New Trends in Ophthalmology - Vol. VIII - n. 1/93

A clinical comparison of two topical indomethacin formulations (0,1% solution versus 1% suspension) after cataract surgery

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SUMMARY: *To compare the efficacy and safety of two topical formulations of indomethacin eye drops (0,1% solution versus 1% suspension) 227 patients were included in a european multicenter randomized double masked trial in cataract surgery for a one month follow up.*

The anti-inflammatory activity was mainly evaluated by the assessement of Tyndall effect (cellular and proteinic) and secondary by a total scoring of different signs of inflammation (conjunctival hyperhemia, perikeratic circle, retrocorneal precipitates, posterior synechiae). The use of steroids was allowed in very strict conditions (severe inflammation).

The equivalence of efficacy between both treatments was shown by a similar trend in reducing the inflammatory reaction until the end point. Only 6% of the patients received steroids.

They did not appear to change intraocular pressure or provoke any unexpected adverse events.

Local tolerability of indomethacin 0,1% solution was very satisfactory and highly statistically significant compared to indomethacin 1% suspension.

KEY WORDS: Cataract surgery, topical indomethacin eyedrops, post-operative inflammation, safety.

European Study Group

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INTRODUCTION

The development of ocular inflammation is usual after cataract extraction and, depending on different parameters (surgeon experience, peroperative complications, risk factors), can be severe without any anti-inflammatory treatment.

In studies performed in animal eyes, prostaglandins are released after blood aqueous barrier (B.A.B.) breakdown and have been shown to be mediators of intraocular inflammation.

Topical non steroidal anti-inflammatory (NSAI) drugs (indomethacin, flurbiprofen, diclofenac) have been evaluated as alternatives to the use of topical steroids in treating inflammation following ocular surgery (Araie et al., 1983; Sabiston et al., 1987). Such drugs could reduce clinical inflammation without adverse effects generally associated with topical steroids (Havener, 1978) (cataract, glaucoma, delayed wound healing, proinfective effect).

Indomethacin 1% suspension, inhibits the release of prostaglandins from arachidonic acid by blocking the cyclooxygenase pathway. It also has been shown extensively to prevent the post-operative inflammation in the particular case of cystoid macular edema (Miyake et al., 1978). However some discomfort signs have been associated with this formulation. Another formulation, indomethacin 0,1% solution, has been proposed. It reduces blood aqueous barrier breakdown on the 3rd day after cataract surgery (Coulageon et al., 1991).

Netherveless it has not been compared with the suspension. Therefore it was justified to conduct a study to compare both formulations in terms of efficacy and safety in cataract surgery.

MATERIALS AND METHODS

227 patients who needed manual extra capsular cataract extraction with implantation of a posterior chamber lens without iridectomy and who had given their written informed consent were admitted in the study after agreement of the Ethical committee. They were excluded if they had glaucoma, pre-existing ocular inflammatory disease, history of uveitis, diabetic retinopathy. In case of bilateral surgery, the second eye was excluded. Patients with a known hypersensitivity to NSAI drugs or patients currently being treated with one of the preparations were also excluded.

Patients were randomly assigned to receive indomethacin 0,1% solution (Indocollyre® Lab. Chauvin, France) or indomethacin 1% suspension (Indocid® Lab. msd-Chibret, France). On the day before surgery, patients began instillations and instilled one drop four times a day; on the day of surgery, one drop was instilled two hours before surgery, one hour before, and one drop before going into the operating room. During the post-operative period, treatment was continued one drop q.i.d., during the day up to day 30. The study was conducted in a double masked fashion according to Good Clinical Practice.

The extent of conjunctival hyperemia, perikeratic circle, was graded on a scale of 0 (none) to 3 (very important); cellular Tyndall was scored from 0 (absent) to 4 (fibrinous exsudate); retrocorneal precipitates and posterior synechiae were graded respectively on a scale of 0 (absent) to 3 (more than 20) and of 0 (absent) to 4 (pupillary seclusion), Table I. Total score and Tyndall effect (cellular Tyndall and proteinic Tyndall) were assessed on days 1, 2, 6, 14 and 30.

In case of a major post-operative inflammatory reaction, the use of corticoid was allowed if a threshold evaluated by the clinical score of inflammation was reached for one symptom at least: conjunctival hyperemia (3), perikeratic circle (3), cellular Tyndall (3), proteinic Tyndall (4), retrocorneal precipitates (1) and posterior synechiae (1).

Tolerability of instillation, evaluated according to a scale of 5 grades, and intraocular pressure were recorded at each visit.

The analysis of treatment efficacy was based on the principal criterion: "Tyndall effect" and on the secondary criteria: total score, as well as each symptom. A model of non parametric analysis of variance with three factors, was used for the statistical analysis (SAS Institute): treatment factor and period factor, as well as treatment – period interaction –.

TABLE I - INFLAMMATION ASSESSMENT

This reaction was evaluated by the score of the following symptoms:

- *Conjunctival hyperemia*
  0 = absent 1 = mild 2 = pronounced 3 = very important
- *Perikeratic circle*
  0 = absent 1 = mild 2 = pronounced 3 = very important
- *Cellular Tyndall*
  0 = absent 1 = 5 to 10 cells 2 = 10 to 20 cells
  3 = more than 20 cells 4 = hypopyon
- *Proteinic Tyndall*
  0 = absent 2 = presence without exsudate
  3 = fibrinous exsudate
- *Retrocorneal precipitates*
  0 = absent 1 = 1 to 10 2 = 10 to 20 3 = more than 20
- *Posterior synechiae*
  0 = absent 1 = ≤ 1/4 of pupil 2 = 1/4 to 1/2 of pupil
  3 = 1/2 to 3/4 of pupil 4 = pupillary seclusion

RESULTS

Of the 227 patients who participated in this study, 114 received indomethacin 0,1% solution and 113 instilled indomethacin 1% suspension. The distribution of patients within the two groups was similar with regard to demographic and surgical characteristics (Table II).

TABLE II - CHARACTERISTICS

Patients included in the study n = 227

	INDO 1%	INDO 0,1%
Age (years)	72,4 ± 10,7	70,6 ± 12,5
I O P pre surgery (mmHg)	15 ± 2,9	14,5 ± 3,0
Sex	Males : 41 Females : 72	Males : 47 Females : 67
Iris color	Light : 58 Dark : 52	Light : 57 Dark : 56
Operated eye side	Right : 46 Left : 67	Right : 62 Left : 52
	p<0,05	
Duration of surgery (min)	29,4 ± 8,4	31,6 ± 8,8

The only significant difference is related to the operated side. According to the randomization of patients this feature is not of any relevance as far as efficacy is concerned.

During the surgical procedure the following events occurred and consequently patients were with drawn (Table III).

The results have shown a similar efficacy according to the treatment group cellular and proteinic Tyndall effect is reported on figures 1 and 2. Global score of inflammatory symptoms is given on figure 3. After a peak on the first postoperative day, the inflammatory reaction tends to decline during the follow-up under control by the medical therapy.

TABLE III - PEROPERATIVE COMPLICATIONS

	INDO 1%	INDO 0,1%
Capsular rupture plus vitreous loss	1	2
Capsular rupture	1	2
Zonular rupture plus vitreous loss	1	

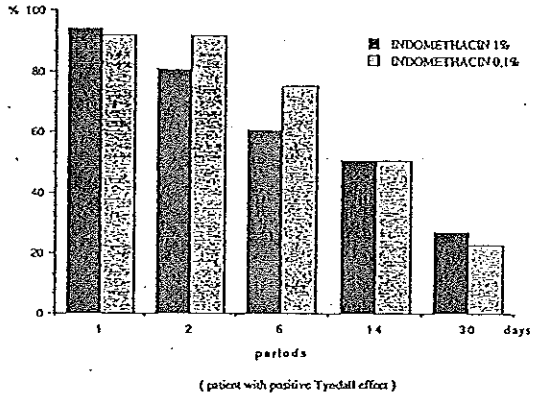

Fig. 1 - Time-course changes in cellular Tyndall effect.

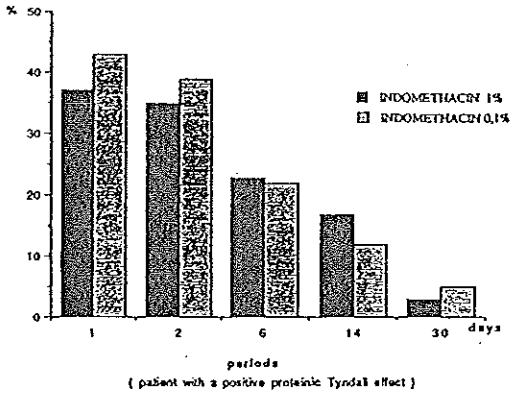

Fig. 2 - Time-course changes in proteinic Tyndall effect.

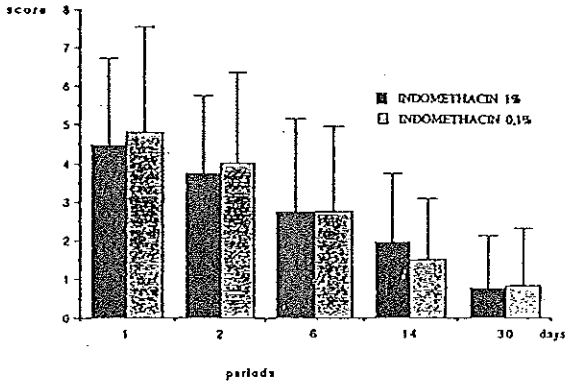

Fig. 3 - Time-course changes in inflammation score.

If the post-operative therapeutical management is considered, no difference in term of corticosteroids use is observed (5 cases for indomethacin 1% and 8 cases for indomethacin 0,1%) indicating that the inflammatory reaction was in the same range. The low rate of patients (no more than 5%) who have needed a complementary steroid agent administration has to be pointed out.

The general trend of adverse reactions is very similar in the two groups. Eight patients reported adverse events responsible for treatment discontinuation (see Table IV). Five patients were lost of follow-up (3 in group indomethacin 0,1% and 2 in group indomethacin 1%). Two patients discontinued the trial post-surgical complications (pupillary synechiae and IOL displacement).

The post-operative intraocular pressure (IOP) assessment dit not provide any evidence of increase after the second day in both groups of treatment (figure 4).

The local tolerability of 0,1% indomethacin solution eye drops was better than indomethacin 1% suspension ($p<0,0001$) as shown on figure 5.

TABLE IV - ADVERSE EVENTS WITH TREATMENT DISCONTINUATION

ADVERSE EVENTS	INDO 1%	INDO 0,1%
Endophthalmitis	2	1
Toxic syndrome		1
Ocular pain		1
Superficial punctate keratitis	3	

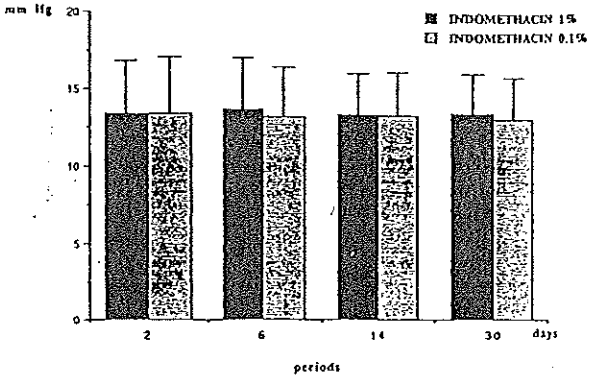

Fig. 4 - Time-course changes in IOP.

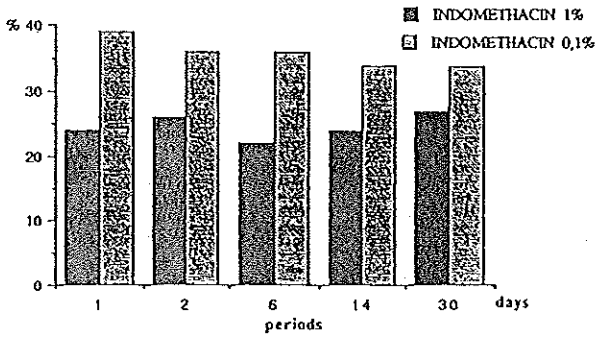

Fig. 5 - Time-course changes in the proportion of tolerability assessed as "very good".

DISCUSSION

As the ECCE is a widely used procedure and efficient if done by trained surgeons, inflammation still remains a major concern; in case of no control, it could be responsible of vision deficiency.

Corticosteroids have been extensively prescribed by different routes with a large and well known side effect profile. To avoid this latter, NSAI agents were proposed and indomethacin was the first agent developed.

Different formulations have been used. In order to check the efficacy and safety of indomethacin 0,1% solution and the possibility to use it alone, we undertook a comparison with the 1% suspension which was shown clearly superior to placebo.

In a large multicentric european study, 227 subjects were included in 8 different hospitals among 4 countries. The selected population was strictly standardized and randomized in every center.

The group comparability was satisfactory at the first day after surgery. All inflammatory signs were significantly elevated as usually observed. Both treatments showed a similar trend in reducing the inflammatory reaction until the end point. The steroid treatment was allowed in very strict conditions (severity of inflammation) as previously notified and concerned only 5% of the patients with no statistical difference between the two groups. This fact confirms the equivalence between the two eye drops. Moreover the use of a indomethacin therapy was

shown to be sufficient to control the post-operative reaction in most of the cases. In case of failure, the combination with steroids could be synergistic as previously reported by Sanders (Sanders and Kraff, 1984).

The safety profile of the two indomethacin formulations in this study was good. Both treatment did not appear to change IOP for a one month of follow-up or provoke any unexpected adverse events. No hyphema or bleeding disorders were noticed.

The main difficulty of topical administration remains the subjective symptoms of discomfort reported by the patient including pain, burning or prickling or tingling sensation after the instillation in the cul de sac. Indomethacin 0,1% solution has demonstrated in this trial a strong evidence of better local tolerability compared to indomethacin 1% suspension as well as its efficacy in controlling the post-operative inflammatory reaction.

In summary, by means of its satisfactory safety and tolerance profile and its therapeutic activity, indomethacin 0,1% solution eyedrops could be recommended as a first line therapy after cataract extraction, avoiding in that way the unnecessary steroid agents use in a large scale of patients.

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