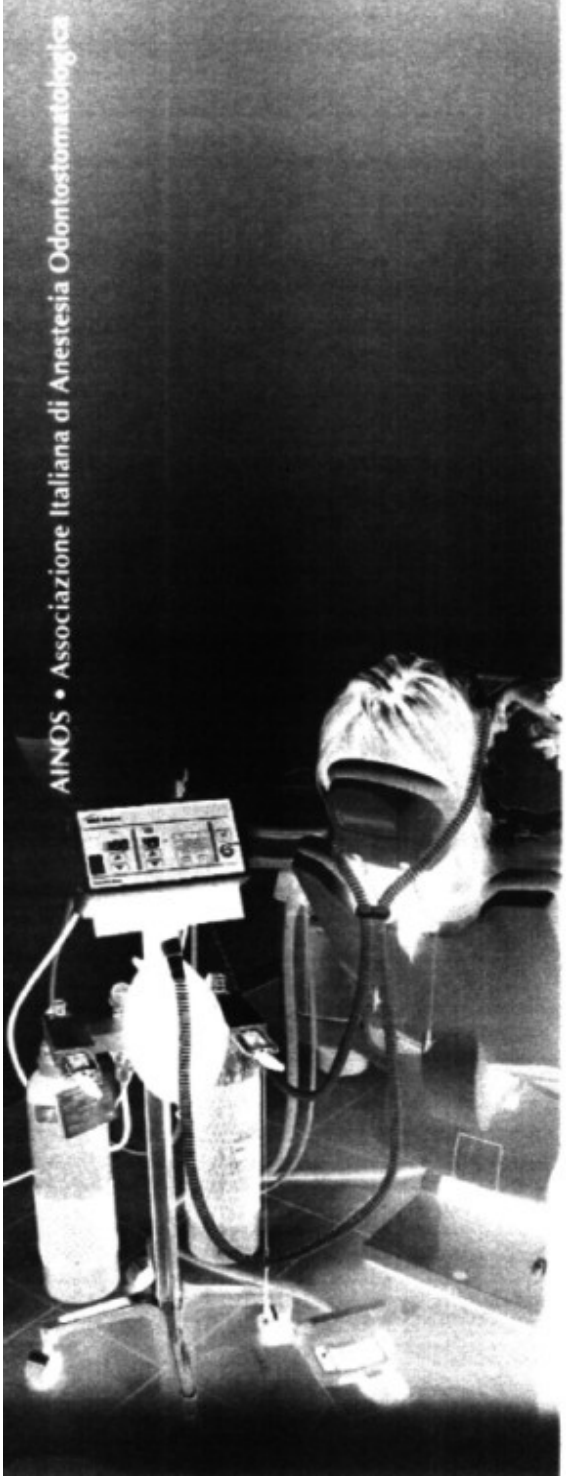

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Summary
This study included 46 patients undergoing implantology after anxiolysis, subdivided in three groups by randomization. The first group (n=16) had taken 8 mg, the second group (n=15) and the third group (n=15) 16 mg of lornoxicam one hour before intervention. The postoperative pain was treated by administering 16 and 6 mg of lornoxicam at the first appearance of pain in the first and second group respectively and 6 mg of lornoxicam at the end of the intervention in the third group. The operative wound was infiltrated with 0.5% bupivacaine and 1:200.000 epinephrine in all patients at the end of the intervention. The results show that the administration of 16 mg lornoxicam one hour before intervention and 8 mg lornoxicam at the end of intervention decrease on the average incidence and intensity of postoperative pain and increase the time of reappearance of sensitivity and disappearance of paresthesias in the operative area compared to the other groups. The analgesic treatment with lornoxicam did not induce different side-effects in the groups. In all groups drowsiness was equally present on the day of intervention.

Key words: Non-steroid analgesic drugs: lornoxicam; dental pain

Introduction
Lornoxicam is a non-steroid analgesic drug (NSAID) of the oxicam group, endowed with potent anti-inflammatory and analgesic effects. In preceding studies, doses corresponding to 4-8 mg, after extraction of the third molar were shown to correspond to 650 mg of acetylsalicylic acid (1). Lornoxicam is completely metabolized and its pharmacokinetic profile is not significantly modified in elderly subjects (2) with irrelevant irritating effects on gastric mucosa even after prolonged treatment. In the present study we considered the analgesic and anti-inflammatory effect of lornoxicam, whose characteristics are suited to short term treatments with single doses sufficient to prevent the postoperative dental pain which is stronger in the first 12 hours after intervention (3). We also wanted to inquire whether lornoxicam could be successfully used in the technique called "pre-emptive analgesia" which consists of the preoperative administration of the drug in order to prevent the effects of the operative trauma on the production of the pro-inflammatory prostanoids.

Table 1. Anthropological, physical characteristics and anxiety levels in the three groups of patients. Means±S.D. (** p<0.01; comparison between third and second group).

	Group I	Group II	Group III
N	16	15	15
Age (years)	52.0 ± 6.2	49.4 ± 8.4	50.9 ± 8.9
Sex (M/F)	4/12	4/11	1/15
Weight (Kg)	67.6 ± 12.7	70.6 ± 9.6	60.3 ± 7.9**
Height (cm)	166.1 ± 8.1	170.7 ± 10.0	163.3 ± 5.7
ASA I/II	12/4	13/2	9/6
Anxiety (cm)	5.2 ± 2.3	7.3 ± 6.8	6.1 ± 1.8
C.F. (beats/min)	75.3 ± 7.5	77.9 ± 7.6	78.9 ± 11.4
MAP (mm Hg)	95.5 ± 11.0	96.2 ± 9.6	87.8 ± 12.2
RPP (c.f x s.a.p.)	9611 ± 1630	9766 ± 1658	9368 ± 1451

Table 2. Characteristics of the intervention, of the anaesthesia and related pathologies in the three groups. Means±S.D.

	Group I	Group II	Group III
N	16	15	15
Duration (min)	66.8±22.9	58.6±17.4	65.7±21.7
Local anaesthetics			
Mepivacaine 2% +	16	15	15
epinephrine 1.100.000			
Bupivacaine 0.5% +	16	15	15
epinephrine 1.200.000			
Type of intervention			
Implantology	12	12	10
Rise of maxillar sinus	3	3	3
Cyst removal	1	–	1
Apicectomy	–	–	1
Pathologies			
Hypertension	2	–	3
Rheumatic disease	1	–	2
Endocrine diseases	–	1	3

Materials and methods

Patients. The study was made on 46 patients undergoing implantology in the Dental Clinic, University of Padua, subdivided by preordinate randomization in three groups receiving different treatment of the postoperative pain with differently combined doses of lornoxicam (4).

Each patient with a known age, sex, height, ASA, basic cardiovascular parameters and anxiety evaluated by a visual analogue of 10 cm (Visual Analogue Scale=VAS) was treated with local anaesthetics for the induction of anaesthesia and long term local anaesthetics at the end of an intervention of known duration.

Preoperative visit. The patients received, 10 days before intervention, a preoperative visit in which they were informed on the type of perioperative analgesic treatment and, after their consent, were also informed on the technique of intraoperative anxiolysis and on the technique of local analgesia to be used. Patients sensitive to oxicam drugs (5), with hemorrhagic gastrointestinal pathologies (6), with hematic disorders, coagulation diseases and hemorrhagic diatesis (7), with serious hepato-renal illness (8), women with ascertained or presumed pregnancy who got a pregnancy test immediately before intervention (9), patients over 65 and those with allergies of the tracheo-bronchial tract (10), alcoholics or drug-addicted patients (11), those who presumably could not complete the study as from the protocol (12) and patients under corticosteroid treatment for more than 20 days were excluded from the study. At the end of the preoperative visit three tablets of 8 mg lornoxicam were given to the patients of the first group (n=16) instructing them to take one tablet one hour before the beginning of the intervention and two tablets (16 mg) in the postoperative period at the first appearance of pain. Patients of the second group (n=15) were invited to take two lornoxicam tablets one hour before intervention and one tablet in the postoperative period at the first appearance of pain. Patients of the third group (n=15) were invited to take two tablets one hour before intervention. The third tablet had to be given at the end of the intervention by the dentist who performed the anxiolysis. The tablets had to be taken with a sufficient amount of water before ingestion of any food. The patient was invited to take, together with the tablets taken before intervention, a tablet of 200 mcg misoprostol, a synthetic analogue of PGE_1 capable to prevent NSAID-induced gastro-duodenal lesions. Patients of the third group were informed that on the first appearance of pain they had to take 1000 mg paracetamol *per os*.

All patients were informed that on the evening of the day of intervention and on the successive day they would have been contacted on the phone by a dentist to know about the postoperative pain indicated by the patient on the questionnaire. The exact time of the end of intervention was recorded for each patient.

The questionnaire. To each patient at the end of the preoperative visit a questionnaire was given consisting of 13 questions.

*Table 3. Effects of loco-regional anesthesia and appearance of the first pain symptoms in the three groups. Means±S.D. (§§ p<0.01; comparison between first and third group; ** p<0.01; comparison between second and third group).*

	Group I	Group II	Group III
N	16	15	15
Sensitivity appearance (min)	205.6 ± 137.4	258.6 ± 175.1	372.0 ± 212.8 §§,**
Paresthesias disappearance (min)	209.3 ± 137.0	252.6 ± 170.5	418.0 ± 224.4 §§,**
Incidence of postoperative pain (YES/NO)	15/1	11/4	4/11§§,**
Appearance of postoperative pain (min)	174.3 ± 81.2	342.3 ± 272.3	208.7 ± 156.3

The first four questions concerned the sensitivity recovery times, the swelling feeling and post-anaesthesia paresthesias disappearance and the time of the first pain symptom after the end of the analgesic effect of the local anaesthetic injected at the end of the intervention. The patient was invited to cross the box corresponding to the time of disappearance or appearance of the symptoms. For that, a table of 24 horizontal boxes numbered in progression from the first up to the 24th hour of the intervention day was prepared. The 5th question was the time when the patient took the first one or two tablets of lornoxicam or paracetamol, according to the group. The 6th question was on the disappearance or not of the pain after drug assumption, inviting the patient to answer yes or no. The 7th and 8th question concerned pain intensity on a 10 score numerical scale one or two hours after taking the tablets. The 9th question asked to each patient whether after assumption of the tablet or tablets the pain reappeared, inviting a yes or no answer. The 10th question asked to the patient whether the pain reappeared on the first or the second day after intervention. The last three questions were on the side-effects and comments of the received analgesic treatment. The 11th question was on the time the patient went to sleep after the end of the intervention. The 12th question asked whether the patient expected more or less pain than that experienced. The 13th question asked on the following symptoms: nausea and/or vomiting, abdominal pain, headache, general discomfort, drowsiness and bleeding.

The study was carried out according to the Helsinki Declaration II and modifications and the guidelines of European Community on the clinical management (13).

Statistical elaboration. The comparison of the data was made with the analysis of the variance. When necessary the χ^2 corrected according to Yates was used. In all cases the minimum level of probability chosen was $p<0.05$.

Results

Table 1 summarizes the anthropological and physical characteristics together with the anxiety levels of the subjects. No difference was observed among the groups if the mean values of weight are excluded being lower in the patients of the third group compared to those of the second group ($F=10.1$; $p<0.01$). Table 2 shows the characteristics and type of intervention and the local anaesthetic used. No difference among the experimental groups was observed.

Effects of anaesthesia and first symptom of pain. Table 3 shows the times of the effects of loco-regional anaesthesia, of the appearance of the first pain symptom and of postoperative pain incidence. The times of appearance of sensitivity progressively increase from the first to the third group

*Table 4. Intensity of the first postoperative pain after assumption of the pain killer. Means±S.D. (§§ p<0.01; comparison between first and third group; **p<0.01; comparison between second and third group).*

	Group I	Group II	Group III
N	16	15	15
Intensity of the first pain symptom (cm)	3.4 ± 2.3	2.4 ± 2.4	0.5 ± 0.9§§,**
First dose of pain killer (min)	214.3 ± 115.0	435.9 ± 283.7	253.7 ± 130.9
Pain intensity after pain killer (cm)			
After 60 min	0.5 ± 0.9	0.3 ± 0.9	0.4 ± 1.0
After 120 min	0.8 ± 1.2	0.1 ± 0.4	0.3 ± 0.7

Table 5. Incidence of pain killer assumption, incidence of patients experiencing pain after pain killer assumption in the postoperative period. Means±S.D.

	Group I	Group II	Group III
N	16	15	15
Pain killer assumption	15	10	6
Reappearance of pain	9	5	5
The day of the intervention	2	1	1
The day after intervention	7	4	4
Time of pain reappearance after assumption of the pain killer (min)	588.0 ± 680.1	654.0 ± 222.4	798.0 ± 408.5

being longer on average only in the patients of the third group compared to those of the first group ($F=6.3$; $p<0.05$). On the contrary, the times of disappearance of paresthesia due to local anesthetic in the intervention area were longer in the patients of third group compared to those of first group ($F=8.1$; $p<0.01$) and second group ($F=7.6$; $p<0.01$). The postoperative pain incidence was 26.6% in the third group compared to 73.3% in the second group ($\chi^2=8.1$; $p<0.01$). The times of appearance of the first pain symptom varied from 40 to 690 min and on the average were overlapping in the three groups.

Intensity of the first postoperative pain. The intensity of the experienced pain was lower in the third group both compared to the first ($F=17.8$; $p<0.01$) and to the second ($F=7.6$; $p<0.01$) (table 4).

Effects of assumption of pain killing drugs (table 4). The assumption of the first postoperative dose of analgesic occurred after different time intervals, overlapping on the average in the three groups (from 9 to 1065 min). The incidence of analgesic assumption was lower in the third group (n=4) both compared with the first group (n=15) ($\chi^2=7.3$; $p<0.01$) and the second group (n=11) ($\chi^2=6.5$; $p<0.02$). The assumption of the pain killer caused the disappearance of the pain in all patients of the second group (n=11) and the third group (n=4), while in the first group the disappearance occurred in 14 of the 15 patients. The postoperative pain intensity experienced by patients in the first and second hour after drug assumption was identical in the three groups and on the average >1.0 cm VAS. No statistically significant difference was observed between pain intensity of the third group patients compared to those of second and first group, both in the first and in the second hour after analgesic drug assumption (table. 4).

The postoperative pain after assumption of the pain killer reappeared in 56.2% of the first group patients and in 33.3% of the patients of the second and the third group. The higher incidence of pain reappearance occurred in the second day after the intervention. The mean times of appearance of postoperative pain are shown in table 5. No statistically significant difference was observed between the incidences and the times shown in table 5.

The times of appearance of drowsiness which induced the need of going to sleep are shown in table 6. No statistically significant difference was observed between the times of the third group and those of the first and second group after the end of intervention. The patients claiming to feel a higher pain intensity were equally represented within the three groups (first group 68.7%, sec-

Table 6. Impressions and side effects in the three groups. Means±S.D.

	Group I	Group II	Group III
N	16	15	15
Prediction of higher postoperative pain	11	13	11
Sleeping time after intervention (min)	419.3±233.0	467.3±221.8	342.0±258.4
Side effects			
Nausea and/or vomiting	-	-	-
Abdominal pain	-	-	-
Headache	3	3	4
Discomfort	3	1	3
Drowsiness	11	5	11
Bleeding	3	4	7

ond group 86.6%, third group 73.3%). Finally the incidence of the side effects experienced by the patients in the first two days of the postoperative period was almost equally represented in the two groups of patients (table 6).

Discussion

The traditional approach to the treatment of postoperative dental pain implies its late beginning, at different times from the intervention and on the request of the patient. The present trend in such a treatment includes the use of analgesics in the preoperative phase in order to prevent the sensitization due to the surgical stimulation (14). Preceding studies have shown that piroxicam might be used preoperatively to decrease the postoperative pain after extraction of the lower third molar under general anaesthesia (15; 16) and in the treatment of intermediate intensity pain due to procedures such as implantology and parodontal surgery (17, 18). The recent introduction of a new oxicam derivative, the lornoxicam, with pharmacological effectiveness ten times higher than that of tenoxicam and piroxicam (19) prompted several dentists to use this drug in the treatment of the acute postoperative pain after extraction of included lower third molars in loco-regional (20) and general anaesthesia (1).

The application of analgesia before a rise of the pain symptom called "pre-emptive analgesia" appears to decrease or totally abolish both the postoperative pain appearance and the need to treat pharmacologically the pain itself. If the administered drug is a NSAID it will prevent hyperalgesia due to release of chemical mediators of inflammation through a COX-2 inhibition which is responsible for a decreased prostaglandin, prostacyclin, tromboxan and leucotrien production, i.e. the production of the main responsibles for inflammation and postoperative pain (21). In our study, we associated the preventive lornoxicam-induced analgesia with anxiolysis and injection of long term local anesthetics at the end of the intervention since the combination of those treatments requires a lower amount of postoperative analgesics even compared to patients undergoing dental surgery under general anaesthesia (22).

The results show that by concentrating the lornoxicam doses in the immediate postoperative period, that is administering a dose of 16 mg lornoxicam 60 min before intervention, and a dose of 8 mg immediately after intervention the best results of postoperative pain reduction are obtained, confirming the value of pre-emptive analgesia as a technique for preventing postoperative pain. Such a combination decreases the incidence and intensity of the postoperative pain which is 5-7 times lower than that found in the other groups of patients of this study. The analgesic effect is dose-dependent but not time-dependent. The appearance of the first pain symptoms is in fact observed, independently of the employed doses, when the effect of the long term local anaesthetic injected at the end of the intervention in the operative wound area had disappeared. For those reasons our evaluations are deeply different from those of other authors who, using lornoxicam at the time of appearance of the first pain symptoms, could follow the effects as a function of time from the immediate postoperative phase (23). Our study is clinically relevant because it shows that it is possible to almost completely eradicate the postoperative pain after implantology with the preventive use of lornoxicam at the pre- and immediately postoperative doses we proposed. The employed technique does not interfere with the analgesic drugs consumption in the day after the intervention. Lornoxicam has in fact a half-life of 3.5-4.5 hours (24) and its analgesic effect hence persists only in the day of drug assumption.

Our studies showed that in the hours after assumption of a dose of lornoxicam for analgesia in the postoperative period the patient experiences a fast decrease of pain intensity due both to the high speed of absorption of the drug, corresponding to a t_{max} of 0.33-0.75 hours, and to the elevated bioavailability of 105% (25).

To conclude we believe that the preoperative use of lornoxicam may limit the inflammatory process of the intervention through the inhibition of the proinflammatory prostanoids. This is not however the only antinociceptive mechanism of action of lornoxicam which also increases the blood levels of dynorphine and ß-endorphin contributing to potentiate the analgesic effects of the drug (26). It is significant in this regard the observed prolongation of the analgesic effect of long term local anaesthetics and in the swelling feeling or paresthesia with the employed doses of lornoxicam. Since such prolongations were proportional to the employed doses of lornoxicam we may hypothesize an integration between effects of the local anaesthetics used and the increased synthesis of central analgesic neuropeptides due to lornoxicam.

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