	19	18.5	5.5
17	18	15	15	14	14	16	18	20	18	6.0
18	12	11	9	9	10	10	11	12	12	3.0
19	14	13	11	11	11	13	14	15	14	4.0
20	16	14	12	12	11	13	15	17	16	6.0
21	12	11	10	10	10	11	11	11	13	3.0
22	13	12	12	11	12	13	13	14	14	3.0
23	13.5	12	11	10.5	10.5	12	12	14	12.5	3.5
24	16.5	15	13	12	12.5	13.5	15.5	17.5	17	5.5
25	13.5	11.5	9.5	8	8.5	10	11.5	14	13	6.0
26	13	12	11	10	10	12	13	13	13	3.0
27	16.5	14.5	14.5	13	13.5	14.5	16	17	16.5	4.0
28	14	13	10.5	10	11	13	14	14	13	4.0
MEAN	14.4	12.8	11.7	11.1	11.4	12.7	13.8	15.1	14.3	4.0

Mean highest IOP (6 a.m.) = 15.1 mm Hg
Mean lowest IOP (6 p.m) = 11.1 mm Hg
Mean amplitude of variation = 4.0 mm Hg
Range of amplitude of variation = 2.5-6.0 mm Hg

Fig. 5.3: Graph showing the mean intraocular pressure variation in the normal eyes.



V) DISCUSSION

1. EFFECT ON PULSE

Most of the patients in the levobunolol group (12 out of 15) showed a drop in pulse at the end of 6 hours. The mean baseline pulse was 74.8/min. while the mean pulse at 6 hours was 71.3/min with a drop of 3.5 representing 4.7% of the baseline pulse.

When subjected to tests of significance, these pulse changes were found to be statistically significant (at P=0.05 t=4.05). The changes were however not clinically significant since the final pulse remained within the normal range for all the patients.

As for the pilocarpine group, 7 patients had no pulse changes, 6 had a slight fall and 2 had a slight rise. Pulse was recorded at 2 hours when the drug had its peak ocular hypotensive effect.

The mean baseline pulse was 72.1/min, and mean pulse at 2 hours was 71.5/min giving a fall of 0.6 (0.8%). This was found to be statisitically insignificant (at P=0.05 t=1.42). In the combined pilocarpine/levobunolol group the pulse was lowered in 9 of the 10 patients. the mean baseline pulse was 73.4/min and mean final pulse was 70.6/min with a fall of 2.8 (3.8%) which was statistically

significant (at P=0.05 t=6.50).

There were no significant pulse changes in the placebo group. Mean baseline pulse was 73.8/min, mean pulse at 2 hours was 73.8/min and mean pulse at 6 hours was 7.4/min with a rise of 0.2 (at p=0.05, t=0.47).

From the results, it was evident that levobunolol, topically applied on the eyes produced some systemic effect on the cardiovascular system by lowering the pulse. Blockage of BI-adrenergic receptors slows the pulse rate and weakens myocardial contractility which may lead to bradycardia, cardiac arrhythmias, heart failure and syncope (4). In a two year follow-up of patients on levobunolol, the fall in pulse was found to be minimal with no reports of adverse effects. (4)

Pilocarpine on the other hand had an insignificant effect on the pulse in this study, but elsewhere it has been shown that pilocarpine, depending on the degree of autonomic stimulations may produce variable cardiovascular effects, pulse and BP may rise or fall. The pulse lowering effect of the pilocarpine/levobunolol combination was attributable to the systemic effect of levobunolol in this study.

2. EFFECT ON BLOOD PRESSURE

Most of the levobunolol patients had a fall in BP. Both systolic and diastolic BP were affected. The mean baseline BP was 140/86mmHg while final BP was 136/81mmHg giving a drop in systolic BP of 4mmHg and diastolic BP of 5mmHg.

On testing for significance the changes in both systolic BP (at p=0.05 t=3.09) were found to be statistically significant, but clinically not significant. The BP changes in the pilocarpine group were variable with a mean baseline BP of 128/80 and mean BP at 2 hours of 126/80. Thus there was no net change in diastolic BP while systolic BP dropped by 2mmHg (at p=0.05 t=1.3). The changes were statistically insignificant and hence could be attributed to chance alone.

Similar findings were found in the placebo group both at 2 hours and at 6 hours, systolic BP change at 2 hours (P=0.05 t=0.96), diastolic BP change at 2 hours (p=0.05 t=0) and systolic BP change at 6 hours (p=0.05 t=0.88) and diastolic BP change at 6 hours (P=0.05 t=0.65).

Those in the combined drug group however showed BP changes comparable to those of the levobunolol group and therefore statistically significant. Mean baseline BP

was 130/81mmHg and mean final BP was 123/78mmHg with systolic BP drop of 7mmHg and diastolic BP drop of 3mmHg for systolic BP change at P=0.05 t=2.57 while diastolic BP change at P=0.05 t=2.65 both of which were significant.

Again these BP changes were evidently due to the effect of levobunolol on the cardiovascular system. In all patients however, the final BP remained within the accepted normal range.

That the BP changes due to levobunolol were minimal were further proven by the chi-square test comparing the changes in the levobunolol and pilocarpine groups whereby it was found that X^2 = 2.04 which was statistically not significant at P=0.05.

3. MAGNITUDE OF RESPONSE TO TREATMENT

Levobunolol treated eyes had IOP falls ranging from 6-27mmHg. The average fall was 12.3mmHg at the end of 6 hours corresponding to 39.9% of the baseline IOP, (at P=0.05, t=8.65). The control eyes in this group also showed a fairly large but lesser drop in IOP ranging from 3-9mmHg with an average of 6.3mmHg (23.2%). This drop was approximately half of the magnitude of response in the levobunolol treated eyes and was both clinically and statistically significant (at P=0.05 t=14.35)

The pilocarpine treated eyes had a magnitude of response ranging from 4-26mmHg with an average of 10.5mmHg (34.3%) at the end of 2 hours. (at p=0.05 t=7.64). The control eyes in this group had decrease in IOP ranging from 0-5mmHg with an average of 3.2mmHg (10.8%). Whereas this drop was statistically significant (p=0.05 t=8.09) it was not as large as that noted in the levobunolol controls.

Those treated with pilocarpine/levobunolol combined showed a greater magnitude of response than when the drugs were used singly. This was so both at 2 hours and at 6 hours. At 2 hours the mean drop in IOP was 12.7mmHg (38.6%) and at 6 hours 14.4mmHg (43.8%) with a significance of p=0.05 t=11.61.

The control eyes in this group had at 2 hours a mean IOP drop of 5.3mmHg (18.7%) and at 6 hours a mean drop of 6.3mmHg (22.3%) (p=0.05 t=17.16). Like in the levobunlol controls, these changes were clinically significant.

In the group treated with placebo alone, the IOP fall ranged from 2-5mmHg with an average of 3.3mmHg (10.4%) at six hours (significance valve P=0.05 t=10.98). The controls in this group had a fall ranging from 2-4mmHg with an average of 3.2mmHg (10.1%) (p=0.05 t=12.8)

Several inferences can be made from the results of this study: Firstly, levobunolol 0.5% produced a greater magnitude of response than pilocarpine 2%. Secondly, there was an additive effect when the two drugs were used in combination. Thirdly, there occured a contralateral drop in IOP on monocular instillation of levobunolol. Fourthly, the decrease in IOP in the pilocapine controls was most probably due to the normal diurnal variation alone since it was similar to the drop noted in both treated and control eyes of the placebo gorup, both of which being similar ruled out saline as an ocular hypotensive. The normal diurnal IOP variation in non-glaucomatous eyes (to be discussed later) showed a fall of 2.8mmHg over this period of the day (9am - 3pm) when the study was done. The mean drops in IOP in the pilocarpine controls as well as both sets in the placebo group were all higher than 2.8mmHg, but this is not unusual since it is known that diurnal variation is usually exaggerated in glaucomatous eyes (5).

The phenomenon of contraleteral lowering of IOP by monocularly instilled levobunolol has also been reported in studies with other B-blockers. Zimmerman & Kaufman (9) in their one drop study on 30 glaucoma patients with timolol 0.5% reported a significant contralateral effect.

The mechanism by which this happens has not yet been fully elucidated. It is however thought to be either due to systemic absorption of the medication or due to an effect mediated by the central nervous system (14). From the results of this study it seems that the former theory is most probable since it has been shown that levobunolol gets absrobed systemically and hence its effects on the cardiovascular system.

Krieglstein (19) in another study with timolol 0.5% in 39 glaucomatous eyes, reporged an average pressure fall of 13mmHg with the individual effects ranging between 6 and 32mmHg. This corresponded to 46% of the pre-treatment pressure level at the 6th hour.

The results in my study compare favourably with those quoted above.

4. ONSET OF ACTION

From the graphs on tables 1.9, 2.9 and 3.9 it is evident that the IOP in the drug treated eyes dropped rapidly from 0-2 hours. Thereafter the pressure started rising slowly again in the case of pilocarpine while it continued to fall slowly in the case of levobunolol and combined pilocarpine/levobunolol.

Out of the mean IOP fall at 6 hours of 12.3mmHg in the levbunolol group, 10.3mmHg drop occured in the first 2 hours i.e. 83.7% of the total TOP fall occured within the first 2 hours. Pilocarpine group, wherein the mean IOP fall at 2 hours was 10.5mmHg had 100% of the fall within the 2 hours, and combined pilocarpine/levobunolol group 12.7mmHg drop occured at 2 hours out of the total drop at 6 hours of 14.4mmHg i.e. 88.2% of the total fall occured by the end of the 2nd hour.

The deduction to be made from these graphs and figures is that the peak effect of both pilocarpine and levobunolol occured at 2 hours, and that the onset of action of pilocapine 2% was more prompt than that of levobunolol to a slight extent.

Other workers, Zimmerman & Kaufman (9) and Katz, Hubbard, Getson & Gould (10) working with timolol 0.5%, found that the peak effect of this B-blocker occured at 2 hours and the ocular hypotensive effect persisted for 24 hours. Studies with pilocarpine on animal eyes have shown that following topical instillation, the maximum concentrations in the aqueous were reached in 20 minutes (11) and were gone in 4 hours (12). This explains why the IOP starts to rise again at the 4th hour.

A similar study in human eyes showed that the peak effect

of pilocarpine occured at 2 hours and the pressure remained within acceptable levels for about 8 hours. (13) It is therefore essential to instill B-blockers 12 hourly and pilocarpine 6 hourly to maintain good IOP control.

5. EFFECT OF BASELINE IOP ON RESPONSE TO TREATMENT

In all eyes that were treated with the drugs there was an apparent tendency towards a large drop in IOP in eyes with a relatively higher baseline IOP. Out of the 40 eyes that were treated with either levobunolol or pilocarpine or both, 21 eyes had a baseline IOP of 30mmHg and above, while 19 eyes had a baseline IOP below 30mmHg. Those whose baseline IOP was 30mmHg and above had a mean IOP fall of 15.3mmHg (42.5%) while those in the other category had a mean drop of 9.1mmHg (34.7%). It can therefore be stated that the magnitude of response to treatment was found to be directly proportional to the initial pretreatment IOP. The difference between the magnitude of IOP fall in the two groups was found to be statistically significant (X^2 = 4.88 at p=0.10). Further work needs to be done on this issue to determine whether this finding is a medical fact or a chance occurence

6. THE NORMAL DIURNAL INTRAOCULAR PRESSURE VARIATION

The knowledge of the diurnal variation of intraocular pressure is of great importance in the medical treatment of glaucoma. It enables us to predict the peak pressure on the basis of a single measurement of the intraocular pressure which is important for the installation of a proper medical regimen. Secondly, it enables us to accurately evaluate the efficacy of drugs used for treating glaucoma as is the case in this study.

From the table showing intraocular pressure changes with time (Fig. 5.2) it can be seen that all the eyes exhibited a gradual fall in pressure during the day and a gradual rise at night. The highest pressures were those taken at 6 am (average 15.1mmHg) and the lowest were those taken at 6 pm (average 11.1mmHg). The amplitude of variation ranged from 2.5-6mmHg with an average of 4mmHg.

Thus among the normal local population the intraocular pressure variation pattern is that of a fall during the day and a rise during the night (ref. Fig. 5.3).

This is consistent with standard knowledge that the

pressure is usually highest about the time of awakening and lowest in the evening. (15) However, studies carried out elsewhere in the world have revealed exceptions to this rule.(4) In a study carried out in Japan, measuring the intraocular pressure hourly for 24 hours in 21 normal subjects it was found that the pressure was the lowest in the morning and highest in the daytime in the majority of the subjects.(16) (17)

The mechanism of diurnal intraocular pressure variation is uncertain but is thought to be related to adrenocortical steroids. It has been shown that this variation parallels the circadian rhythm of plasma cortisol levels, like many other physiological parameters.(18)

VI CONCLUSIONS

This study has shown that both levobunolol 0.5% and pilocarpine 2% are effective in lowering the IOP in glaucomatous eyes. the two drugs in combination are even more effective due to their additive effect. It would therefore be in order to use the two drugs together in eyes whose pressures cannot be controlled by one drug alone. This should however not be done on a long term basis bearing in mind the cost constraints.

That there were no clinically significant adverse effects noted in this one drop study does not rule out such effects on long term use of the drugs. A long term study needs to be carried out among our patients to assess adverse effects.

Levobunolol is relatively new in the market but its effects, and indeed those of all the other ocular hypotensive B-blockers, on the cardiovascular sytem and obstructive pulmonary disease are already well known. This limits its use in such patients.

It is however convenient in long term medical treatment of glaucoma because its infrequent regimen of application is likely to insure compliance.

For economic reasons advantage can be taken of the contraleteral effect of levobunolol when applied to one eye by reducing the number of drops used per day by half. My suggestion is that after adequately controlling the initial IOP rise, levobunolol can thereafter be applied to one eye only in the morning and to the fellow eye in the evening. This applies also to any other B-blocker exhibiting the contralateral effect, since this study has shown that the contralateral drop in IOP is significant.

Af for pilocaprine, its disadvantages, notably miosis, induced myopia and the need for frequent instillation all militate against good compliance. Indeed studies have been carried out in USA with electronic timing drug droppers which confirmed the poor compliance with this drug.(20) Other studies have shown that compliance is much higher with a 12 hourly regime (of B-blocker) than with a 6 hourly regime (pilocarpine). (21)

It has also been shown that in pigmented eyes pilocarpine binds to melamin reducing its availability. This necessitates the use of stronger and stronger concentrations on prolonged use. (5)

Finally, in our context where the vast majority of the population is rural and there is difficulty in getting

the drugs regularly, long term medical treatment is probably not yet safe. Such treatment should be given while planning for survery.

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