CLINICAL STUDY

The effect of pre-operative topical flurbiprofen or diclofenac on pupil dilatation

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Abstract

Purpose **To assess the clinical benefit and relative efficacy of pre-operative diclofenac and flurbiprofen drops in routine cataract surgery.**

Methods **Fifty-two patients undergoing extracapsular cataract extraction with lens implantation were randomised in a double-masked study to compare the efficacy of diclofenac, flurbiprofen and placebo drops in maintaining per-operative mydriasis and reducing post-operative inflammation. Balanced salt solution containing adrenaline was used in all patients. Pupil size was measured prior to the corneal section and after the completion of the operation. The degree of pain, redness, flare and cells in the anterior chamber and intraocular pressure were recorded on the day after surgery. The three groups were analysed with respect to change in pupil size, intraocular pressure and degree of inflammation.**

Results **The change in pupil size was significantly different among the three groups ($p = 0.01$), there being a smaller decrease in the treatment groups compared with the placebo group and in the diclofenac treatment group compared with the flurbiprofen treatment group. Significantly less post-operative redness was recorded in the diclofenac treatment group compared with the other groups ($p = 0.001$). No significant difference was found between the groups as regards anterior chamber cells, flare or intraocular pressure change.**

Conclusions **Pre-operative diclofenac and flurbiprofen drops are effective in maintaining intraoperative mydriasis. Diclofenac reduces post-operative redness on day 1. These effects are of debatable clinical benefit.**

Key words Cataract, Diclofenac, Flurbiprofen, Mydriasis, Pre-operative, Pupil size

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The maintenance of mydriasis is important during cataract surgery to facilitate uncomplicated cortex removal and intraocular lens insertion.[1,2] The administration of pre-operative topical non-steroidal anti-inflammatory drops (NSAIDs)[3–12] and the use of adrenaline in the irrigating solution[4,6,13,14] are both effective at maintaining mydriasis. An additive effect on the maintenance of pupil size has been demonstrated when both methods are used together.[4,6,15,16] However, this effect has been small. This study attempted to quantify this effect and to determine whether flurbiprofen or diclofenac is the more effective preparation.

In addition it has been our impression that pre-operative NSAIDs give whiter eyes post-operatively. We therefore looked for a clinically observable difference in post-operative inflammation on the first post-operative day.

Methods

A randomised, double-masked, placebo-controlled method was used with two active treatment groups and a placebo group.

Consecutive patients listed for elective extracapsular cataract extraction with intraocular lens implantation were invited to take part in the study. Local research ethics committee approval was obtained, as was informed written consent from all patients entering the trial. Stringent exclusion criteria were employed in patient selection to minimise the possible confounding effects of concurrent medication or previous eye treatment (Table 1).

Fifty-two patients were randomly assigned to either the control group or one of two treatment groups. All patients received routine pre-operative dilating drops consisting of 4 drops each of cyclopentolate 1% and phenylephrine 10%. In addition group A received placebo drops (diclofenac vehicle solution was used), group B received diclofenac sodium 0.1% and group C received flurbiprofen

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Table 1. *Exclusion criteria applied in the selection of study participants*

Age < 18 years
Pregnancy or lactation
Known hypersensitivity to diclofenac, flurbiprofen or other NSAIDs
Concurrent or recent (within the two preceding weeks) medication with systemic steroids or NSAIDs, cytotoxic or other immunosuppressant agents
Concurrent medication with systemic drugs with autonomic side effects
Previous ocular surgery or serious injury in the operated eye
History or signs of recurrent uveitis and/or evidence of iris sphincter atrophy
Use of any topical ophthalmic medications in the preceding two weeks apart from ocular lubricants or prophylactic topical antibiotics
Participating in another trial
Non-compliance with protocol
Glaucoma patients

sodium 0.03%. One drop was given every 30 min starting 2 h before surgery for a total of four doses of the stated agent in each group.

All surgery was performed by the same surgeon using a standard extracapsular cataract technique with a corneal section under a general or local anaesthetic. Sodium hyaluronate (aspirated at the end of the procedure) was used as was a balanced salt solution containing adrenaline, at a concentration of 1 part per million, for irrigating the anterior chamber.

Pupillary diameter was recorded in millimetres using a caliper by the surgeon prior to the corneal section and at the end of the operation following reformation of the anterior chamber.

The degree of surgical iris trauma was graded as mild (= 1), moderate (= 2) or severe (= 3). Patients with severe complications such as vitreous loss, or with complications such as circumlimbal subconjunctival haemorrhage which would prevent post-operative assessment of conjunctival redness, were excluded from analysis.

Table 2. *The clinical grading scales employed to assess post-operative pain and inflammation in 52 cataract patients*

Category	Scale	Criteria
Post-operative pain	0	None
	1	Mild
	2	Moderate or constant
	3	Severe/analgesia required
Redness (bulbar injection)	0	Absent
	1	Mild
	2	Moderate/circumlimbal
	3	Severe/whole bulbar conjunctiva
Flare	0	None
	1	Barely detectable
	2	Mild
	3	Moderate
	4	Strong
	5	Severe/coagulated aqueous
Cells	0	None
	1	Occasional
	2	Few
	3	Moderate
	4	Many
	5	Hypopyon

On the first post-operative day, the degree of pain, redness, flare and cells in the anterior chamber were assessed according to set grading scales (Table 2).

The intraocular pressure was recorded pre-operatively (within 1 month of surgery) and of the first post-operative day.

An analysis of variance (ANOVA) test was used to compare pupil size and intraocular pressure results among the three groups. A Kruskal–Wallis analysis of variance was used on the ordinal data recorded from the graded scales. A p value of less than 0.05 was considered to be statistically significant.

Results

Fifteen patients were assigned to the placebo group, 17 to the flurbiprofen group and 20 to the diclofenac group. Only 2 patients in the study had general anaesthesia: 1 in the placebo and 1 in the diclofenac group. All other patients had a local anaesthetic.

No statistically significant difference was noted among the groups in the pre-operative intraocular pressure measurement ($p = 0.79$), the post-operative intraocular pressure ($p = 0.29$), or in the pre- to post-operative change in intraocular pressure ($p = 0.39$). There was no statistically significant difference in degree of iris trauma among the groups ($p = 0.79$).

Pupil size in the three treatment groups pre-operatively was comparable ($p = 0.79$). Change in pupil size from pre-operative to post-operative measurements was statistically significant among the treatment groups ($p = 0.01$) (Table 3). A follow-up analysis using least significant difference showed that the change in pupil size was significantly smaller in both the NSAID groups compared with the placebo group and also in the diclofenac treatment group as compared with the flurbiprofen treatment group.

There was a statistically significant difference in the degree of redness post-operatively among the three groups ($p = 0.001$). A follow-up analysis using least significant difference showed diclofenac caused a statistically significant reduction in the degree of redness post-operatively compared with flurbiprofen and placebo. Flurbiprofen caused no significant difference in redness compared with placebo drops.

Table 3. *Results of ANOVA analysis on pupil size*

	Placebo	Flurbiprofen	Diclofenac	*p* value
No. of patients	15	17	20	
Mean pre-operative pupil size (mm)	8.00	8.15	7.98	0.79
Mean post-operative pupil size (mm)	7.47	7.94	7.93	0.26
Mean change in pupil size (mm)	−0.53	−0.21	−0.05	0.01

There was no clinically significant difference among the three groups in the flare ($p = 0.51$), cells ($p = 0.53$) or pain ($p = 0.07$) levels recorded post-operatively. We found no adverse effects from either drop other than mild stinging on instillation.

Discussion

It is now well established that NSAIDs reduce intraoperative miosis during cataract surgery.[3–12] This is confirmed in this study. Of the two NSAIDs, diclofenac was found to be more effective than flurbiprofen in producing this effect (Table 3).

Several studies have shown that adrenaline is more effective in maintaining intraoperative mydriasis than pre-operative treatment with NSAIDs,[4,6] which may indicate that there is little to gain from using NSAIDs in place of adrenaline in the anterior chamber irrigation fluid. Adrenaline is also more convenient, as the recommended pre-operative treatment regime for NSAIDs is 4 drops over 2 h while our routine pre-operative mydriatics are administered over 1 h, so that patients requiring NSAIDs must be admitted an hour sooner than they might otherwise be.

We found a statistically significant reduction in the degree of redness on the first post-operative day in eyes pre-treated with diclofenac. This bears out our clinical impression prior to commencing this study.

Our study showed no statistically significant difference in the flare and cells in the anterior chamber post-operatively, nor in post-operative pain. Therefore the benefit of this reduction in redness is isolated and may not be clinically significant.

It could be argued that measurement with a laser cell/flare meter might have been a more sensitive and accurate way of assessing inflammation. Nevertheless, a study has shown close correlation between laser flare and cell measurements and clinical assessments following cataract surgery.[17] Our purpose was to demonstrate whether there was a clinically significant anti-inflammatory effect from NSAIDs, using a method which we use in everyday practice. For this we consider grading by slit-lamp microscopy to be adequate. Blaydes *et al.*[18] also found no significant difference (using clinical slit-lamp grading) in the day 1 post-operative anterior chamber inflammation between patients undergoing phacoemulsification cataract extraction and receiving either NSAIDs or placebo drops pre-operatively.

Our findings relate specifically to a standard surgical technique. The post-operative intraocular pressure rise was not influenced by the trial drops. This agrees with the findings of Strelow *et al.*[19] Arguably corneal incisions tend to cause less redness, inflammation and pressure. Therefore extrapolation of our results to limbal sections or phacoemulsification surgery should be done with caution.

In our attempt to exclude confounding factors, such as diseases or treatments known to affect the autonomic control of pupil function or post-operative inflammation, we were surprised to find a high exclusion rate approaching 40% of patients listed for cataract surgery. A surprising number of patients are already on oral NSAIDs. It is likely that without these exclusions the clinical significance of the differences which we have been able to demonstrate would be even smaller.

The additional cost of the routine use of NSAIDs is about £4 per patient. Whilst not high, this would add an annual cost of £1200 for a surgeon doing 300 cataract operations a year.

More recently there has been evidence that ketorolac and flurbiprofen may have a role in preventing pseudophakic cystoid macular oedema.[20,21] The efficacy of diclofenac has not been tested in this role to our knowledge by a masked prospective study. It is known that indomethacin inhibits lens epithelial cell proliferation *in vitro*,[22] though whether the use of NSAIDs affects the YAG capsulotomy rate following cataract surgery is unknown.

In conclusion, this study provides little support for the routine use of pre-operative diclofenac or flurbiprofen drops in extracapsular cataract surgery, as the effect of these drugs, though statistically significant in some parameters, was small and probably of little clinical benefit. Diclofenac was the more effective agent in maintaining mydriasis.

The intraocular forces acting on the pupil during phacoemulsification are different. Maintaining pupil size during phacoemulsification is important for sculpting of the lens nucleus and subsequent cortex aspiration. Further masked prospective studies are required to assess the usefulness of NSAIDs during this surgical procedure. There is also a need for more clinical investigations to ascertain whether these topical preparations are useful in the prevention of post-operative cystoid macular oedema and posterior capsule opacification.

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