Effect of Dexamethasone and Dipyrone on Lingual and Inferior Alveolar Nerve Hypersensitivity Following Third Molar Extractions: Preliminary Report

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Aims: *To study the effect of dexamethazone and dipyrone on sensory changes in the innervation territories of the inferior alveolar, infraorbital, and lingual nerves caused by third molar extractions.* ***Methods:*** *Fourteen patients (8 men and 6 women) were divided randomly into 2 groups. The first group received dipyrone preoperatively, while the second group received dipyrone and dexamethazone preoperatively. All patients in the study received a prophylactic preoperative dose of amoxicillin (500 mg) as well as dipyrone postoperatively. In all patients, a single mandibular third molar was removed, while in 2 patients the contralateral third molar was removed at a subsequent time. Electrical detection thresholds were assessed in the inferior alveolar, lingual, and infraorbital nerve regions prior to surgery and 2 and 8 days following surgery. The level of perioperative pain, difficulty of extraction, and distance of molar root apices from the inferior alveolar nerve canal were also assessed.* ***Results:*** *Patients who received only dipyrone had significantly reduced lingual and inferior alveolar nerve electrical detection thresholds 2 days after surgery, which returned to nearly baseline values by the eighth day postoperatively. In patients who received dexamethasone, no significant reduction in the electrical detection threshold was found.* ***Conclusion:*** *Preoperative treatment with dexamethasone and dipyrone but not dipyrone alone prevents sensory hypersensitivity following third molar extraction.* J OROFAC PAIN 2004;18:62–68.

Key words: dexamethasone, dipyrone, pain measurement, third molar, tooth extraction

Recently, it has been shown that inflammatory processes following the extraction of mandibular third molars produce altered sensation in the peripheral innervation territory of the lingual and inferior alveolar nerves. These alterations seem to be associated with changes mainly in large-diameter Aβ afferent (sensory) fibers, since they include an increased sensitivity to light touch and reduction of electrical detection threshold.[1] These changes peak 2 days after extraction of mandibular third molars and return to baseline within 1 to 2 weeks.[1]

Acute postoperative pain following third molar extraction is predominantly a consequence of inflammation due to tissue injury. Pain, edema, local hyperthermia, erythema, and loss of function are the typical signs of inflammation. These inflammatory processes are not observed immediately following surgery but rather

begin gradually, peaking 2 days after the extraction.[2] This correlates well with the sensory changes described at the same time period following the extraction.[1]

Inflammatory pain hypersensitivity comprises both allodynia (pain in response to normally innocuous stimuli) and hyperalgesia (enhanced pain in response to noxious stimuli). Aβ fibers appear to contribute to inflammatory hypersensitivity by switching their phenotype to resemble nociceptive afferent fibers, thereby enhancing synaptic transmission and exaggerating the central response to innocuous stimuli.[3] They cause a pattern of increased responsiveness in flexor motor neurons similar to that produced by low-intensity mechanical stimuli applied to inflamed skin.[4] The stimulus required is either mechanical or electrical stimulation of Aβ afferents that innervate inflamed tissue.

Quantitative sensory testing (QST) may be a useful tool to quantify the level of sensory changes. Electrical stimulation QST can be used to test whether tactile-evoked pain sensations can be mediated by the Aβ mechanosensitive afferents that under normal conditions mediate only nonpainful touch sensations. Unlike natural stimulation, electrical stimulation may bypass receptors, thus directly stimulating primary afferent axons. Aβ fiber axons are the most sensitive to this stimulation, so that at threshold levels for detection, these fibers alone are activated.

The present study utilized QST to test the hypothesis that strong anti-inflammatory effects of corticosteroids may diminish the sensory effects of the inflammatory process in the innervation territories of the inferior alveolar, infraorbital, and lingual nerves following extraction of a mandibular third molar. Corticosteroids such as dexamethasone are potent inhibitors of inflammation and have been used in varying regimens and routes to lessen inflammatory sequelae after third molar surgery. They induce the synthesis of endogenous proteins, which block the enzymatic activity of phospholipase A2. Blockade at this point prevents the release of arachidonic acid from its cell membrane constituents, thus preventing the ultimate synthesis of prostaglandins, leukotrienes, or thromboxane-related substances.[5,6] These effects are the basis for the clinical utility of corticosteroids. Following preoperative intravenous dosing with 125 mg of methylprednisone for third molar surgery, patients used 42% less pain medication.[7] Dipyrone is a commonly used analgesic agent in Israel and Europe with a known potential side effect of agranulocytosis. It is a pyrazolone derivative whose best-known agent in the United States is phenylbutazone, which is used in the treatment of rheumatoid arthritis and related disorders.[8] However, unlike phenylbutazone, dipyrone is not a nonsteroidal anti-inflammatory drug but an analgesic with minimal anti-inflammatory effects.

Therefore, the aim of this study was to study the effect of dexamethasone and dipyrone on sensory changes in the innervation territories of the inferior alveolar, infraorbital, and lingual nerves caused by third molar extractions. The authors examined patients both prior to and after a local inflammatory insult was introduced by the extraction of a single mandibular third molar.

Materials and Methods

Fourteen patients (8 men, 6 women) were chosen randomly to participate in this study after they signed a consent form. Patients with systemic illnesses were excluded from participating in the study, as were patients who were taking antibiotics or nonsteroidal anti-inflammatory medications during the 2 weeks prior to the study. Indications for extraction of mandibular third molars were based on clinical and radiographic examinations. Sensory nerve responses to stimuli in the innervation territories of the infraorbital, inferior alveolar, and lingual nerves were evaluated prior to the extraction and again 2 and 8 days postoperatively. All sites (the tip of the tongue, the anterior mandibular skin, and the infraorbital skin) were tested bilaterally in the same location.

An effort was made to ensure that the location of all sites tested was the same both pre- and postoperatively. All sites were tested preoperatively as well as at 2 and 8 days postoperatively. The inferior alveolar nerve, which innervates the pulp of the extracted mandibular third molar, was assumed to be both inflamed and mechanically traumatized by the extraction. The lingual nerve, which branches proximally from the inferior alveolar nerve to innervate the tongue, was assumed to be exposed to inflammatory processes caused by the extraction, resulting in minimal damage. The infraorbital nerve, which emanates from the maxillary branch of the trigeminal nerve, was assumed to be affected by a more central consequence of the extraction.[1]

A visual analog scale (VAS) was used to measure each patient's subjective pain rating both pre- and postoperatively (range: 0 = no pain at all to 10 = worst pain imaginable). Sensory nerve testing consisted of electrical sensory threshold detection. The detection threshold was assessed by an ascending

method of limits. The stimulating current was increased slowly until the subject indicated that he or she detected sensation. Continuous trains of constant-current electrical stimuli were delivered to the skin or mucosa through 8-mm-diameter, spherical, gold-plated electrodes spaced 10 mm apart. The normal current intensity and duration used were 20 to 40 mA and 0.1 millisecond in the inferior alveolar nerve region, 50 to 80 mA and 0.1 millisecond in the lingual nerve area, and 20 to 40 mA and 0.1 millisecond in the infraorbital nerve territory. The stimulus frequency was 100 Hz with a 50% duty cycle. Polarity of the electrodes was randomized. During stimulation of the tongue tip, the tongue was extended, dried, and isolated with 2×2-inch cotton gauze pads.

The level of difficulty of the extractions was evaluated prior to the surgical appointment. Any patients who preoperatively had any overt signs of infection that clinically would manifest as erythema, pain, swelling, purulent drainage from the pericoronal soft tissues, or trismus were excluded. The distance of the third molar roots from the inferior alveolar canal was extrapolated with periapical orthoradial radiographs to provide baseline information, and the degree of difficulty associated with the molar extractions was graded based on clinical and radiographic data. On the basis of radiographic data, patients were subdivided into 2 groups according to the distance of the third molar apices from the inferior alveolar nerve. One group comprised patients who had mandibular third molar roots superimposed upon the inferior alveolar canal, and the second group had molar apices with a 0.1 mm minimal distance from the inferior alveolar canal. Patients with fully erupted third molars, soft tissue–impacted third molars, or partially or full bony impacted third molars were included for this study. The Dionne scale of classification[8] was used to classify the level of difficulty of extractions. Simple extractions received a score of 1, soft tissue impactions received a score of 2, partial bony impactions received a score of 3, and full bony impactions received the highest score of 4.

All oral surgical procedures were carried out by the first author using only local anesthetic in carpules consisting of 2% lidocaine with 1:100,000 epinephrine. Patients were divided randomly into 2 groups. The first group (DIP group, n = 8) received dipyrone (1 g orally) 30 minutes preoperatively, while the second group (DEX group, n = 6) received dipyrone (1 g orally) and dexamethasone (8 mg orally) 30 minutes preoperatively. All patients received amoxicillin (Moxypen, 0.5 g; Teva Pharmaceutical Industries) 30 minutes preoperatively. Postoperatively, patients received only dipyrone (500 mg 6 times a day) for 1 week. This study was carried out as a double-blind study, since neither the patients nor the examiner knew who received dexamethasone. This study received the approval of the Israeli Research Council prior to its undertaking.

Data Analysis

The alpha level for significance was set at .05. The data were tabulated and analyzed with StatView 5 (SAS Institute). To quantify the electrical detection threshold, the authors correlated a ratio comparing the operated regions to the nonoperated regions. Since all but 2 patients had only 1 mandibular tooth extracted, the contralateral side served as a control. Threshold ratios for each nerve territory were evaluated by overall analysis of variance (ANOVA) followed by the Fisher PLSD pairwise comparison. Paired *t* tests within the extracted and control sides were achieved for each nerve territory. Therefore, ANOVA was used for intergroup statistical analysis, followed by the Fisher test, but *t* tests were used for intragroup analysis. Data were summarized as mean ± standard error.

Results

The baseline (preoperative) recordings provided a control to evaluate any pre-existing sensory changes, such as might occur if the patients had experienced any traumatic nerve injuries preoperatively. Such injuries, however, would have precluded these patients from participation in the study.

During preoperative testing, none of the patients were found to have any abnormal sensory changes, ie, for all patients, pain = 0. In the DIP group (Fig 1), on the second postoperative day, paired *t* tests for the extracted side showed that the electrical detection ratio (operated side versus nonoperated side) threshold was reduced significantly in the inferior alveolar nerve territory to 0.77 ± 0.6 (P = .05 compared to baseline) and in the lingual nerve territory to 0.74 ± 0.6 (P = .01 compared to baseline). In contrast, the electrical detection ratio was not attenuated in the infraorbital region (the ratio of extracted/control region was 1.03 ± 0.02). On the eighth postoperative day, the electrical detection threshold returned to normal in the inferior alveolar (0.90 ± 0.15) and lingual (1.19 ± 0.2) regions and remained normal in the infraorbital region (1.04 ± 0.06).

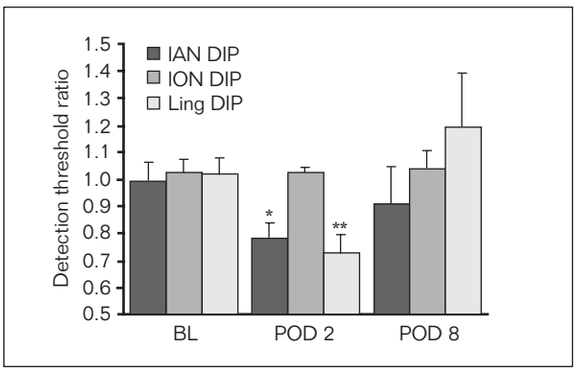

Fig 1 Comparison of the ratio of detection thresholds of the operated side to the control (ie, contralateral, unoperated) side in the 3 tested regions—inferior alveolar nerve (IAN), lingual nerve (Ling), and infraorbital nerve (ION) territories—at baseline (BL) and at 2 and 8 days postoperatively (POD 2 and POD 8) after administration of dipyrone (DIP, n = 8). For the inferior alveolar group, this ratio was reduced at POD 2 (*P = .05) and returned to near baseline levels at POD 8. For the lingual nerve, this ratio was significantly reduced at POD 2 (**P = .01) and returned to baseline levels at POD 8. No significant change was noted in the infraorbital nerve territory for POD 2 or POD 8.

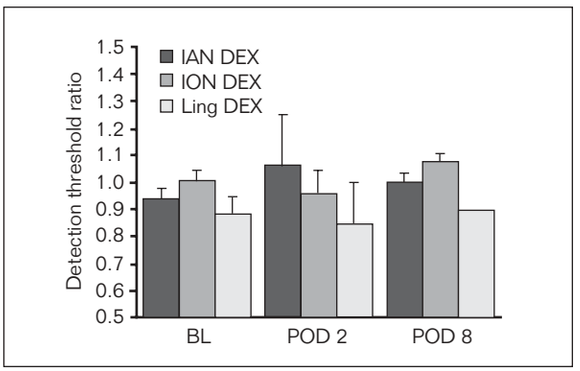

Fig 2 Sensory detection threshold ratios of operated side versus control side in the inferior alveolar nerve (IAN), lingual nerve (Ling), and infraorbital nerve (ION) territories at baseline (BL) and at 2 and 8 days postoperatively (POD 2 and POD 8) after administering dexamethasone (DEX, n = 6) preoperatively. No significant changes were found in any of the groups.

In the DEX group, no significant changes in any electrical detection threshold were found compared to baseline for inferior alveolar, lingual, and infraorbital nerve territories (Fig 2). On the second postoperative day, the electrical detection threshold ratios were 1.06 ± 0.18 in the inferior alveolar nerve territory, 0.85 ± 0.15 in the lingual nerve territory, and 0.96 ± 0.08 in the infraorbital nerve territory. On the eighth postoperative day, the values were 0.99 ± 0.04, 0.92 ± 0.09, and 1.08 ± 0.03, respectively.

The operated side was compared to the control side for sensory detection threshold differences at baseline and at 2 and 8 days postoperatively based on the Dionne scale of difficulty of tooth extraction. Figure 3 illustrates the thresholds based on difficulty levels, which ranged from 1 to 4 (1 = fully erupted third molar, 2 = soft tissue–impacted molar, 3 = partial bony impaction, 4 = fully impacted third molar). The lingual nerve territory exhibited significantly reduced sensory detection from baseline to postoperative day 2 at the 1 to 2 level of difficulty. The other nerve territories did not exhibit significant sensory reduction with respect to difficulty of procedure.

With the use of VAS, no pain was reported preoperatively in either group, but both groups reported significant pain postoperatively. There was some difference in the VAS pain ratings between the DEX and the DIP groups 2 days after the extractions (Fig 4). Eight days after the procedure, the VAS rating was reduced significantly compared to the 2-day data in the DEX group (at 2 days: 4.71 ± 0.69; at 8 days: 0.429 ± 0.28) but not in the DIP group (2 days: 3.89 ± 2.13; 8 days: 2.83 ± 3.2).

The sensory detection thresholds from patients with third molars that were superimposed upon the inferior alveolar canal were compared to those from patients with teeth that were a minimum 0.1 mm distance from the inferior alveolar canal (Fig 5). The electrical threshold was significantly reduced (P = .01) from baseline to postoperative day 2 only in the superimposed molar group and only in the lingual nerve territory.

Discussion

In accordance with earlier findings,[1] the data obtained in the present study indicate that following third molar extractions, a reduced electrical detection threshold could be detected 2 days postoperatively in both the inferior alveolar and lingual nerve innervation territories. By the eighth

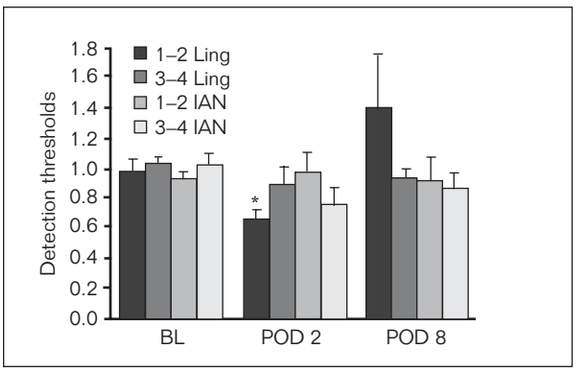

Fig 3 Comparison of sensory detection threshold between operated side and control side at baseline (BL) and at 2 and 8 days postoperatively (POD 2 and POD 8) based on Dionne scale of difficulty of tooth extraction. This figure represents 4 difficulty levels: 1 = fully erupted third molar, 2 = soft tissue impaction, 3 = partial bony impaction, 4 = full impaction. The lingual nerve territory had significantly reduced sensory detection from BL to POD 2 at the level of difficulty of 1 to 2 (*P = .045). The other nerve territories did not exhibit significant sensory reduction with respect to difficulty of procedure.

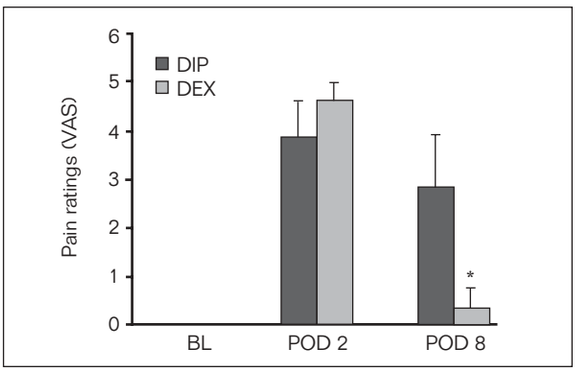

Fig 4 Comparison of efficacy of dipyrone (DIP, n = 8) versus dexamethasone (DEX, n = 6) in reducing VAS ratings of postoperative pain. Significant changes (mean ± SEM) in pain intensity were observed in both the dexamethasone and the dipyrone groups from baseline (BL) level to postoperative day 2 (POD 2) and from BL to postoperative day 8 (POD 8) (DEX, 2 days: 4.71 ± 0.69; 8 days: 0.429 ± 0.28; $P < .001$; DIP, 2 days: 3.89 ± 2.13; 8 days: 2.83 ± 3.2; $P = .15$). The most significant change was observed between POD 2 and POD 8 in the DEX group *(*)*; however, this difference was not significant for the DIP group.

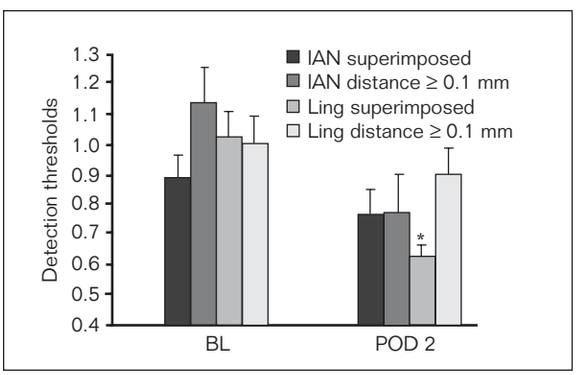

Fig 5 Comparison at postoperative day 2 (POD 2) versus baseline (BL) of sensory detection thresholds of patients with third molars superimposed upon the inferior alveolar nerve (IAN) canal to those of patients with teeth that had a minimum 0.1 mm distance from the IAN canal. A significantly reduced electrical threshold occurred only in the superimposed teeth group in the lingual nerve (Ling) territory (*P = .01).

day postoperatively, the electrical detection thresholds had returned to normal. Preoperative treatment with dexamethasone and dipyrone, but not with dipyrone alone, prevents sensory hypersensitivity following third molar extraction. Dexamethasone has significant anti-inflammatory properties and prevents inflammation. This supports the view that hypersensitivity of the peripheral afferent endings is the result of neuritis caused by a chronic inflammatory process, rather than by direct nerve damage.

Baseline data obtained (preoperatively) confirmed that none of the patients complained of any subjective symptomatology prior to surgery, such as pain, swelling, or trismus; nor were there any objective clinical findings, such as pericoronitis, pocket depths greater than 6 mm, or erythema. We also did not find any relationship between difficulty of the extractions and sensory changes. These results indicate that the level of difficulty of extractions exerted no influence on changes in the sensory threshold in all the nerve territories, unless nerve damage occurred. A possible source of error was the Dionne scale, which we used to measure extraction difficulty, since it has not been validated. Also, a larger clinical trial is needed to confirm these results.

We also found no correlation between the treatment rendered and the degree of pain at postoperative day 2. However, at postoperative day 8, patients who had received dexamethasone felt less pain than those who received dipyrone alone. Consequently, the anti-inflammatory effects of dexamethasone and dipyrone were useful to relieve

pain at postoperative day 8. Since pain reduction was greater than expected (in particular, from baseline to postoperative day 8), there are several possibilities to explain this finding. First, the efficacy of dipyrone as an anti-inflammatory agent may have been weak, or the edema and inflammation that occurred postoperatively responded better to the single preoperative dose of corticosteroids. Second, we did not gauge the efficacy of the single preoperative prophylactic 500-mg dose of amoxicillin. In addition to its function as a prophylactic agent against infection, amoxicillin also has anti-inflammatory properties. Based on our study sample, it was not possible to determine its efficacy in reducing inflammation and pain. Consequently, we can only suggest that preoperative administration of a low dose of corticosteroids may have a potentially clinically significant impact on the inflammatory process and on postoperative pain at postoperative day 8. This finding remains to be confirmed in further investigations.

We also evaluated radiographically the distance of third molar roots from the inferior alveolar canal to ascertain whether there was a relationship between the distance from the canal and the level of sensory changes. Surprisingly, superimposition of third molar teeth upon the inferior alveolar nerve affected only the results from the lingual nerve and not from the inferior alveolar nerve territory. As reported in a previous study,[1] the lingual nerve can be assumed to be affected by inflammatory processes and not directly by the surgery itself. The inferior alveolar nerve was subjected to mechanical trauma with peripheral and potential central consequences and was relatively unexposed to inflammatory processes. The inferior alveolar nerve, traveling through its canal, was relatively well protected from distant inflammatory events.

In the present study we employed electrical stimulation that activates large, myelinated fibers.[11,12] Unlike natural stimulation, electrical stimulation bypasses receptors, directly stimulating primary afferent axons, while mechanical testing can be influenced in pathologic conditions that increase receptor sensitivity of other types of afferents.[13] The Aβ axons are most sensitive to this stimulation,[11,12] so it is likely that at the levels employed for threshold detection, only these fibers were activated.[13]

Inflammation along a nerve results in increased sensitivity, especially to inputs from large-diameter Aβ afferents.[1,14,15] This altered sensitivity may serve as a marker for this inflammation and indicate both the magnitude and time course of the inflammation. Inflammation changes the character and sensitivity of Aβ afferents, which may undergo a phenotypic change.[3] They acquire properties of nociceptors; they release substance P at their presynaptic terminals and increase the excitability of central neurons.[16] Both N-methyl-D-aspartate (NMDA) and non-NMDA (eg, AMPA) receptor mechanisms underlie the involvement of excitatory amino acids (glutamate, aspartate), which are crucial to causing prolonged increasing neuronal excitability.[17] Both central and peripheral excitatory amino acid and neuropeptide receptor mechanisms may play a role in the expression of neuroplasticity in somatosensory and motor pathways related to orofacial pain.[17] Once inflammation is present and Aβ sensitivity is increased, gentle mechanical stimulation results in a progressive increase in innocuous and noxious tactile sensitivity. This increase is accompanied by changes in fos expression, which is usually seen with noxious stimulation, and is blocked by tachykinin neurokinin-1 receptor antagonists.[16]

Conclusions

Preoperative treatment with dexamethasone and dipyrone, but not dipyrone alone, prevents sensory hypersensitivity following third molar extraction. Further studies may use this method to characterize the anti-inflammatory effects of various compounds, for example, by comparing the effects of nonsteroidal anti-inflammatory drugs to the effects of both dipyrone and dexamethasone.

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