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The efficacy of 2.5% phenylephrine and flurbiprofen combined in inducing and maintaining pupillary dilatation during cataract surgery

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PURPOSE. *To evaluate the effectiveness of phenylephrine 2.5% and flurbiprofen 0.03% combined in inducing and maintaining mydriasis during extracapsular cataract extraction (ECCE).*

METHODS. *One hundred patients undergoing ECCE + intraocular lens (IOL) implantation were randomly divided into four groups. The first group was given phenylphrine 10%, the second group phenylephrine 10% + flurbiprofen, the third group phenylephrine 2.5% and fourth group phenylephrine 2.5% + flurbiprofen. Cyclopentolate 1% was used in all patients. Phenylephrine and cyclopentolate were instilled preoperatively four times during 1 hour and flurbiprofen was given four times the day before surgery and twice with an hour's interval before operation. Pre-operative and post-cortex aspiration horizontal pupil diameters were measured with callipers viewed through the operating microscope.*

RESULTS. *Pupil diameters in pre-operative and post-cortex aspiration were no different in the 2.5% and 10% phenylephrine groups ($p>0.05$). Both diameters were larger and pupillary constriction was smaller in the flurbiprofen groups ($p<0.05$).*

CONCLUSIONS. *2.5% phenylephrine was as effective as 10% phenylephrine, with and without flurbiprofen, in inducing and maintaining pupil dilatation during ECCE surgery. (Eur J Ophthalmol 2000; 10: 144-8)*

KEY WORDS. *2.5% phenylephrine, 10% phenylephrine, Flurbiprofen, Extracapsular cataract extraction (ECCE), Mydriasis*

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INTRODUCTION

Modern cataract surgery requires adequate mydriasis for performing capsulotomy, removing the nucleus, complete removal of lens cortical remnants, and placement of an intraocular lens (IOL) in the capsular bag (1). Therefore, sufficient pupillary dilatation during extracapsular cataract extraction and posterior chamber IOL (ECCE+PC IOL) surgery is important (1-3). Currently preoperative sympathomimetics and anticholinergics are used topically to produce and maintain dilatation.

The systemic side effects from topically administered drugs are recognised. Several different adverse reactions have been reported after topical ocular use of 10% phenylephrine. These include severe hypertension, subarachnoid hemorrhage, ventricular arrhyhmias, and myocardial infarction (1). The dose of phenylephrine administered can be reduced by using more dilute drops such as 2.5% phenylephrine.

This study compared the effects of a combination of topical phenylephrine 2.5% and flurbiprofen with phenylephrine 10% and flurbiprofen for inducing mydriasis preoperatively and inhibiting surgically induced miosis during ECCE.

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PATIENTS AND METHODS

One hundred patients scheduled for ECCE+ PC IOL implantation were admitted to the study. Patients who had already had ocular surgery or disease in the same eye, were taking miotic glaucoma medications or non-steroidal anti-inflammatory drugs (NSAIDs) or had diabetes were excluded. This was a prospective, randomised, double-blinded clinical trial.

The patients were assigned to four groups:

Group I (n=33): phenylephrine 10% + cyclopentolate 1%

Group II (n=21): phenylephrine 2.5% + cyclopentolate 1% + flurbiprofen 0.03%

Group III (n=21): phenylephrine 2.5% + cyclopentolate 1%

Group IV (n=25): phenylephrine 2.5% + cyclopentolate 1% + flurbiprofen 0.03%

Phenylephrine and cyclopentolate 1% drops were instilled four times in 1 hour before surgery. Flurbiprofen drops were instilled four times the day before surgery and two times at hourly intervals before surgery.

Peribulbar anesthesia was induced with jetocain. Mannitol 20% 150 cc i.v. in 15 mm was given for ocular hypotony. Ocular massage was done for approximately 3 minutes. Healon® was used as a viscoelastic substance and BSS as an irrigation solution.

The horizontal pupillary diameters were measured with callipers under the standard magnification of the operating microscope at the beginning of surgery and after aspiration of cortical lens material. Results were evaluated by the Kruskal Wallis, Mann-Whitney U and Wilcoxon tests at $p<0.05$ significance level.

RESULTS

Pupil diameters in both pre-operative and post-cortex aspiration were no different in groups I and II (phenylephrine 10%) and groups III and IV (phenylephrine 2.5%) ($p>0.05$). Pupil diameters in pre-operative and post-cortex aspiration were larger and pupillary constriction was smaller in the flurbiprofen groups ($p<0.05$) (Tabs I, II). Pupil diameters in pre-operative and post-cortex aspiration and pupillary constriction in groups with or without flurbiprofen were not significantly different ($p>0.05$) (Tab. I).

DISCUSSION

Phenylephrine, a strong sympathomimetic agent, is routinely used in cataract surgery to provide preoperative mydriasis. Phenylephrine 10% is usually administered topically together with cyclopentolate 1%, an anticholinergic agent, four times over one hour before surgery (4). This preoperative drug combination is thought to ensure maximal stimulation of dilator pupillae while paralysing constrictor pupillae (4).

It has been reported that 10% phenylephrine is contraindicated in the elderly and in hypertensive patients even if normotensive on medication (5, 6) and the maximum recommended dose in any patient is one drop per hour (1). Phenylephrine 2.5% is as effective as the 10% formulation for fundus examination and for inducing and maintaining mydriasis in ECCE operations (4, 7-9). We compared the efficacy of phenylephrine 2.5% or 10% in combination with flurbiprofen 1% and cyclopentolate 1%.

After any surgical trauma autacoids and neurotransmitters (prostaglandins, leucotriens, substance P, acetylcholine, bradykinin and histamine) are released from the ciliary body into the aqueous humor, causing miosis (10-12). Topical NSAID can prevent surgically induced miosis to different degrees by inhibiting prostaglandin synthesis (2, 3, 10, 11, 13-15).

Phenylephrine is a powerful sympathomimetic drug. Administered systemically, it raises systolic and diastolic blood pressure and causes reflex bradycardia leading to peripheral vasoconstriction. Several different adverse reactions have been reported after topical ocular phenylephrine 10%. These include severe hypertension and cerebrovascular events (16-18), myo-cardial infarction (19), ventricular arrhythmia (20) and subarachnoid hemorrhage (21). A drop of approximately 35-50 µl 10% phenylephrine contains at least 3.5 mg of the active drug. In the treatment of acute hypotension in adults the upper limit of safety for a systemic dose of phenylephrine is 1.5 mg by slow intravenous infusion or 10 mg subcutaneously (4). Systemic absorpion of drugs instilled into the conjunctival sac is through the conjunctival capillaries and nasal mucosa after passage through the nasolacrimal canal (22). Drugs

TABLE I - PUPIL DIAMETERS (MM) AT THE START OF EXTRACAPSULAR CATARACT EXTRACTION (ECCE) (1) AND AFTER ASPIRATION (2) WITHIN AND BETWEEN GROUPS

	Group A*				**Group B**				**Group C**				**Group D**			
	A_1			A_2	B_1			B_2	C_1			C_2	D_1			D_2
	Min	Max	Mean±SD	Min Max Mean±SD	Min	Max	Mean±SD	Min Max Mean±SD	Min	Max	Mean±SD	Min Max Mean±SD	Min	Max	Mean±SD	Min Max Mean±SD
	7	9.5	8.4± 0.1	5 8 6.4±0.1	8	9.5	8.8±0.1	5.5 8.5 7.4±0.2	7	9	8.3±0.1	4 7.5 6.2±0.2	8	9.5	8.8±0.8	5 8.5 7.1±0.2
A_1				T=-19.9, P<0.001			U=216.5, P<0.05				U=296.5, P<0.05				U=256.5, P<0.05	
A_2								U=119, P<0.001				U=329, P>0.05				U=208, P<0.01
B_1								Z=-4.1, P<0.001			U=109.5, P<0.001				U=2.5, P>0.05	
B_2												U=74.5, P<0.001				U=212, P>0.05
C_1												Z= -3.9, P<0.001			U=126, P<0.001	
C_2																U=124.5, P<0.001
D_1																Z=-4.37, P<0.001

* Group A: Phenylephrine 10% + cyclopentolate 1%; Group B: Phenylephrine 10% + cyclopentolate 1% + flurbiprofen 0.03%; Group C: Phenylephrine 2.5% + cyclopentolate 1%; Group D: Phenylephrine 2.5% + cyclopentolate 1% + flurbiprofen 0.03%; Note: 1. Preoperative pupil diameters are shown as A_1, B_1, C_1, D_1, postoperative values as A_2, B_2, C_2, D_2; 2. Note U and Z values at square of groups intersection

TABLE II - PUPIL SIZES (MM) AT THE START OF ECCE (1) AND AFTER ASPIRATION (2)

Pupil size	A_1-A_2 (1.95±0.56)	B_1-B_2 (1.43±0.58)	C_1-C_2 (2.05±0.43)	D_1-D_2 (1.62±0.55)
A_1-A_2		t=3.31, P<0.001	t=0.46, P>0.05	t=2.27, P<0.05
B_1-B_2			t=2.68, P<0.05	t=-1.16, P>0.05
C_1-C_2				t=3.61, P<0.001

Group A: Phenylephrine 10% + cyclopentolate 1%; Group B: Phenylephrine 10% + cyclopentolate 1% + flurbiprofen 0.03%; Group C: Phenylephrine 2.5% + cyclopentolate 1%; Group D: Phenylephrine 2.5% + cyclopentolate 1% + flurbiprofen 0.03%; Note: 1. Preoperative pupil diameters are shown as A_1, B_1, C_1, D_1, postoperative values as A_2, B_2, C_2, D_2; 2. Note t values at square of groups intersection

applied to the conjunctiva are thought to be absorbed systemically almost as fast as the equivalent dose given intravenously (4). Therefore the routine application of four drops of phenylephrine 10% can potentially result in an elderly person receiving up to nine times the maximum recommended dose for a young adult.

Topical phenylephrine 10% increased systolic and diastolic blood pressure in normotensive and hypertensive patients in some studies (9, 17, 19). The low frequency of reported reactions to this concentration may be partly due to the fact that the drug's activity is seen 20 minutes after topical application and then decreases rapidly (4); 20 minutes after instillation of phenylephrine eye drops before cataract operations, most patients are not monitored, so hypertensive reactions due to systemic absorption may pass unnoticed. The use of phenylephrine 10% is contraindicated in the newborn because of its systemic hypertensive action (23).

NSAIDs are known to prevent surgically induced miosis (2, 3, 13, 14, 24, 25). Flurbiprofen has been reported to be more effective than indomethacin in some experimental and clinical studies (14, 25-27). However other studies reported no difference between the two drugs (3, 14). We found topical phenylephrine 2.5% was as effective as the 10%, formulation and topical flurbiprofen increased this effect significantly. The supplementary mydriatic effect of flurbiprofen might result from an enhancing effect of phenylephrine, in addition to the inhibition of prostaglandin synthesis. Flurbiprofen increased corneal penetration of phenylephrine 5 to 11-fold in a rabbit model (28).

We could find no reports on the effect of the 2.5% phenylephrine and flurbiprofen combination in extracapsular cataract extraction. Therefore, we could not compare this combination with similar studies. However, topical phenylephrine 2.5% + cyclopentolate 1% + flurbiprofen 0.03% appears to be a safe and effective combination for inducing and mantaining adequate mydriasis during ECCE procedures.

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