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LETTER TO THE EDITOR

EFFECT OF THERMOSETTING GEL WITH DOXYCYCLINE HYCLATE 3% + KETOROLAC TROMETHAMINE 0.5% ON POSTOPERATIVE DISCOMFORT AFTER THIRD MOLAR SURGERY: A PROSPECTIVE RANDOMIZED STUDY

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This study compared the analgesic and anti-inflammatory efficacy of intra-alveolar administration of a thermosetting gel containing Doxycycline Hyclate 3% + Ketorolac Tromethamine 0.5% (Tg-DHKT) (Thermosetting gel, Monteresearch, Bollate, Italy) on patient discomfort after third molar surgery. This study was a single-blind, randomized clinical trial, including two study groups of 39 and 41 patients each, who required surgical removal of a single mandibular impacted third molar. After the extraction the test group received an intra-alveolar injection with Tg-DHKT and the second group a thermosetting gel containing only Doxycycline Hyclate 3% (Tg-DH). Each patient's symptoms (pain, swelling, reddening, bleeding and body temperature) was assessed with a follow-up questionnaire (PoSSe scale). Nimesulide 100 mg, a painkiller, every 8 hours was prescribed to the Control and Test groups if necessary (maximum 3 doses); if they needed to assume it they were asked to mark it on the questionnaire. Results showed that on the second day after surgery pain, oedema and reddening decreased faster in the Control group (Tg-DH). There was no difference between the two groups when postoperative bleeding was evaluated. In both groups bleeding decreased in the same way, probably due to the mechanical characteristics of the gel itself. 46% of patients of the Test group did not require to take any painkiller at home. Our data demonstrate that the use of Tg-DHKT is less effective in the prevention of postoperative symptoms after third molar extraction compared to Tg-DH. However, almost half of patients in the Test group did not need to take more pain medication at home, suggesting that a single postoperative local administration of Tg-DHKT is a safe and effective concept for controlling pain, oedema and inflammation after third molar extraction.

The surgical removal of impacted third molars is one of the most frequently performed procedures in oral surgery and afterwards complications such as post-operative pain, swelling and trismus may occur, and in some cases fever, during the first few postoperative days. As prostaglandins are presumed to be a primary mediator of acute postsurgical inflammatory changes, these patients, are therefore ideal clinical subjects for studying the effect of anti-inflammatory agents on sequelae of teeth extractions.

Key words: third molar surgery, doxycycline, thermosetting gel, post-operative discomfort

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These postoperative sequelae cause stress to the patient and affect the patient's quality of life after surgery (1-3). Prediction of impaction of third molars in patients could be of great help in the planning of orthodontic treatment, surgery, or prostheses (4-8).

There are different strategies for postoperative pain management, including the use of local anaesthesia or the administration of diverse types of analgesics, mainly non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (9).

The combination of different analgesics, or 'balanced analgesia', can increase the safety and duration of pharmacological analgesia. The rationale for balanced analgesia is to provide sufficient pain relief through additive or synergistic effects using different analgesics, with a concomitant reduction of side effects due to the resulting lower doses of individual drugs.

Orally administered analgesics are the primary drug therapy used to manage acute postoperative pain in dentistry. Because monotherapy often provides inadequate pain relief, investigators have advocated combinations of two or more analgesic drugs.

Due to the high index of postoperative complications and discomfort after third molar surgeries, many dentists routinely prescribe antibiotics and corticosteroids. The aim of the antibiotic prophylaxis is to protect the patient from the consequences of transient bacteraemia and to reduce the incidence of postoperative complications such as alveolar osteitis or alveolar infection.

While there is some evidence that antibiotics can reduce the incidence of postoperative complications (10), there is equal evidence to the contrary (11). Facing the controversy, some authors also ponder that antibiotics may be efficacious in reducing the incidence of complications following third molar extraction but should not be prescribed in all cases. Guidelines have been proposed by various international organizations, although to date there is still no consensus.

In clinical practice the choice of antibiotic prophylaxis, in the absence of an antibiogram, is directed towards the administration of agents with a broad spectrum of action, active even against antibiotic-resistant strains (12-15).

Moreover, different methodological approaches have been described: antibiotics can be administered systemically or topically with different posologies. Furthermore, oral administration, which is the most common, has several side effects such as hypersensitivity reactions, development or presence of bacterial resistance, gastrointestinal intolerance.

Topical administration of the antibiotic can reduce these risks and, at the same time, provide pharmacologically active concentrations in the areas where the therapeutic action is required. The therapeutic effect in such cases is assured due to the pharmaceutical formulations that give a prolonged and controlled release of active substances at the application site.

Prolonged drug release offers numerous benefits: high efficiency, control of the concentration of active ingredient at the application site, thus reducing adverse reactions (16-17).

Our previous study (18) highlights the advantages of the use of a new film-forming antibiotic solution (Tg-DH) in clinical practice, which has shown to be useful for the prophylaxis and reduction of postsurgical local complications.

The aim of the present study is to compare the Tg-DH added with an anti-inflammatory drug (Ketorolac Tromethamine) and to investigate the possibility of using a topical dose of anti-inflammatory drug in order to substitute the post-operative oral drugs after third molar surgery.

MATERIALS AND METHODS

Eighty non-smoker or light smoker consecutive patients, of both sexes (37 males and 43 females), aged between 16 and 33 years, requiring surgical removal of mandibular impacted third molars under local anaesthesia were included in this randomized study. The trial was conducted in accordance with the declaration of Helsinki, and the study design was approved by the local ethics committee.

The study protocol was explained to all patients in detail and written informed consent was obtained from all patients or patient's parent or guardian.

Inclusion criteria were as follows: patients were free of caries, extensive periodontal disease, pain, or other inflammatory symptoms at the time of operation. Exclusion criteria were hepatic or renal disease, blood dyscrasias, gastric ulcer, heart disease, known hypersensitivities, allergies or reactions to any of the study medications, pregnancy and lactation, incapacity to complete adequate neurosensory examination, patients

with history of head injury, mentally retarded patients with a history of neurological disorders, heavy smokers (>20 cigarettes/day for a year before enrolment). In addition, patients who had taken any drug within the two weeks prior to surgery were

excluded from the study. All the participants were asked to give an account of their smoking habits, and light smokers (<5 cigarettes/day) were included. Cases in which surgery lasted more than 60 minutes, or if surgery was affected by any complication, and cases in which concomitant use of non-trial drugs were used during the observation period were excluded.

At the initial examination a single blinded clinical examiner recorded the information regarding administration of the test medication. The surgeon had never operated on the patients involved in the preoperative or postoperative assessment.

Surgery

To minimise differences due to operator variability, the same oral surgeon performed all of the surgical extractions. With the exception of the use of topical antibiotics, each patient had similar operative procedures, in the same operative room and under similar conditions. Surgery of the impacted third molars was carried out under local anaesthesia using 2% mepivacaine with epinephrine 1:100.000 without a sedative premedication.

A single dose of dexamethasone 4 mg (Soldesam; Lab Farmacologico Milan Srl, Milan, Italy) was then injected into the buccal vestibule tissues.

Access to the third molar was achieved from the buccal aspect, and bone removal was carried out with a round bur in a straight handpiece under continuous irrigation with a sterile saline solution. If necessary, sectioning of crown and roots was performed with a fissure bur. After tooth extraction, the alveolus was inspected and curetted to remove granulation tissue. The alveoli of the test group were filled with a needle bevel syringe with 1 mL Tg-DHKT, while the alveoli of the control group with 1 mL Tg-DH. Primary closure was obtained using a 4-0 silk suture. An ice pack was then applied to the patient's face for 20 min.

Medication

Patients were randomly allocated into two groups: the subjects in one group were given the test medication (Tg-DHKT) and in the other the control medication (Tg-DH).

Oral perioperative antibiotics [2 g amoxicillin/clavulanic acid (Augmentin; GlaxoSmithKline, Verona, Italy)] were administered to all patients 1 h before surgery; chlorhexidine gluconate 0.2% ((Dentosan; Pfizer Consumer Healthcare, Rome) was given to all patients as mouth wash for 10 days after surgery for 1 min thrice daily. Oral nimesulide 100 mg (Aulin; Roche S.p.A., Milano, Italy) was administered immediately after surgery. Patients were instructed to take the medication only when needed and to mark on the questionnaire if they assumed or not post-surgical anti-inflammatory drugs. The patients were advised to avoid any drugs apart from those prescribed and to not seek any medical help elsewhere for post-operative problems.

Post-operative assessment

The patient was given the usual postoperative instructions and received a questionnaire as in our previous study (16), after being instructed on its use. The benchmarks in the evaluation of signs of inflammation were subjective (pain, oedema, reddening, bleeding). Patients recorded their assessment daily on a special card during the 10 days following surgery, on which they could also record the occurrence of any side effects (Posse scale). Patients were also instructed to measure and record their body temperature (°C) in order to monitor the occurrence of any fever.

Patients of the Test group (Tg-DHKT) were asked to answer whether or not they needed to assume post-operative anti-inflammatory oral nimesulide.

To evaluate the recorded parameters during the ten-day test, two groups were created in order to highlight the presence (scores above zero) or absence (scores equal to zero) of symptoms. The statistical analyses were performed with a computerized statistical program (SPSS version 11.5 for Windows NT, SPSS Inc., Chicago, Illinois, USA). The statistical significance of results was assessed with the *chi*-square test.

RESULTS

Data from all of the 80 patients (37 males and 43 females) were included in the analysis. There were 39 patients (16 males and 23 females) in the Test group, and 41 (21 males and 20 females) in the Control group. There were no statistically significant differences between study groups with regard to patient characteristics or duration of surgery. At the follow-up, no patient had developed local infection or serious postoperative complications. No adverse effects or complications related to surgery were recorded in any treatment group throughout the study period.

Pain

For the first week after surgery the pain was less severe and decreased faster in the Control group (Tg-

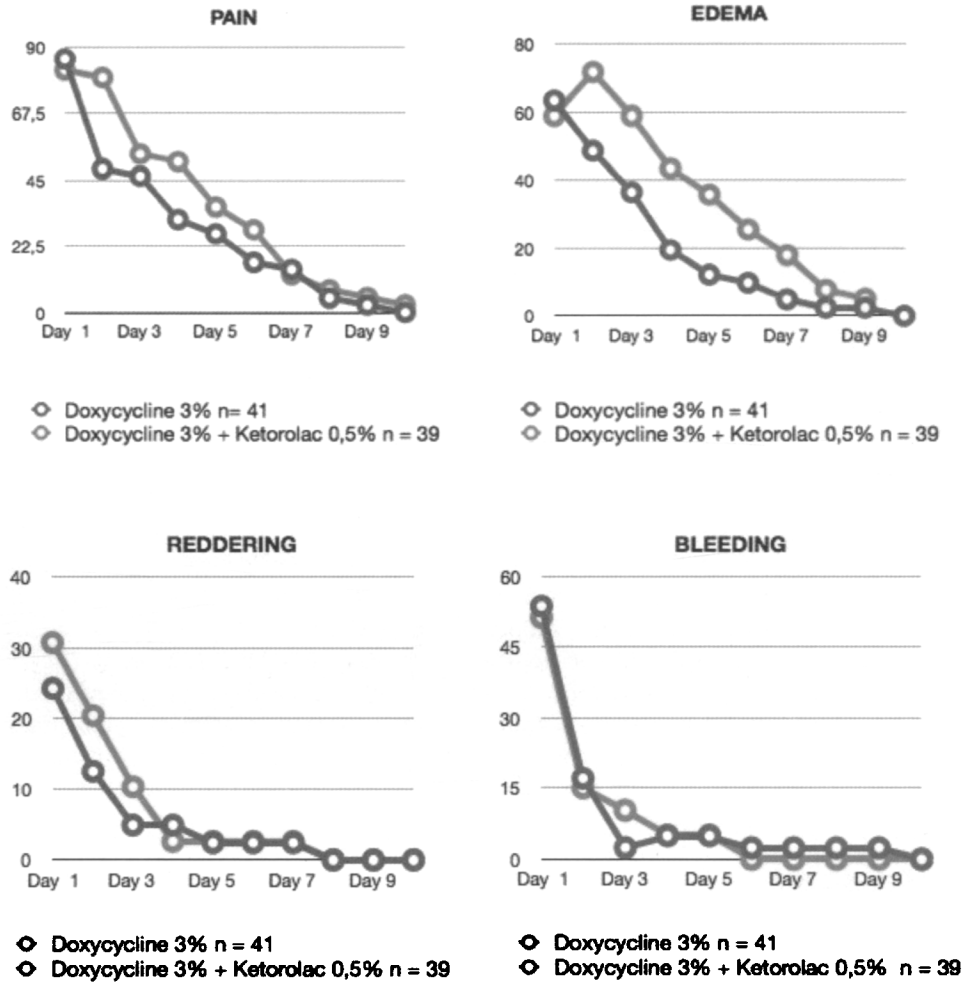

Fig 1. *Values of the Test group (Tg-DHKT) and the Control Group (Tg-DH) for pain, oedema, reddening and bleeding.*

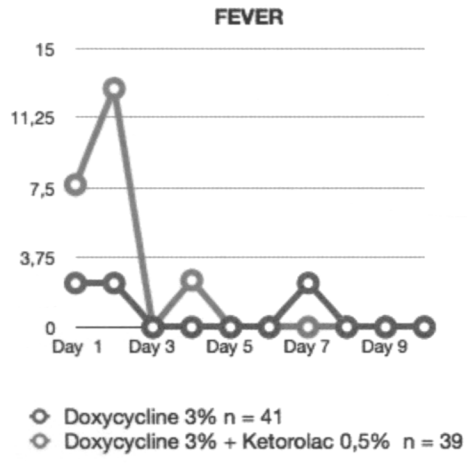

Fig 2. *Values of the Test group (Tg-DHKT) and the Control Group (Tg-DH) for fever.*

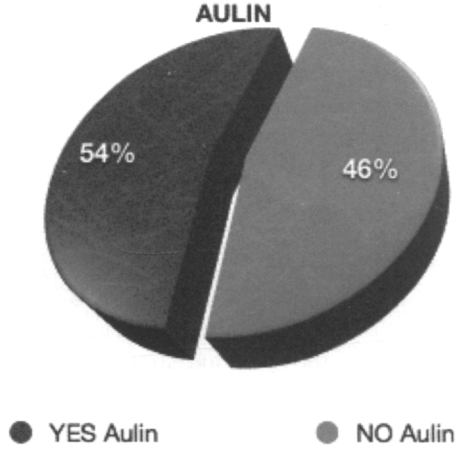

Fig 3. *Percentage of patients in the Test group (Tg-DHKT) who needed to assume an extra dose of anti-inflammatory drug (Aulin) at home.*

DH) than in the Test group (Tg-DHKT). From the seventh day the pain in the two groups was almost the same (Fig 1. Pain).

Oedema

In the Test group facial swelling was most severe the second day after surgery and began to return to normal baseline facial contour by the eighth postoperative day. Post-operative oedema shows the same decrement in both groups but less severe values were observed in the Control group (Fig 1. Oedema).

Reddening

In the Control group reddening was less severe than in the Test group, but from the third day after surgery they showed no differences (Fig 1. Reddening).

Bleeding

There were no differences between the two groups in the evaluation of bleeding. From the third day patients of both groups revealed no more bleeding (Fig 1. Bleeding).

Body temperature

Patients in the Test group had a body temperature higher than 37°C for more days compared to the Control group. No patient, however, described the increase of the body temperature recorded as a fever episode (Fig 2. Fever)

Nimesulide

46% of the patients of the Test group did not need to take any other dose of oral nimesulide, apart from the one given immediately after surgery (Fig. 3 Aulin).

DISCUSSION

The surgical extraction of third molars under local anesthesia is a standardized, very common clinical procedure for controlling problems produced by their impaction. This procedure is usually followed by postoperative pain, swelling, oedema and discomfort, even when teeth are removed using gentle surgical techniques (1, 6, 7). The parental use of dexamethasone, administered as an intraoral injection (4 mg) at the time of surgery, is effective in preventing postoperative oedema by inhibiting the conversion of phospholipids into arachidonic acid by phospholipase A_2, thus halting the resultant synthesis of prostaglandins, leukotrienes, or thromboxane-related substances as mediators of the inflammatory response (1, 6).

In this clinical trial both groups received 4 mg dexamethasone (Soldesam; Lab Farmacologico Milan Srl, Milan, Italy), injected into the buccal vestibule tissues to reduce oedema, and the thermosetting gel added with an anti-inflammatory drug (1 mL/5 mg Ketorolac Tromethamine) was used to investigate the possibility of introducing a topical dose of anti-inflammatory drug in order to substitute the post-operative intake. All the parameters were determined subjectively according to the patient's perception of the changes using a PoSSe subscale (19).

The suitability of the use of the PoSSe scale to subjectively assess postoperative parameters in third molar extraction was previously proved by Grossi et al. (1).

The results of this controlled clinical trial show a greater efficacy for the Tg-DH rather than the Tg-DHKT; the Test group values were higher than those of the Control group, and 46% of the patients did not need any anti-inflammatory medication. Presumably, injection of Tg-DHKT into the surgical site using a thermosetting gel as a carrier achieves a higher effective drug concentration at the site of injury without loss due to distribution to other compartments or the onset of elimination processes.

The results thus provide a basis for the use of Tg-DHKT injected into the tooth in alveolus after third molar surgery to reduce postoperative symptoms, even if the values are shown to be higher compared to those treated with thermosetting gel containing Tg-DH.

The clinical data presented in this comparative study provide a better knowledge of clinical drug anti-inflammatory dose and administration route in order to establish the most effective regimen needed by the patient after third molar extraction to control pain, oedema and inflammation.

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