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Double-blind controlled trial to compare anti-inflammatory effects of tolmetin 2%, prednisolone 0·5%, and placebo in post-cataract extraction eyes

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SUMMARY This paper compares the efficacy of tolmetin, prednisolone, and placebo (vehicle only) in controlling post-cataract extraction inflammation in a double-blind trial involving 120 patients. Seventeen patients were excluded from analysis. The results of the 103 patients analysed showed that 94% of the prednisolone treated group was judged to have been successfully treated as compared with 53% of the tolmetin treated group and 46% of the vehicle treated group. The differences between the prednisolone treated group and the other two groups were statistically significant ($p<0·001$). No statistical significance was found between the tolmetin and vehicle groups.

Tolmetin is a non-steroidal anti-inflammatory drug (NSAID) which acts by inhibiting prostaglandin synthesis.[1] Animal studies have shown tolmetin to reduce the level of inflammation in anterior uveitis.[2] These studies have also shown that tolmetin did not tend to raise intraocular pressure as can be the case with prolonged use of topical steroids.[3]

The use of topical steroids following cataract surgery is common practice, and it is not unusual for this treatment to be continued for several weeks, which can lead to a rise in intraocular pressure.[4,5] An agent controlling postoperative inflammation without this effect would be a useful addition to the clinician's armoury. This has led to a double-blind controlled clinical trial to compare the efficacy of tolmetin 2%, prednisolone 0·5%, and placebo (tolmetin vehicle) in the inflammation following uncomplicated intracapsular cataract extraction.

Material and methods

One hundred and twenty patients for intracapsular cataract extraction without intraocular lens implantation were selected for study. Table 1 shows the parameters recorded preoperatively and postoperatively for five days, and then at two and six weeks. More frequent examinations were performed if clinically necessary.

The following criteria excluded patients from the trial: (1) current treatment with systemic anti-inflammatory agents; (2) glaucoma, uveitis, or corneal disease; (3) operative use of α-chymotrypsin; (4) age under 60.

The study was randomised, doule-blind, and conducted at two centres concurrently. Randomisation

Table 1 *Parameters recorded*

Symptoms	
Watering	0=absent
Photophobia	1=mild
Pain	2=moderate
	3=severe
Signs	
Ciliary injection	0=absent
Aqueous cells	1=mild
Aqueous flare	2=moderate
Keratic precipitates	3=severe
Pupil diameter	0=well dilated
	1=moderately dilated
	2=poorly dilated
Intraocular pressure	mmHg

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Table 2 *Reasons for exclusion from analysis*

Reason	*Tolmetin 2%*	*Vehicle*	*Prednisolone 0·5%*
Missing records	1	0	2
Concurrent treatment with anti-inflammatory drugs	3	2	2
Could not applanate	0	0	1
Hypopyon on day 1	2	0	0
Lost to follow-up	0	3	1
Total	6	5	6

Table 3 *Summary of results*

Parameter	*Tolmetin 2%*	*Vehicle*	*Prednisolone 0·5%*
Total patients	34 (100%)	35 (100%)	35 (100%)
Successful treatment	18 (53%)	16 (46%)	32 (94%)
Treatment failures	16 (47%)	19 (54%)	2 (6%)
Episode of IOP >22 mmHg	6 (18%)	3 (9%)	7 (24%)
Discomfort	7 (21%)	4 (11%)	0 (0%)

was achieved by a blocked randomised code, balanced for treatments every 15 patients. Informed consent was obtained from all participants, who were given a trial number which allocated them to one of three groups: (1) tolmetin treated; (2) vehicle treated; (3) prednisolone treated.

Patients were examined by one of three ophthalmologists, who recorded the above parameters using a modification of the method described by Hogan.[6] In order to standardise the scoring system a pretrial assessment of five patients was performed by the three ophthalmologists. The method of cataract extraction was standardised so far as was possible to the use of a limbus-based conjunctival flap, scleral section, one peripheral iridectomy, cryoextraction, and closure with five interrupted 8/0 virgin silk sutures. All patients received treatment with the allocated trial drops and chloramphenicol drops, both four times daily. Mydriatics were used only if indicated.

The trial was concluded at six weeks. Patients who developed an adverse reaction or showed increasing inflammation during the trial period were withdrawn, and suitable alternative treatment was prescribed. Patients who still had inflammation at the end of the trial period were considered treatment failures, and suitable alternative treatment was prescribed. Successful treatment was considered to be resolution of postoperative inflammation within six weeks, with no adverse effects and requiring no additional or alternative treatment.

Results

Of the 120 patients entered into the trial 17 were excluded from analysis for various reasons (Table 2).

Of the 103 patients analysed, 34 received tolmetin, 35 received vehicle, and 34 received prednisolone. The results are summarised in Table 3. Apart from a statistically significantly lower proportion of males to females in the vehicle group, compared with the other two treatment groups, no major imbalance in age, race and side treated between treatment groups was detected (Table 4).

Eighteen out of 34 (53%) of the tolmetin treated group and 16 out of 35 (46%) of the vehicle treated group were considered to have been successfully treated as compared with 32 out of 34 (94%) patients in the prednisolone treated group. The differences between the prednisolone group and the other groups were highly significant ($p<0{\cdot}001$, χ^2 test), but no significant difference between the tolmetin group and the vehicle group was demonstrated.

Sixteen out of 34 (47%) of the tolmetin group, 19 out of 34 (54%) in the vehicle group, and two out of 34 (6%) of the prednisolone treated group were judged to be treatment failures. From the total symptom scores tolmetin (85%) and prednisolone (97%) appeared to relieve the symptoms of inflammation similarly and significantly better than vehicle (63%).

Although six out of 34 (18%) of the tolmetin group, three out of 35 (9%) of the vehicle group, and seven out of 34 (24%) of the prednisolone group had intraocular pressures over 22 mmHg during the trial, these differences were not found to be statistically significant. Seven out of 34 (21%) patients in the tolmetin group and four out of 35 (11%) in the vehicle group reported discomfort, with the drops ranging from smarting and stinging to one case of severe burning sensation. No discomfort was reported in the prednisolone group.

Discussion

The results of this study indicated that prednisolone was the most effective treatment in reducing the clinical signs of inflammation and patient symptoms. It was also the best tolerated treatment.

There was no statistically significant difference between tolmetin and its vehicle in the resolution of postoperative inflammation. This suggested that the inflammation which follows surgical trauma can be self-limiting. However, tolmetin was significantly more effective than its vehicle in relieving symptoms. It could be inferred from this that tolmetin has an anti-inflammatory effect which is limited to the external ocular structures. This would cast doubt on the ocular penetrance of the drug in man, despite

Table 4 *Analysis of treatment groups*

Parameter	*Tolmetin 2%*	*Vehicle*	*Prednisolone 0·5%*
Age			
Mean	76	75	73
Range	63–99	60–92	35–91
SD	8	7	10
Sex			
Male	13 (38%)	6 (17%)	11 (32%)
Female	21 (62%)	29 (83%)	23 (68%)
Side			
Right	17 (50%)	19 (54%)	17 (50%)
Left	17 (50%)	16 (46%)	17 (50%)

animal studies which have shown that both 2% and 5% tolmetin gain access to the anterior chamber (D Gilbert, personal communication). The potential advantage of tolmetin in being less likely to raise intraocular pressure was not confirmed in this study.

A previous study showed no statistically significant difference between tolmetin, prednisolone, and placebo in reducing inflammation in acute endogenous, non-granulomatous anterior uveitis.[7] These studies on the use of topical non-steroidal anti-inflammatory drugs cast a doubt on their efficacy in the treatment of intraocular inflammation in general. There is no doubt that, when used systemically, NSAIDs have anti-inflammatory activity, as shown by carrageenin induced inflammation.[8]

On the basis of this trial the use of topical tolmetin as a replacement for topical steroids in the treatment of intraocular inflammation cannot be recommended without further research.

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