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Combined indomethacin/gentamicin eyedrops to reduce pain after traumatic corneal abrasion

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PURPOSE. *To evaluate the analgesic action of combined indomethacin 0.1% / gentamicin eyedrops in traumatic corneal abrasion.*
METHODS. *We evaluated 123 patients presenting traumatic corneal abrasion in a multicentre, randomised, double-masked study comparing two parallel treatment groups: indomethacin / gentamicin (group 1) or gentamicin alone (group 2). Study treatments were administered four times daily for 5-6 days. Pain (visual analogue scale), associated symptoms and safety were assessed.*
RESULTS. *Starting from a comparable level, pain was reduced by 30% in group 1 and 15% in group 2, one hour after the first instillation, and by 59% and 42% respectively after the second. The global difference in pain relief from day 0 to day 4/5 was significantly better in group 1 ($p = 0.015$). Associated ophthalmic symptoms showed a greater decrease in group 1 after the first instillation ($p = 0.007$). Both treatments were well tolerated.*
CONCLUSIONS. *Combined indomethacin/gentamicin eyedrops were effective and well tolerated in reducing the pain and discomfort associated with traumatic corneal abrasion. (Eur J Ophthalmol 2001; 11: 233-9)*

KEY WORDS. *Indomethacin, Gentamicin, Eyedrops, Corneal abrasion, NSAIDs*

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INTRODUCTION

Patients with traumatic corneal abrasions usually suffer from intense pain along with other symptoms such as blepharospasm, photophobia, headache and loss of visual acuity. Although the majority of these abrasions heal within one to three days, the pain generally requires analgesic treatment. Local antibiotics are routinely given together with the analgesic to reduce the risk of infection.

An eyedrop combining the analgesic and the antibiotic in the same bottle could therefore be more convenient for the patient, and facilitate compliance with treatment.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are effective as analgesics to control ocular pain after excimer laser photorefractive keratectomy (1). They also reduce the pain associated with traumatic corneal abrasions (2-4). Eyedrops containing the NSAID indomethacin, 0.1%, help relieve pain after excimer laser photorefractive keratectomy without any deleterious effect on corneal healing (5). In patients presenting corneal edema and abrasion, treatment with indomethacin significantly reduced ocular symptoms, including pain (6-8).

Gentamicin is a broad-spectrum antibiotic frequently used as an ophthalmic solution in the treatment of eye infections, particularly infectious complications of corneal foreign bodies.

A ready-to-use ophthalmic solution, containing a fixed combination of indomethacin 0.1% and gentamicin sulphate 300 000 IU/100 mL, has recently been de-

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veloped. It has been shown to be effective and safe in preventing inflammation after cataract surgery (9). The aim of the present study was to investigate the efficacy of this combined eyedrop in controlling the pain caused by traumatic corneal abrasion.

METHODS

This was a randomized, double-masked, parallel-group study carried out from January to June '98 at six centres, in France and Portugal. The study was approved by Ethics Committees in both countries, and conducted in accordance with European Good Clinical Practice. All patients provided freely-given, written informed consent.

Patients

Out-patients of either sex, aged over 18 years, with traumatic corneal abrasion or requiring ablation of a superficial corneal foreign body and/or curettage, and in whom the pain due to the lesion was > 20 mm on a horizontal Visual Analogue Scale (VAS; 0 mm = no pain, 100 mm = unbearable pain) were eligible for the study. In cases with bilateral lesions the more painful eye was studied. The main exclusion criteria were previous intolerance to the tested products (indomethacin and gentamicin) or any NSAID or aminoside, local or systemic anti-inflammatory treatment within the five days before the initial visit, systemic analgesia (e.g. paracetamol) within the 24 hours before the initial visit, evolutive ocular pathology (such as glaucoma or uveitis), any other concomitant traumatic lesion of the eye, deep corneal lesion (beyond the anterior stroma), abrasions caused by contact lenses or chemical agents, plant foreign body still present on the cornea at the initial visit, complications of a traumatic corneal lesion requiring any treatment other than the study treatments, and monophthalmia.

Study design

Patients were randomly assigned to strictly identical treatment with either combined indomethacin 0.1%/gentamicin sulphate 300 000 IU/100 mL eyedrops (indo-genta) or with eyedrops containing gentamicin sulfate 300 mg/100 mL alone. The drops were instilled in the eye with the corneal abrasion four times daily from day 0 to day 4 or 5. Visits were scheduled on day 0 (baseline assessment at T0), day 1, and day 4 or 5. In addition, self-evaluation of pain and associated symptoms was recorded one hour after the first study treatment instillation (T1) and one hour after the second (T2).

After baseline assessment of pain on day 0, one drop of the study treatment was instilled in the treated eye. One drop of topical anesthetic (Cebesine®) and/or tropicamide was allowed if necessary for eye examination or removal of a foreign body. In this case, the study treatment was administered immediately after baseline assessment which was done 30 to 60 minutes after instillation of the anesthetic eyedrop. Then an eye patch was applied and if the pain was unbearable, the patient was allowed only to take 500 mg of oral paracetamol up to six times daily.

Efficacy

The primary efficacy variable was the level of pain, assessed using a horizontal Visual Analogue Scale (VAS) on which the patient drew a vertical line corresponding to the degree of pain between the two extremes of 0 mm (no pain) and 100 mm (unbearable pain). Evaluations were made at baseline (before study treatment started), at T1 and T2 on day 0, then on day 1, and day 4/5. The total score for the following associated symptoms was evaluated at the same times as pain: photophobia, tearing, burning, irritation (itching or stinging) and foreign body sensation. Each symptom was rated by the patient on a scale of 0 to 3 (0 = absent; I = mild; 2 = moderate; 3 = severe), giving a maximum total score of 15. Conjunctival hyperemia and ciliary injection were each assessed at the day 0, day 1, and day 4/5 visits using the same 0-3 severity scale. The surface area of the corneal abrasion was measured at each visit (length x width). All use of systemic analgesics was recorded.

Safety

Adverse events and tolerance upon instillation (assessed by the patient as 'very good', 'good', 'poor' or 'very poor') were recorded at the day 1 and day 4/5 visits. If the tolerance was 'poor' or 'very poor', the main symptom and its duration were noted.

Statistical methods

The randomization list was established using the PROC RANUNI procedure (SAS® Institute). A block size of four was used, balanced and separated for each participating centre. Statistical analyses were done using SAS® software, version 6.12 (SAS® Institute). Quantitative data were analyzed using Student's t-test, covariance analysis (ANCOVA), and analysis of variance for repeated measures. Qualitative data were analyzed using chi-square tests, Fisher's exact test, and the Cochran-Mantel-Haenszel test. The significance level was 5% in a two-tailed design. The primary efficacy variable (VAS pain assessments) was studied using ANCOVA with the following factors: treatment, centre and the baseline value.

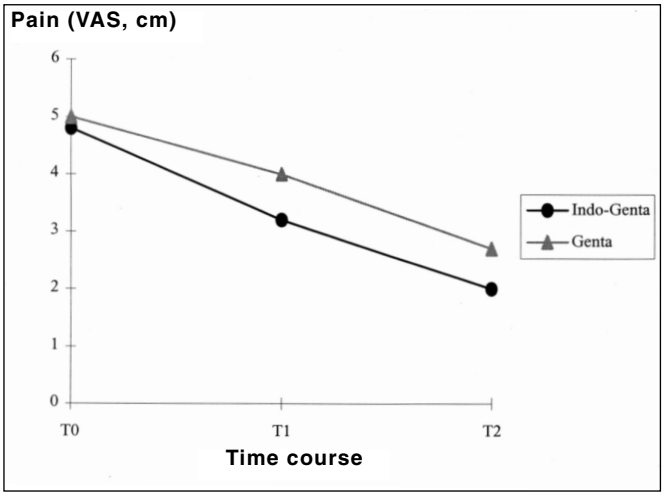

Fig. 1 - *Pain evolution (first day).*

RESULTS

A total of 126 patients were included In the study. As three were lost to follow-up after D0, 123 patients were analyzed, 62 assigned indomethacin/gentamicin eyedrops (indo-genta) and 61 gentamicin eyedrops. Some patients did not complete the study until D4/5 for reasons shown in Table I.

The main demographic and baseline characteristics of the patients are shown in Tables II and III. There were no major differences between the treatment groups, except for the distribution of iris colour (p = 0.026), the higher proportion of patients in group 2 with a deep corneal lesion reaching the anterior stroma (p = 0.05) and the higher global score for associated symptoms in the gentamicin group (p = 0.03). In addition, conjunctival hyperemia at baseline was significantly more pronounced in group 2 (p = 0.001). Regarding the primary end-point (pain), there was no significant difference between the two groups at baseline: p = 0.57. Anesthetic eyedrops (Cebesine®) were required by 67.5% of patients, and tropicamide for 4.9% for the eye examination at baseline. In most cases, the abrasion was unilateral. For the two patients with a bilateral lesion (phototraumatism), the more painful eye was selected for analysis.

TABLE I - EARLY TERMINATION (before day 5)

	Indo-genta (no. = 11)	Gentamicin (no. = 3)
Lost to follow-up	4	2
Rapid healing	3	-
Adverse event	1	1
Withdrawal of consent	2	-
Transport problems	1	-

In both treatment groups, the level of pain decreased rapidly over the first 24 hours, as expected in this clinical situation, and more slowly over the next few days (Tab. IV). Analysis of the time course of pain improvement (Fig. 1) over the entire treatment period from day 0 to day 4/5, using ANOVA for repeated measures adjusted for baseline values, showed a significant treatment effect (p = 0.015). The combined scores for photophobia, tearing, burning, irritation (itching or stinging) and foreign body sensation improved in both groups (Tab. V).

ANOVA adjusted for the baseline values at each assessment time showed a significant treatment effect at T1: one hour after the first instillation the improvement was greater in the indo-genta group than in the gentamicin group (p = 0.007). Nevertheless the score for symptoms at baseline was significantly lower in the indo-genta group (p = 0.03).

Three patients in the gentamicin group required additional or prolonged treatment due to conjunctival redness: tropicamide in one patient on Day 0 for severe hyperemia, and fluorometholone or NSAID in

two patients for residual hyperemia on day 4/5. There was no difference between the two groups in the severity of ciliary injection at any time point.

The mean surface area of the abrasion decreased in both groups with no significant difference between treatments at any time. In 86% of patients, the lesion had completely healed by day 4/5 (incomplete healing in 6 cases in the indo-genta group and 9 in the genta group).

An oral analgesic for ocular pain (paracetamol) was taken by four patients in each group in the 24 hours after starting the study treatment. In one of these patients, in the indogenta group, paracetamol was combined with codeine.

TABLE II - DEMOGRAPHIC CHARACTERISTICS

Parameter		**Indo-genta (no. = 62)**	**Gentamicin (no. = 61)**
Age (years)	Mean + SD	39.0 ± 17.0 (n = 60)	37.1 ± 14.8 (n = 59)
Sex	Male	50 (80.7%)	51 (83.6%)
	Female	12 (19.4%)	10 (16.4%)
Iris colour	Blue/green/grey	28 (45.2%)	21 (34.4%)
	Hazel	7 (11.3%)	19 (31.2%)
	Brown	27 (43.6%)	21 (34.4%)

TABLE III - BASELINE CHARACTERISTICS

Parameter		**Indo-genta (no. = 62)**	**Gentamicin (no. = 61)**
Origin of abrasion	Foreign body:		
	- metallic without rust	7 (11.3%)	6 (9.8%)
	- metallic with rust	20 (32.3%)	21 (34.4%)
	- mineral	6 (9.7%)	3 (4.9%)
	- other	3 (4.8%)	2 (3.3%)
	Direct traumatism	25 (40.3%)	28 (45.9%)
	Phototraumatism (electric arc)	1 (1.6%)	1 (1.6%)
Time of onset before presentation (minutes)	Mean ± SD	1534.8 ± 1757.7	1405.8 ± 1282.1 (n = 60)
Surface area of the abrasion (mm^2)	Mean ± SD	5.2 ± 13.3	4.3 ± 6.2 (n = 59)
Depth of abrasion	Epithelial	47 (75.8%)	36 (59.0%)
	Anterior stromal	15 (24.2%)	25 (41.0%)
Curettage or reaming	Yes	28 (45.2%)	29 (47.5%)
Lesion cleansing	Curettage	21 (33.9%)	19 (31.1%)
	Reaming	3 (4.8%)	9 (14.8%)
	Both	4 (6.5%)	1 (1.6%)
VAS of pain intensity	Mean ± SD	48.2 ± 19.8	50.2 ± 20.3
Global score of associated symptoms (0-15 scale)	Mean ± SD	7.9 ± 3.5	9.3 ± 3.2

TABLE IV - VAS OF PAIN

Time	Indo-genta (no. = 62)	Gentamicin (no. = 61)
D0		
n	62	61
Mean ± SD	48.2 ± 19.8	50.2 ± 20.3
Adjusted mean ± Standard error	--	--
T1		
n	62	59
Mean ± SD	32.5 ± 19.1	40.4 ± 21.5
Adjusted mean ± Standard error	29.1 ± 2.6	36.6 ± 2.6
T2		
n	61	59
Mean ± SD	20.2 ± 18.5	27.4 ± 19.9
Adjusted mean ± Standard error	15.4 ± 2.5	24.6 ± 2.5
D1		
n	59	61
Mean ± SD	8.3 ± 12.2	v12.5 ± 17.9
Adjusted mean ± Standard error	7.3 ± 1.8	11.0 ± 1.8
D4		
n	53	59
Mean ± SD	0.3 ± 1.4	1.5 ± 4.1
Adjusted mean ± Standard error	0.5 ± 0.5	1.5 ± 0.5

TABLE V - TOTAL SCORE FOR ASSOCIATED SYMPTOMS

Time	Indo-genta (no. = 62)	Gentamicin (no. = 61)
D0		
n	62	61
Mean ± SD	7.9 ± 3.5	9.2 ± 3.2
Adjusted mean ± Standard error	--	--
T1		
n	60	60
Mean ± SD	5.6 ± 3.1	7.5 ± 3.5
Adjusted mean ± Standard error	6.0 ± 0.4	7.6 ± 0.5
T2		
n	60	58
Mean ± SD	3.8 ± 2.6	5.1 ± 3.4
Adjusted mean ± Standard error	4.1 ± 0.4	5.1 ± 0.4
D1		
n	58	60
Mean ± SD	1.8 ± 2.0	2.7 ± 3.0
Adjusted mean ± Standard error	2.1 ± 0.4	2.8 ± 0.4
D4		
n	52	59
Mean ± SD	0.4 ± 0.8	0.6 ± 1.4
Adjusted mean ± Standard error	0.5 ± 0.2	0.6 ± 0.2

Safety

No serious adverse events occurred. Six patients (9%) experienced a total of eight adverse events in the indo-genta group and seven patients (11%) experienced nine adverse events in the gentamicin group. Of the 17 adverse events, 13 involved the eye and adnexa, and all were assessed as unrelated to the study treatment. Four adverse events led to treatment discontinuation, three in the indo-genta group (photophobia and visual disorders on day 1; conjunctival hyperemia and tearing on day 5; and urticaria on day 3) and one in the gentamicin group (corneal abscess on day 1). The urticaria affected the forearms, chest and neck of the patient, but not the eyelids, and a relationship to the study treatment was therefore considered to be excluded. The corneal abscess was probably due to an infection linked to the mineral foreign body in this patient. All signs and symptoms resolved with ciprofloxacin.

There was no significant difference between the treatment groups in the assessment of tolerance upon instillation (Tab. VI). One case of discomfort and photophobia in the indo-genta group resulted in treatment discontinuation, and was therefore classified as an adverse event, as described above. All other reported symptoms were transitory burning sensations which lasted between 20 seconds and two minutes in the indo-genta group.

TABLE VI - TOLERANCE UPON INSTILLATION

	Indo-genta (no. = 62)	Gentamicin (no. = 61)
D1		
n	59	61
Very good	27 (45.8%)	30 (49.2%)
Good	29 (49.2%)	30 (49.2%)
Poor	3 (5 I %)	1 (1.6%)
Very poor	--	--
D4		
n	53	58
Very good	36 (67.9%)	43 (74.1%)
Good	14 (26.4%)	14 (24.1%)
Poor	3 (5.7%)	1 (1.7%)
Very poor	--	--

DISCUSSION

Corneal abrasions are a frequent pathology encountered in the casualty department or in private practice. Generally, this condition resolves without complication but pain is the major concern. Usual treatment includes a topical antibiotic and analgesic, often oral medications. Recently, the use of NSAID ophthalmic solutions has been advocated. Topical anaesthetics are used for foreign body removal but are not continued because of their toxicity.

In our study the patient assessed the intensity of pain using a VAS. The sensitivity and accuracy of this method of evaluation has been demonstrated (10). We prefer to avoid categorical values so as not to influence the patient. As far as pain is concerned average values were less severe than after photorefractive keratectomy using the excimer laser, which is more painful. The relief of pain is probably partly related to the healing process and can obviously be influenced by subjective parameters; in addition topical gentamicin may have a kind of placebo effect on the inflammatory response because it can wash away breakdown products of inflammatory cells.

These results, indicating a modest but real role of indomethacin, are in accordance with previous reports (8) comparing two groups of patients with corneal abrasions, but not in a complete double-masked fashion: one group had two eyedrops (netilmicin and indomethacin) and the second group had only one (netilmicin). Similarly, pain reduction was recorded in the two groups at T1 and T2 during the first day, but the relief was significantly more marked in the group receiving indomethacin. In our study the score of associated symptoms followed the same trend as pain with better improvement in the indo-genta group.

The local analgesic effects of NSAIDs are not completely understood. Part of the analgesia is secondary to an inflammatory response with the inhibition of prostaglandin synthesis, but there is also an effect independent from the anti-inflammatory properties, such as a reduction in the responsiveness of the corneal epithelium (8). Aragona et al (11) showed that diclofenac has specific hyposensitizing effects on the cornea, conversely to indomethacin 0.1% and other NSAIDs. The corneal hypoesthesia induced by diclofenac may, however, be responsible for a delayed healing process which is not observed with indomethacin (5).

The use of contact lenses in painful conditions of the cornea has been advocated after either photorefractive keratectomy or corneal abrasions (12). We did not use this strategy in order to simplify the management of recruited patients.

In conclusion we observed rapid recovery of the corneal surface in both groups and better pain reduction in the indo-genta group.

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