Attenuation of C-Reactive Protein Increases After Exodontia by Tramadol and Ibuprofen

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The anti-inflammatory effects of ibuprofen and tramadol were investigated by measuring C-reactive protein concentrations after removal of an impacted lower third molar. Forty-five American Society of Anesthesiologists Class I patients were randomly categorized into 3 equal groups according to postoperative analgesic medication. The first group received tramadol (100 mg every 8 hours), the second group received ibuprofen (400 mg every 8 hours), and the last group received half doses of both drugs in combination (50 mg tramadol every 8 hours and 200 mg ibuprofen every 8 hours). C-reactive protein was measured before surgery to exclude the presence of any preexisting inflammatory condition that might interfere with the study. C-reactive protein was also determined immediately after surgery and 72 hours postoperatively. At 72 hours, C-reactive protein had increased over postsurgery baseline by 123% in the tramadol group ($P < .001$), 84% in the ibuprofen group ($P < .001$), and only 37% in the combined analgesic group ($P = .078$). These results suggest that tramadol may produce supra-additive anti-inflammatory effects with ibuprofen after third-molar extractions.

Key Words: C-reactive protein; Ibuprofen; Tramadol; Dentistry; Oral surgery.

Postoperative sequelae to third-molar surgery include pain, trismus, and buccal swelling.¹ Acute inflammation, which develops as a consequence of the surgical manipulation of the hard and soft tissues, is the principal cause of these signs and symptoms.² Analgesics are commonly prescribed to alleviate pain induced by inflammation.¹ The analgesic agent tramadol is increasingly being used for the management of pain associated with acute and chronic inflammatory conditions.^{3,4} It is neither a nonsteroidal anti-inflammatory drug (NSAID) nor a true opioid.⁵ Tramadol exerts a unique dual mechanism of action: It binds weakly to μ -opioid receptors and inhibits neuronal reuptake of norepinephrine and 5-hydroxytryptamine (serotonin).⁶ Recently, an anti-inflammatory effect has been demonstrated. Tramadol inhibits different types of experimental inflammation in

rats.⁷ Acute administration of tramadol significantly reduces edema and hyperalgesia induced by yeast injection in the paw⁸ and reduces the amount of inflammatory exudate, as well as the concentration of prostaglandin E_2 .⁹

Several recent studies have reported that the combined use of tramadol and an NSAID provides effects superior to each drug used separately.^{10,11} The purpose of this investigation was to compare the anti-inflammatory effect of tramadol with that of ibuprofen as assessed by changes in C-reactive protein (CRP) concentrations and the efficacy of their combined use after third-molar extraction.

METHODS

This study was conducted on 45 American Society of Anesthesiologists Class I patients scheduled for the surgical removal of an impacted lower third molar at the oral surgery clinic of the Faculty of Dentistry, Ain Shams

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Representative standard curve for the calculation of C-reactive protein concentrations. Optical density was measured at C-reactive protein concentrations of 0–800 mg/L, and a standard quadratic curve was generated by the least-squares method.

University. Patients gave written informed consent, and the study was performed after approval of the ethical committee of the Faculty of Dentistry, Ain Shams University. The anticipated degree of difficulty of the impacted tooth as judged by clinical and radiological examinations was similar for all patients. No analgesic or sedative drugs were permitted before surgery.

A venous blood sample (approximately 2 mL) was collected to qualitatively assess the CRP concentration before surgery. The assay (RapiTex® CRP, Dade Behring Marburg GmbH, Marburg, Germany) is based upon the immunochemical reaction between antiprotein C antibodies bound to latex particles and the patient's serum CRP. Elevated CRP concentrations (above 6 mg/L) lead to visible agglutination of the latex particles. Patients with positive agglutination were excluded from the study.

The surgical removal of a single impacted mandibular third molar was performed under local anesthesia by following routine procedures of the oral surgery clinic. Postoperatively, patients were randomly assigned to receive 1 of 3 analgesic regimens. Group 1 received 100 mg tramadol (Ultram, Menapharm Co for Pharmaceutical & Chemical Industries, Tenth of Ramadan City, Egypt) every 8 hours, group 2 received 400 mg ibuprofen (generic, Kahira Pharmaceuticals & Chemical Industries Co, Cairo, Egypt) every 8 hours, and group 3 received 50 mg tramadol plus 200 mg ibuprofen every 8 hours.

A second blood sample was collected immediately after surgery, and a third sample was collected 72 hours postoperatively. Each blood sample was transferred to a plastic tube containing an anticoagulant (EDTA), which was then tightly closed and shaken. The tubes were then centrifuged at approximately 2000g, and the plasma was collected and stored at -70°C .

An enzyme-linked immunosorbent assay was used for

Table 1. Demographics of Patients

Analgesic Group	Mean Age (y)*	Men/Women
Ibuprofen	25.7 $\pm$ 7.7	8/7
Tramadol	26.1 $\pm$ 6.2	7/8
Combination	24.5 $\pm$ 4.2	6/9

* Values are mean $\pm$ SD.

the quantitative determination of CRP in human plasma. The test system (DiaMed EuroGen, Turnhout, Belgium) includes anti-CRP antibody-coated microtiterstrips for incubation with diluted plasma samples or standard solutions. After washing to remove unreacted plasma proteins, the bound CRP antigen-antibody complexes are reacted with specific peroxidase-conjugated antibodies. After a second washing, incubation of the strips with chromogen solution containing hydrogen peroxide produces a color change (measured by spectroscopy at 450 nm) in direct relation to the bound peroxidase. A standard curve (Figure) was obtained for each test by plotting the absorbance values (optical density) for corresponding CRP standards equivalent to plasma concentrations of 0–800 mg/L. The concentrations of CRP in patient samples were then determined by interpolation of their optical density measurements with the corresponding standard curve.

Statistical analysis was performed by using the Statistical Package for the Social Sciences. The Kruskal-Wallis test was used to analyze the overall effect of the 3 groups, and post hoc testing was used to differentiate among individual treatments. The Mann-Whitney *U* test was used in case of 2 independent groups. The Wilcoxon signed-rank test was used for comparing 2 dependent groups, and the Friedman test was used in case of 3 or more paired groups. *P* values of $\leq .05$ and $\leq .001$ were used to indicate significant and highly significant differences, respectively. Nonparametric tests were used in these analyses because the data distribution proved to be non-Gaussian by the Kolmogorov-Smirnov test.

RESULTS

Patients enrolled in this study were healthy young adults (21 men, 24 women) without pre-existing inflammatory conditions as indicated by pretreatment CRP determinations. There were no significant differences among the test groups with respect to age or gender distribution (Table 1). There were also no significant differences in CRP concentrations in the immediate postoperative samples among the groups ($P = .90$), though all groups showed significant elevations as a result of surgery. Blood samples collected 72 hours postoperatively re-

Table 2. C-Reactive Protein (CRP) Concentrations After Third-Molar Extraction

Analgesic Group	CRP (mg/L)†	
	Immediately Postoperative	72 h Postoperative
Ibuprofen	89.6 ± 19.2	165.1 ± 47.2*
Tramadol	92.3 ± 32.2	205.4 ± 45.5**
Combination	94.1 ± 21.7	128.7 ± 35.2

† Values are mean ± SD.

* $P < .05$.** $P < .001$.

vealed further increases in CRP (Table 2). The increase over the postsurgical baseline value was 123% in the tramadol group and 84% in the ibuprofen group. Both of these increases were highly statistically significant ($P < .001$). For the combined analgesic group, the 37% increase in CRP over its postsurgical baseline value approached but did not reach statistical significance ($P = .08$). Comparison among treatments revealed that, compared with the combined analgesic group, the increases in CRP in the ibuprofen group and the tramadol group were significant and highly significant statistically, respectively.

DISCUSSION

Surgical trauma elicits a characteristic metabolic response, including an elevation in circulating stress hormones and an increase in the synthesis and release of various chemical mediators and acute-phase proteins.¹² C-reactive protein is the first acute-phase reactant to rise after trauma or surgery.¹³ Its concentration is normally less than 10 mg/L for healthy persons but increases significantly in the immediate postoperative period, doubling at least every 8 hours before reaching a peak on the third day and returning to normal within 1 week.¹⁴ The magnitude of the CRP response varies directly with the response to treatment¹⁴ and may be increased as much as 2000 times normal.¹⁵ The choice of CRP to assess the anti-inflammatory effects of the drugs in this study was based on the fact that CRP can be a sensitive indicator of low-grade inflammatory problems and acute inflammatory reactions.¹⁶ It has been used to assess the level of inflammation and allows monitoring of the anti-inflammatory effect of drugs.¹⁷

Previous studies have relied on CRP measurements to record postoperative inflammation in dentistry. Freitas et al¹⁸ used CRP titers to assess the anti-inflammatory effect of an 830-nm diode laser for management of postoperative sequelae after the surgical removal of third molars. Also, Iizuka and Lindqvist¹⁹ characterized

CRP responses related to surgical treatment of mandibular fracture and type of fixation used. In our study, CRP revealed no significant differences among groups in the immediate postoperative samples, whereas significant differences in plasma CRP were recorded 72 hours after treatment. Both tramadol and ibuprofen groups were associated with highly significant increases in CRP ($P < .001$).

Ibuprofen, an NSAID, was chosen for study because NSAIDs are generally considered to be first-line therapy for management of postoperative dental pain of inflammatory origin.²⁰ Previous studies suggest that the acute analgesic effects of NSAIDs in the oral surgery model are related to suppression of a nociceptive process, presumably prostaglandin formation, rather than to a generalized anti-inflammatory effect.²¹ Despite the well-documented efficacy of NSAIDs in the amelioration of inflammatory dental pain, some patients do not receive adequate relief with normal therapeutic doses of these drugs, and increasing the dose beyond the maximum recommended amount does not offer any clinical advantage.²² Furthermore, NSAIDs inhibit both cyclooxygenase 1 and 2, and this nonselective inhibition contributes to their characteristic adverse effect profile.²³

A highly significant increase in CRP occurred in the tramadol group. There was a significant difference between the tramadol group and the ibuprofen group, which indicates weak anti-inflammatory effect of tramadol, though a recent experimental study reported that tramadol possess an anti-inflammatory effect.^{7,8}

The combination of analgesic drugs at reduced individual doses may provide better efficacy with less overall morbidity than does a single analgesic drug administered in full doses.¹⁰ In our study, the combined use of tramadol and ibuprofen at half doses each was associated with a relatively small and statistically nonsignificant increase in CRP. There were significant differences between the combined group and the ibuprofen group and a highly significant difference when compared with the tramadol group, which indicates that combined use of tramadol and NSAID provided better anti-inflammatory effects in spite of the reduction of the usual doses used of each drug. This finding is in agreement with previous studies^{10,11} demonstrating that the combined use of tramadol and an NSAID is better than tramadol alone for the management of pain after dental extraction.

Further assessment for the CRP level was performed on 3 patients with bilateral impaction for more evaluation. Two of the patients received tramadol after the first surgery and combined tramadol and ibuprofen after the second operation. The third patient received ibuprofen after the first surgery and combined tramadol and ibuprofen after the second operation. For the first patient, there was an 84.8% increase in the CRP level after tra-

madol treatment and a 3% increase after combined tramadol and ibuprofen treatment. For the second patient, there was a 46.8% increase in the CRP level after tramadol treatment and a 3.47% increase after combined tramadol and ibuprofen treatment. For the last patient with bilateral impaction, who received ibuprofen after first surgery, there was a 43% increase in the CRP level after ibuprofen treatment and a 3% increase after combined tramadol and ibuprofen treatment. It is suggested that enhanced anti-inflammatory effects were obtained through several mechanisms of anti-inflammatory actions provided by each drug.

Wilder-Smith et al²⁴ reported that a combination of different analgesic mechanisms can reduce postoperative pain. NSAIDs exert analgesic and anti-inflammatory effects through inhibition of cyclooxygenase and the biosynthesis of prostaglandins.²³ Recent studies have demonstrated that, in addition to its well-recognized stimulation of μ -opioid receptors and inhibition of biogenic amine reuptake, tramadol reduces prostaglandin E_2 concentrations in inflammatory exudates.^{7,9} Actually, this anti-inflammatory effect of tramadol could stem from the aforementioned effect on serotonergic and noradrenergic transmission, which reduced inflammatory edema in experimental conditions.⁵ In addition, the pharmacodynamic profile of tramadol is different from that of NSAIDs that facilitate its gastric and renal tolerability.²⁵ Therefore, it will be effective to use both drugs in combination to provide the opportunity for better efficacy with less overall morbidity than using each drug separately. In conclusion, the combination of tramadol and ibuprofen appears to produce supra-additive anti-inflammatory effects that may provide clinical advantages in safety or efficacy for treating postsurgical dental pain.

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