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EFFECT OF CERTAIN OPHTHALMIC PREPARATIONS CONTAINING PILOCARPINE HYDROCHLORIDE AND DEXAMETHASONE ON THE INTRAOCULAR PRESSURE OF RABBITS EYE

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The present study deals with the influence of dexamethasone applied locally on the intraocular pressure(I.O.P.) of rabbit and how far this influence may be corrected by the use of the antiglaucoma drug pilocarpine hydrochloride.

It was found that no change in pupillary diameter occurs after instillation of dexamethasone solution. A slight increase in the miotic activity of pilocarpine hydrochloride combined with dexamethasone was observed 15 minutes post-instillation, reaching to maximum within 2-3 hours and then extending to 24 hours.

Dexamethasone plus pilocarpine hydrochloride in a w/o emulsion base produced the highest effect after 2-3 hours. The I.O.P. reached to the inital level, 24 hours after application. The ointment seems to form over the corneal surface , an ocolusive nonrenewable film, from which pilocarpine hydrochloride is depleted from its aqueous phase . On the other hand dexamethasone lipid solubility permits slow diffusion through the vehicle to replenish the concentration of drug in the film adjacent to the corneal surface. For this reason, the I.O.P did not return to its initial level.

Steroids are widely used to treat various inflammatory disorders of the eye and to prevent progressive complications resulting from other ocular diseases. Studies on the extent to which steroids, applied to the eye penetrate into ocular

tissues have received great attention. These investigations were concerned mainly with the intraocular penetration of dexamethasone (1-6), prednisone (6-10), prednisolone (11-13) and other related corticosteroids.

Various pharmaceutical formulations were involved in these studies which include aqueous solutions (2-4 and 10), suspensions (1,7 -9 and 11-13) and various ointment bases (4,5 and 10).

It has been reported that a major side effect of corticosteroid therapy was the elevation in intraocular pressure , especially by dexamethasone and betamethasone.

In order to treat ocular inflammation, it was desirable to combine the steroidal drug with an agent which can minimize the increase in ocular pressure, which still producing sufficient antiinflammatory activity. Severe complications may arise, if both the dose of corticosteroid and frequency of application are not carefully controlled[14].

The present study deals with the influence of dexamethasone on the intraocular pressure of rabbit and how to overcome this effect by the use of water-soluble antiglaucoma drug e.g pilocarpine hydrochloride.

EPERIMENTAL

Material:

Dexamethasone [(a)], pilocarpine hydrochloride[(b)]. Emulgin C_{1500} (Cetyl stearyl alcohol with (30) (Ethylene oxide units) Emulgin 010 (Oleyl cetyl alcohol with (10) (Ethylene oxide units),[c] white soft paraffin, glycerol, stearyl alcohol[(b)]. Adult, male, albino rabbits 1.8 - 2.4 k_g were used throughout this study.

I- Preparation of the solutions:

Solutions containing 0.1% w/v dexamethasone or 0.1% dexamethazone plus 1% pilocarpine were prepared using 10% Tween 80

(a) Sigma Chemicals, St., Louis, U.S.A
(b) BDH Chemical Ltd, Poole England.
(c) Atlas Chemical indstries, Dol. U.S.A.

and 10% polyethylene glycol 600.

II- Preparation of ointments:

Dexamethasone and pilocarpine hydrochloride ointments were prepared according to the following formulaes:

Water - in - oil ointment base:

Dexamethasone	0.1%
Pilocarpine hydrochloride	1.0%
White soft paraffin	80.0%
Emulgin 010	8.0%
Water	11.0%

Oil - in - water ointment base:

Dexamethasone	0.1%
Pilocarpine hydrochloride	1.0%
Stearyl alcohol	25.0%
White soft paraffin	25.0%
Glycerol	12.0%
Emulgin^{C}1500	32.0%

Procedures:

A- Measurement of Intraocular Pressure:

Isotonic xylocaine solution (1 ml of a 1% w/v) was dropped into the rabbit's eyes to anaesthetise the cornea. Topical doses each 0.1 ml of the solution were instilled into the rabbit's eyes. The lower eyelid was retracted from the cornea and the solution was dropped into the conjunctival sac. The eyelids were held closed for 30-45 seconds following instillation so as to stop blinking thereby preventing a large initial loss of the solution from the eye. After instillation or application of the ointment containing the drug, the lower eyelid was taped open, and the intraocular pressure was measured as a function of time after 15, 30 and 60 minutes intervals using a tonometer (10 gm). Measurements were terminated when the measured ocular pressure reache a constant value close to the

initial value.

B- Moasurement Of Pupillary Diameter:

This was carried out before and after instillation of the drug at the same intervals adopted for measurement of ocular tension using Maab's pupillometer.

RESULTS AND DISCUSSIONS

Effect of the drugs in ophthalmic solutions:

The data shown in Fig. 1 represented the effect of dexamethasone eye drops and its combination with pilocarpine hydrochloride on the intraocular pressure (I.O.P.) of the rabbit's eye. The figurs shows that the I.O.P. increases with time reaching to maximum after three houre, then decreases after wards. The curve demonstrates the influence of the use of solubilized system containing 10% w/v polyethylene glycol and 10% w/v Tween 80 together with 0.1% w/v of dexamethasone as ophthalmic solution. The intraocular pressure/versus time profiles demonstrate clearly that the drug had a prolonged action (24 hours) already at a relatively small concentration. The eye used as a control shows a slight increase in the I.O.P. throughout the first five hours; this may be due to the systemic action of the drug.

Combination of dexamethasone with pilocarpine hydrochloride results in a compensation of the increase in I.O.P. caused by dexamethasone. The combination induces a slight decrease in the I.O.P. of the rabbits during the first two hours; beyond this period the I.O.P. starts to increase to reach the initial level. The decrease in the I.O.P. of the rabbit in the first two hours, may be due to the rapid solubility of pilocarpine hydrochloride in lachrymal fluid and consequently, rapid penetration of the drug through the cornea. Also, slight decrease in the I.O.P. of the control eye in

the first two hours may be due to systemic absorption of pilocarpine hydrochloride.

The results obtained for the intensity of miosis in Table 1, show a comparison between the effect of 0.1% w/v dexamethasone and a combination of 0.1% w/v dexamethasone and 1% w/v pilocarpine hydrochloride in aqueous solutions. It was found that no change in pupillary diameter occurs after instillation of dexamethasone solution. A slight increase in the miotic activity of pilocarpine hydrochloride combined with dexamethasone was observed after 15 minutes post instillation , reaching to maxiumum wihtin ½ - 1 hour and then continued for 5 hours. The prolonged duration of action achieved using either dexamethasone or dexamethasone with pilocarpine hydrochloride may be attributed to the longer retention of the drug solutions in the conjunctival sac of the rabbit's eye by the aid of polyethylene glycol used as cosolubilizer for this drug. The increase in the viscosity of the solutions by polyethylene glycol or the incorporation of this drug within the micelles of the non-ionic surfactant may be also the cause of the prolonged of action of dexamethasone in this solubilized system. This may provide an advantage as the drug can be instilled once a day instead of several times.

Effect of the drugs in ointments :

Figure (2) represents the data obtained for dexamethasone and dexamethasone with pilocarpine hydrochloride using o/w emulsion base. It was noticed that the I.O.P. reached to maximum (3.8 mm. Hg)* after three hours. The increase in the I.O.P. persisted almost 18 hours. No change in the ocular pressure of the rabbit's eye used as control was noticed for both formulations. The figure

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* 3.8 mm. Hg is the difference between the initial and the maximum response.

also demonstrates that dexamethasone with pilocarpine hydrochloride produced a slight decrease in the I.O.P. Dexamethasone being lipophilic in nature, was expected to be localized mainly in the oily phase, therefore peak time was not achieved until three hours after application.

Figure (3) represents the effect of dexamethasone and dexamethasone pilocarpine hydrochloride in w/o emulsion ointment base on the I.O.P. of the rabbit's eye. From this figure, it can be shown that the effect of dexamethasone on the I.O.P. of the rabbit is higher(4.9 mm Hg)* than in the case of dexamethasone in o/w emulsion base. This result migher be indicative of the higher availability of dexamethasone from the continuous oily phase. The effect of the sterioid was found to be maintained for up to 24 hours. The release of dexamethasone pilocarpine hydrochloride from w/o emulsion base produced the greatest effect after 2-3 hours. The I.O.P. reached to the initial level after 24 hours. On the other hand, dexamethasone lipid solubility permits alow diffusion through the vehicle to replenish the concentration of drug in the film adjacent to the corneal surface. For this reason, in the abscence of pilocarpine, the I.O.P. did not return to its initial level within 24 hours.

Tables 2 and 3 show a comparisom in pupillary diameter between 0.1% w/v dexamethasone and a combination of 0.1% w/v dexamethasone and 1% w/v pilocarpine hydrochloride in emulsion bases (w/o and o/w). It was found that no change in pupillary diameter taken place after application of dexamethasone, while a decrease in pupillary diameter was noticed after application of dexamethasone/pilocarpine ointments.

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* 4.9 mm. Hg is the difference between the initial and the maximum response.

Table 1: Effect of dexamethasone and dexamethasone pilocarpine hydrochloride ophthalmic drops on the pupillary diameter (mm) of rabbit's eye.

Time (in hours)	*Dexamethasone*				*Dexamethasone + Pilocarpine Hcl*			
	Control	*S.D*	*Experiment*	*S.D.*	*Control*	*S.D.*	*Experiment*	*S.D.*
0	5.6	± 0.58	5.0	± 0.63	6.25	± 0.69	6.5	± 0.55
¼	5.3	± 0.61	5.0	± 0.63	5.18	± 0.52	4.75	± 0.27
½	5.6	± 0.58	4.75	± 0.42	5.25	± 0.42	4.33	± 0.26
1	5.75	± 0.42	5.0	± 0.00	5.25	± 0.42	4.50	± 0.32
2	5.25	± 0.42	5.0	± 0.00	5.83	± 0.26	5.41	± 0.49
3	5.25	± 0.27	5.0	± 0.32	5.83	± 0.26	6.00	± 0.63
4	5.25	± 0.27	5.0	± 0.32	5.83	± 0.26	6.10	± 0.42
5	5.25	± 0.42	5.0	± 0.32	6.08	± 0.74	6.50	± 0.55
18	5.25	± 0.42	5.0	± 0.32	6.08	± 0.74	6.50	± 0.55
24	5.25	± 0.24	5.0	± 0.32	6.08	± 0.74	6.50	± 0.55

Table 2: Effect of dexamethasone and dexamethasone pilocarpine hydrochloride ointment (w/o) on the pupillary diameter (mm) of rabbit's eye.

Time (in hours)	Dexamethasone				Dexamethasone + Pilocarpine Hcl			
	Control	S.D.	Experiment	S.D.	Control	S.D.	Experiment	S.D.
0	6.33	± 0.26	6.66	± 0.26	6.33	± 0.26	6.66	± 0.26
¼	6.00	± 0.63	6.50	± 0.55	6.10	± 0.42	6.25	± 0.36
½	6.10	± 0.42	6.00	± 0.63	5.50	± 0.58	6.00	± 0.63
1	6.16	± 0.52	6.33	± 0.26	5.18	± 0.52	5.20	± 0.52
2	6.33	± 0.26	6.33	± 0.26	4.40	± 0.36	4.50	± 0.36
3	6.33	± 0.26	6.33	± 0.41	4.10	± 0.26	4.10	± 0.26
4	6.33	± 0.41	6.66	± 0.41	5.00	± 0.00	5.0	± 0.00
5	6.33	± 0.26	6.60	± 0.63	5.30	± 0.42	5.50	± 0.58
18	6.33	± 0.41	6.60	± 0.63	6.00	± 0.63	6.00	± 0.63
24	6.33	± 0.41	6.60	± 0.63	6.00	± 0.63	6.66	± 0.26

Table 3: **Effect of dexamethasone and dexamethasone pilocarpine hydrochloride ointment (o/w) on the pupillary diameter (mm) of rabbit's eye.**

Time (in hours)	*Dexamethasone*				*Dexamethasone + pilocarpine Hcl*			
	Control	*S.D.*	*Experiment*	*S.D.*	*Control*	*S.D.*	*Experiment*	*S.D.*
0	6.66	± 0.41	6.66	± 0.41	6.33	± 0.26	6.70	± 0.63
¼	6.50	± 0.45	6.16	± 0.61	6.00	± 0.63	6.18	± 0.52
½	6.50	± 0.45	6.33	± 0.41	6.18	± 0.52	5.00	± 0.00
1	6.66	± 0.41	6.66	± 0.41	6.18	± 0.52	4.50	± 0.32
2	6.33	± 0.41	6.20	± 0.69	6.10	± 0.52	4.60	± 0.26
3	6.00	± 0.63	6.33	± 0.41	5.30	± 0.42	4.80	± 0.36
4	6.66	± 0.41	6.60	± 0.63	5.30	± 0.42	5.00	± 0.00
5	6.66	± 0.41	6.0	± 0.63	6.10	± 0.42	5.20	± 0.24
18	6.66	± 0.41	6.60	± 0.63	6.33	± 0.26	6.70	± 0.63
24	6.66	± 0.41	6.60	± 0.63	6.33	± 0.26	6.60	± 0.63

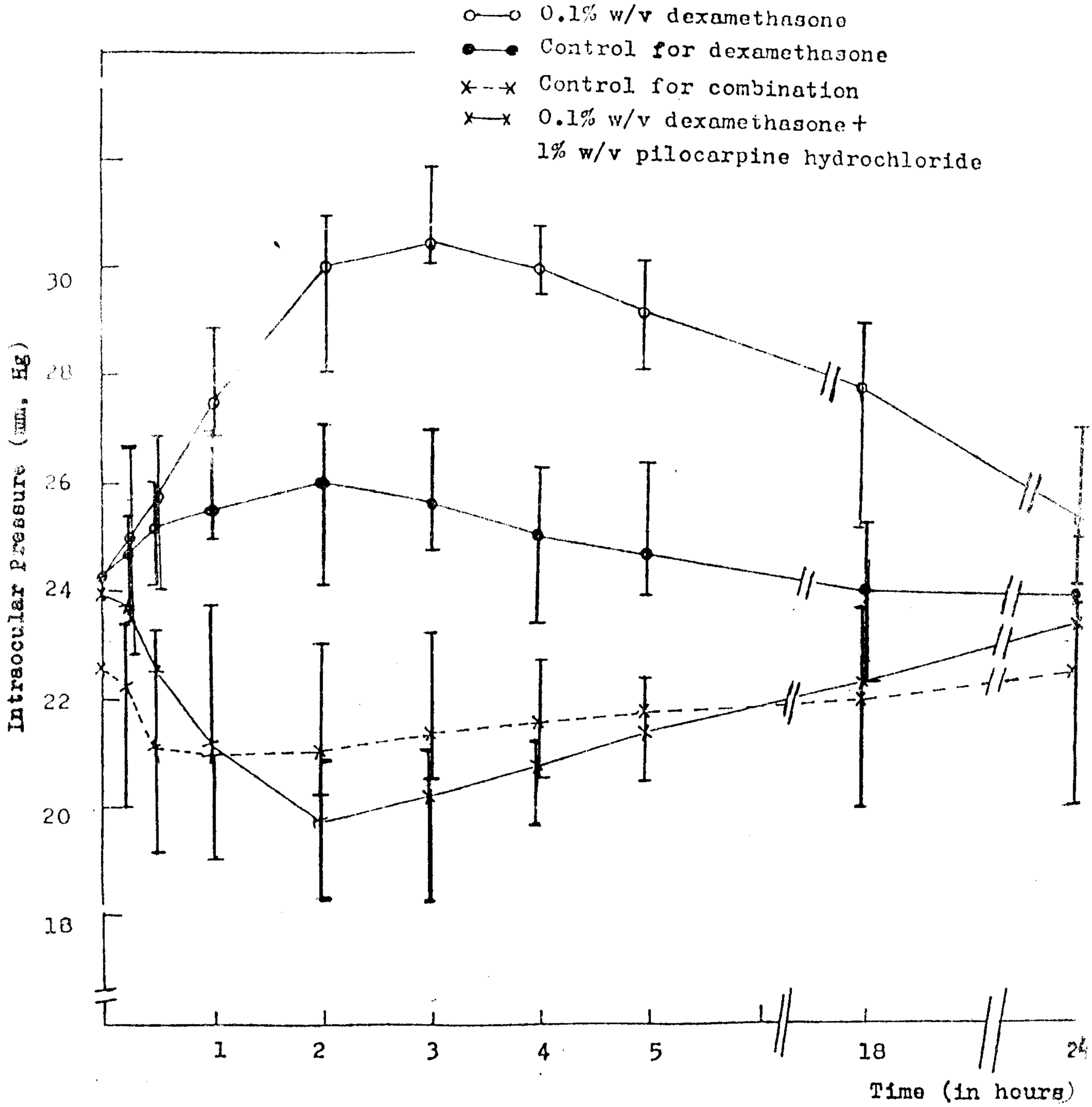


Figure (1) Effect of 0.1% w/v dexamethasone and 0.1% w/v dexamethasone —— 1% w/v pilocarpine hydrochloride combination in ophthalmic solution on the intraocular pressure of rabbits eye. **Each point represents the mean value and range of six or eight reading.**

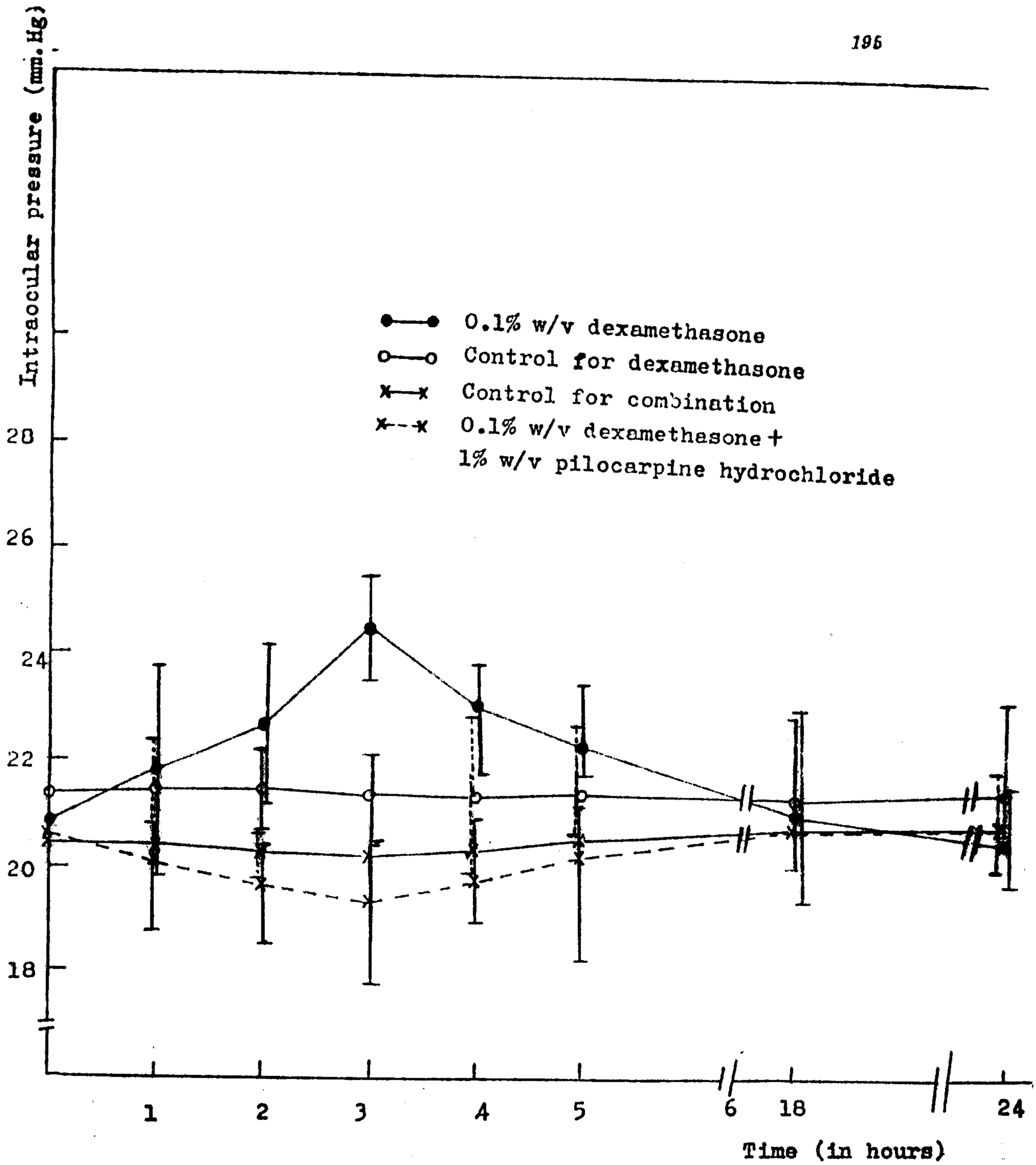
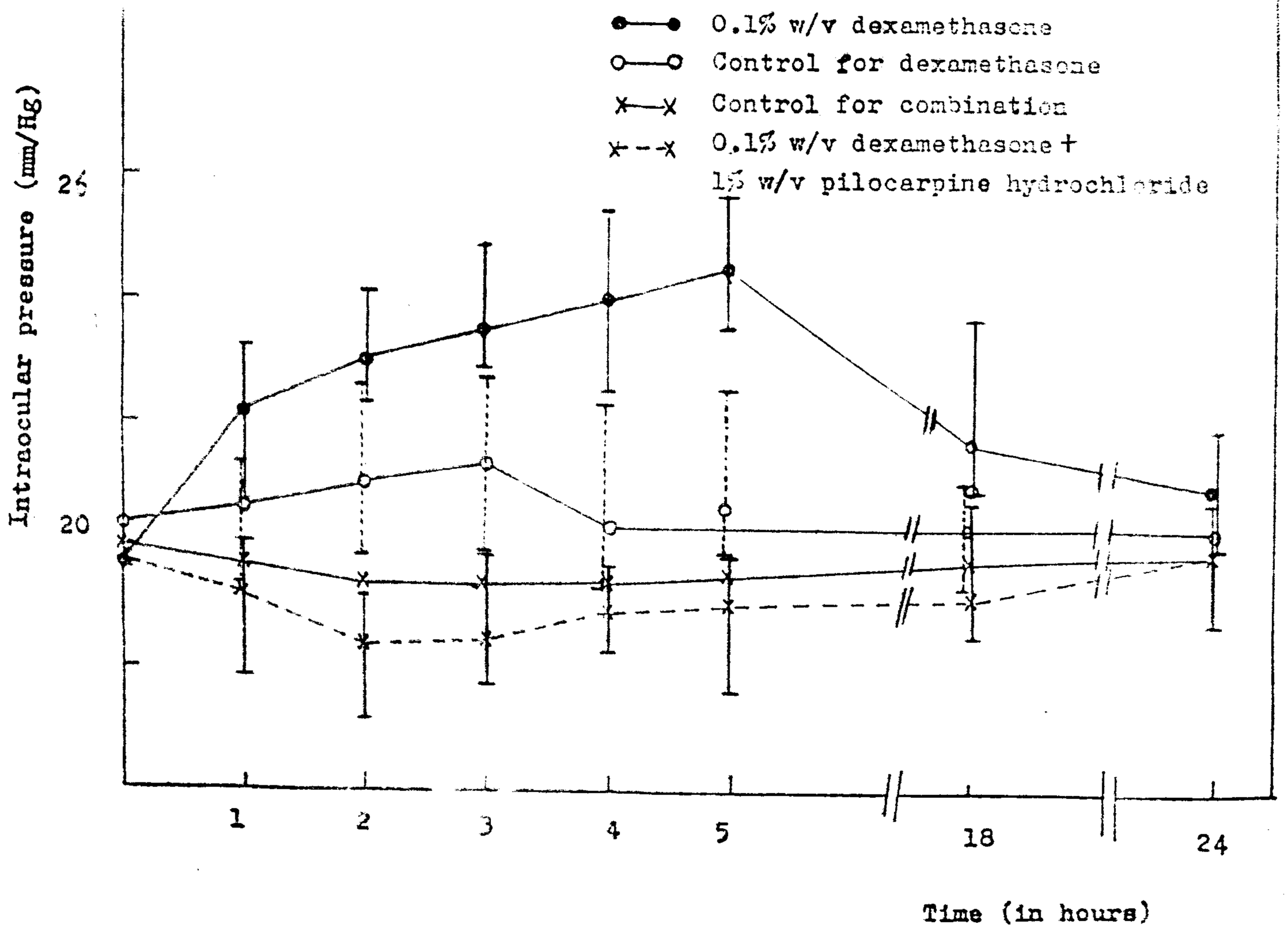


Figure (2) Effect of 0.1% w/v dexamethasone and 0.1% w/v dexamethasone — 1% w/v pilocarpine hydrochloride combination in o/w ointment base on the intraocular pressure of rabbits eye. Each point represents the mean value and ranges of six or eight reading.



Figure(3) Effect of 0.1% w/v dexamethasone and 0.1% w/v dexamethasone hydrochloride combination in w/o ointment base on the intraocular pressure of rabbits eye. Each point represents the mean value and ranges of six or eight reading.

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تأثير بعض مستحضرات العين المحتويه على أيدروكلوريد البيلوكاربين والدكساميثازون على الضغط الداخلى لعين الأرانب

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تحتوى هذه الدراسة على تأثير الدكساميثازون على الضغط الداخلى لعين الأرانب ، وكيفية التغلب على هذا التأثير لعمل مخلوط من هذا الدواء مع ايدروكلوريد البيلوكاربين .

تبين من هذه الدراسة عدم وجود تاثير محسوس على تغيير حدقة العين بعد وضع محلول الدكساميثازون . ووجد أن زيادة بسيطة حدثت فى النشاط الأنقباضى لأيدروكلوريد البيلوكاربين مع الدكساميثازون بعد ١٥ دقيقة من وضع المحلول فى العين ، وتصل الى الحد الأقصى فى خلال الفترة من ٢ ـ ٣ ساعات ، وتستمر هذه الزيادة طوال ٢٤ ساعة .

وتبين أن انطلاق الدكساميثازون وأيدركلوريد البيلوكاربين من قاعدة المستحلب زيت فى ماء تعطى أعلى مستوى من الانطلاق فى خلال الفترة من ٢ ـ ٣ ساعات . ووجد أيضا أن الضغط الداخلى للعين يصل الى مستواه الأبتدائى بعد ٢٤ ساعة من وضع الجرعة فى العين ، وذلك نتيجة أن المرهم يكون طبقة غير متجددة على سطح القرنيه وأن ايدركلوريد البيلوكاربين يزال من الماء الموجود فى طبقة المرهم . ومن ناحية أخرى نجد أن الدكساميثازون له خاصية الذوبان فى الزيوت وبالتالى له درجة نفاذ ضعيفه من السواغ الموجود به . ولهذا السبب نجد أن الضغط الداخلى للعين لا يعود الى مستواه الابتدائى .

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