Clinical Efficacy of Celecoxib with and without Caffeine versus Ibuprofen for Pain Control following Crown Lengthening Surgery

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Abstract

Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed pain control medications following periodontal surgery. This study aimed to compare the efficacy of three drug regimens namely celecoxib, celecoxib + caffeine and ibuprofen for pain relief following crown lengthening surgery.

Methods: This randomized, double blind clinical trial was performed on 45 patients aged 20-60 years requiring crown lengthening of maxillary teeth. The subjects were randomly divided into three groups (n=15) receiving ibuprofen (400mg), celecoxib (200mg) and celecoxib (200mg) + caffeine (30mg). Each patient took one dose of the respective medications 30 minutes prior to surgery. Other doses were prescribed 1, 8, 16 and 24 hours after surgery. Pain scores were recorded using visual analog scale (VAS) at 1, 2, 4, 8, 16, 24 and 48 hours post operation.

Results: The mean VAS scores were significantly lower in celecoxib + caffeine group than in celecoxib group at 1 and 2 hours after surgery (H1: 2.33 (1.95) vs. 4.47 (2.56), p=0.026) (H2: 2.47 (1.60) vs. 4.80 (2.40), p=0.009). The pain scores were significantly lower in celecoxib + caffeine group than ibuprofen group at 8, 16 and 24 hours after the procedure (H8: 1.80 (1.21) vs. 3.73 (1.94), p=0.012) (H16: 1.07 (1.03) vs. 2.73 (1.87), p=0.012) (H24: 0.47 (0.64) vs. 1.87 (1.25), p=0.004). No significant difference was found in analgesic efficacy of celecoxib and ibuprofen.

Conclusion: The combination of celecoxib + caffeine showed higher efficacy than other medications for pain control following crown lengthening surgery. Caffeine may enhance the analgesic effect of celecoxib.

Key words: Caffeine, Celecoxib, Ibuprofen, Pain, Periodontal surgery.

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Introduction:

Pain following periodontal surgery is a common occurrence. In a study by Canakci, post-operative pain was reported by 79% of patients following open flap debridement surgery, 89% of patients after gingivectomy, and 93% following open flap surgery with osseous resection (1). Many factors may affect the severity of pain such as the patient age, duration of surgery, type of surgical procedure, surgical site, extent of incision, and psychological factors like stress and anxiety (2-4). Many inflammatory mediators such as prostaglandins, leukotrienes, interleukins, histamines and bradykinin are released following injury or trauma to the periodontal tissues (2, 5).

Post-operative pain management plays an important role in patient satisfaction and continuation of treatment process (6). NSAIDs

are among the most commonly prescribed drugs for pain control following periodontal surgery (7, 8). NSAIDs inhibit the cyclooxygenase (COX) enzyme, prevent the synthesis of prostaglandins and consequently decrease pain (9). Two isoforms of COX enzyme are found in the body namely COX1 and COX_2 (2).

Celecoxib is a new generation of NSAIDs that selectively inhibits COX_2 enzyme (10-13). It is commonly used for treatment of rheumatoid arthritis, osteoarthritis, acute pain and dysmenorrhea in adults (2, 14). It has analgesic, antipyretic, and anti-inflammatory effects. It does not have gastrointestinal complications or platelet disorders that are among the complications of conventional NASAIDs (13). Due to optimal properties such as long plasma half-life of 11 hours compared to that of conventional NSAIDs (4-6 hours) and also longer dosing interval compared to NSAIDs, patients are more comfortable taking celecoxib (15, 16).

An effective strategy for more efficient pain relief is to combine different analgesics to enhance their efficacy and decrease side effects by reducing their dosage (17). In this process, it is important to find new drug formulations and combinations for more efficient pain control.

Caffeine is an alkaloid central nervous system stimulant from the family of methylxanthines used in conjunction with opioid and non-opioid analgesics to enhance their efficacy (18). It does not have a specific effect per se; but,it enhances the efficacy of analgesics when used in combination with them (17). According to a study by Derry, *et al*. (2012) caffeine in conjunction with analgesics increased their efficacy and resulted in more efficient pain relief of patients (19). The most commonly consumed sources of caffeine include coffee, tea, chocolate and soda (soft drinks) (19, 20).

Considering the boosting effect of caffeine in conjunction with analgesics and limited studies on the efficacy of celecoxib in combination with caffeine, this study aimed to compare the efficacy of three drug regimens namely celecoxib, celecoxib + caffeine and ibuprofen for pain relief following crown lengthening surgery.

Methods:

This double blind clinical trial was conducted on 45 patients aged 20-60 years selected among those presenting to the Periodontology Department of Babol University of Medical Sciences, School of Dentistry for crown lengthening surgery. The study proposal was approved by the Ethics Committee of the university and patients signed written informed consent forms thoroughly explaining the steps of the study. This study was registered in IRCT (ID: IRCT201305253813N2). The inclusion criteria were no history of systemic disease, no allergy to NSAIDs, age range of 20-60 years, taking no pain medications for 48 hours prior to taking the understudy drugs, and being able to read, comprehend and fill out the questionnaire. The exclusion criteria were pregnancy or nursing, gastrointestinal diseases such as peptic ulcer, history of periodontal surgery in the past 6 months and phobia of dental procedures.

The understudy drugs namely 200mg celecoxib (Sajjad Darou, Tehran, Iran), 400mg ibuprofen (Hakim Pharmaceuticals, Tehran, Iran) and caffeine (Merck, Germany) were obtained. The drugs were poured into uniform capsules in separate packs and coded for the understudy groups by a pharmacologist. As such, three groups of drugs, 15 each, with different codes were prepared. The three groups included celecoxib with caffeine, celecoxib without caffeine and ibuprofen.

Qualified subjects were entered in the study after filling out the questionnaire and signing a written informed consent form. Subjects were selected using sequential simple random sampling (13, 15). The three codes were

randomly written on pieces of paper corresponding to the total number of subjects (three groups of 15 of the three codes yielding a total of 45 cards) and patients randomly received a piece of paper indicating their group allocation. Patients underwent crown lengthening by residents of periodontics who had almost equal level of expertise. Patient allocation to residents was matched. The understudy subjects were 45 patients in three groups of 15. Each group received their assigned drugs. In order to match the groups and minimize bias in results and also to eliminate the possible confounders in surgery at different sites of the oral cavity, only patients who required crown lengthening of the maxillary teeth were selected.

Taking the medications: A dose of the respective medication was prescribed for each patient half an hour prior to surgery and then at 1, 8, 16 and 24 hours post-treatment.

Patients were provided with VAS, in the form of a ruler with 10cm length. The leftmost point indicated complete analgesia and the rightmost point indicated the highest level of pain imaginable. Patients expressed their level of pain by marking a point somewhere in-between the two endpoints. The results of changes in VAS score at 1, 2, 4, 8, 16, 24 and 48 hours post-operation were recorded in the respective forms. For ethical purposes, acetaminophen codeine was prescribed for all patients as a supplementary analgesic. The patients were instructed to use it only if they experienced intolerable pain and if so, record their consumed dosage, time of consumption and number of pills taken.

Data were analyzed using SPSS version 18. Descriptive statistics, repeated measures ANOVA and Tukey's post-hoc test were applied for data analysis.

Results:

This study evaluated 45 patients including 28 females (62.2%) and 17 males (37.7%) with a mean age of 33.66 (8.47) years (range 20-60 years). Patients were evaluated in three groups of 15 and surgeries were only performed on the maxilla. The mean pain score in the understudy groups based on VAS at 1, 2, 4, 8, 16, 24 and 48 hours after crown lengthening was calculated.

Table 1- The mean (SD) level of pain after crown lengthening at different time points in the three groups

Group	1 hour	2 hours	4 hours	8 hours	16 hours	24 hours	48 hours
400 mg Ibuprofen	3.13 (1.92) Max= 7 Min= 0	3.13 (2.10) Max= 7 Min= 0	3.27 (1.75) Max= 7 Min= 1	3.73 (1.94) Max= 6 Min= 0	2.73 (1.87) Max= 5 Min= 0	1.87 (1.25) Max= 4 Min= 0	1.20 (1.86) Max= 5 Min= 0
200mg Celecoxib + 30mg Caffeine	2.33 (1.95) Max= 8 Min= 0	2.47 (1.60) Max= 7 Min= 1	2.53 (1.64) Max= 6 Min= 0	1.80 (1.21) Max= 3 Min= 0	1.07 (1.03) Max= 3 Min= 0	0.47 (0.64) Max= 2 Min= 0	0.20 (0.41) Max= 1 Min= 0
200 mg Celecoxib	4.47 (2.56) Max= 9 Min= 2	4.80 (2.40) Max= 9 Min= 2	3.60 (2.06) Max= 8 Min= 1	2.87 (2.00) Max= 8 Min= 0	1.40 (1.55) Max= 6 Min= 0	1.00 (1.36) Max= 5 Min= 0	0.53 (1.06) Max= 4 Min= 0

Comparison of intra- and inter-group data using repeated measures ANOVA revealed a significant reduction in the severity of pain over time ($p<0.0001$ and $p=0.009$, respectively).

The results of Tukey's post hoc test revealed that at 1 and 2 hours post-surgery, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the celecoxib group (H1: 2.33 (1.95) vs. 4.47 (2.56), $p=0.026$) (H2: 2.47 (1.60) vs. 4.80 (2.40), $p=0.009$). The pain scores were significantly lower in celecoxib + caffeine group than in ibuprofen group at 8, 16

and 24 hours after the procedure (H8: 1.80 (1.21) vs. 3.73 (1.94), p=0.012) (H16: 1.07 (1.03) vs. 2.73 (1.87), p=0.012) (H24: 0.47 (0.64) vs. 1.87 (1.25), p=0.004).

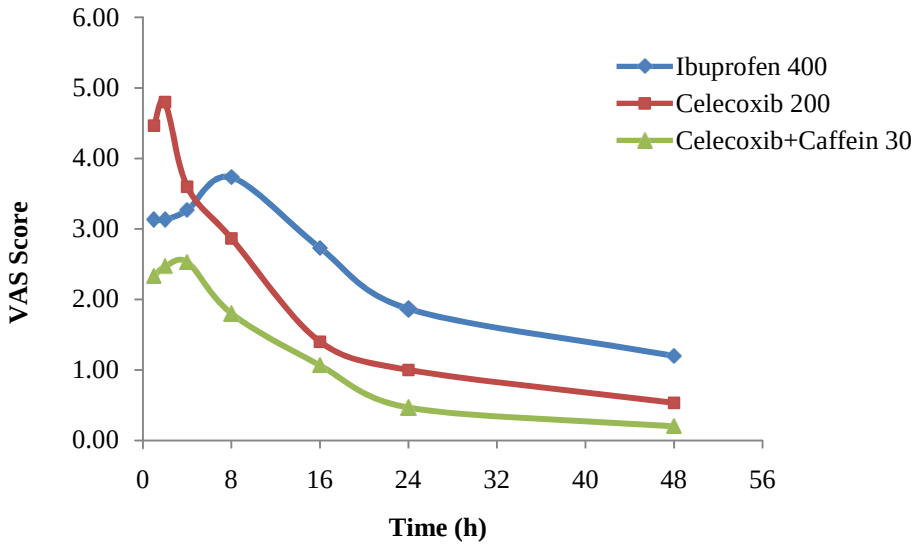

Diagram 1- Comparison of the mean pain score in the three groups at different time pointsfollowing crown lengthening

No significant difference was found in analgesic efficacy of celecoxib and ibuprofen.

No significant difference was noted in degree of pain among the understudy time points in males while in females, at 2 hours post-surgery, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the celecoxib group (p=0.015). This value in the ibuprofen group was lower than that in the celecoxib group (p=0.047). At 4 hours, the mean VAS in the celecoxib + caffeine group was significantly lower than that in the celecoxib group (p=0.011). At 8 hours, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the celecoxib (p=0.027) and ibuprofen (p=0.006) groups. At 16 hours, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the ibuprofen group (p=0.011). At 24 hours, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the ibuprofen group (p=0.007). No other differences were noted in the mean VAS score in females.

Comparison of the three groups in terms of age range at different time points using ANOVA and post-hoc Tukey's test revealed the followings:

In those aged ≤30 years: Significant differences were noted among the three groups at 24 (p=0.026) and 48 (p=0.044) hours post-surgery. At 24 hours, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the ibuprofen group (H24: 0.38 (0.7) vs. 2 (1.6), p=0.03). At 48 hours, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the ibuprofen group (H48: 0.13 (0.35) vs. 1.83 (2.1), p=0.046).

In those aged >30 years: Comparison of the three groups at 1 (p=0.038), 2 (p=0.019) and 8 (p=0.033) hours post-surgery revealed significant differences in the mean pain score. At 1 hour post-surgery, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the celecoxib group (H1: 2.29±2.8 vs. 5.22±2.5, p=0.047). At 2 hours, the mean VAS score in the ibuprofen group was significantly lower than that in the celecoxib group (H2: 3±1.4 vs. 5.33±2.2, p=0.044). The

mean VAS score in the celecoxib + caffeine group was significantly lower than that in the celecoxib group (H2: 2.71 (2.13) vs. 5.33 (2.2), p=0.034). At 8 hours, the mean VAS score in the celecoxib + caffeine group was significantly lower than that in the ibuprofen group (H8: 1.71 (1.11) vs. 4.22 (1.85), p=0.034).

Discussion:

Periodontal surgery is often associated with pain, swelling and local inflammation of the tissue. Thus, a proper choice of analgesic and anti-inflammatory drugs with adequate efficacy and minimal side effects is particularly important for both the clinicians and patients (5). Previous studies have demonstrated that selective COX_2 inhibitors like celecoxib significantly decrease the inflammatory cell count, edema and vascular dilation following inflammation. Decreased inflammation and inflammatory cell count result in less release of pain mediators and thus, these drugs can significantly decrease pain in the first hours following tissue injury (8). Ibuprofen is more effective than celecoxib but has more side effects as well. However, the side effects of ibuprofen are less than those of other NSAIDs (21). Celecoxib is among the first COX_2 inhibitors with side effects less than those of ibuprofen (22).

Cheung, *et al*. in 2007 concluded that celecoxib was more effective in decreasing post-operative pain than ibuprofen. However, in our study, celecoxib and ibuprofen had similar efficacy. This may be due to the use of 400mg dose of celecoxib, which is twice the dose used in their study (16).

Insignificant difference between the analgesic efficacy of celecoxib and ibuprofen in our study is similar to the finding of Salo *et al*. in 2003. They compared the analgesic efficacy of celecoxib and ibuprofen in trauma patients in an emergency ward (23). The results of other studies also indicated no significant difference in efficacy of celecoxib and ibuprofen (13, 22).

Another study showed equal efficacy of ibuprofen and celecoxib in decreasing periodontal pain; which is similar to our finding. Thus, considering the side effects of ibuprofen and also longer dosing interval of celecoxib (2 times daily for celecoxib versus 4 times daily for ibuprofen), celecoxib should be preferably used for pain control (15).

In the current study, caffeine enhanced the analgesic efficacy of celecoxib. Previous studies demonstrated that caffeine increased the analgesic and anti-inflammatory effect of celecoxib (3, 24, 25). McQuay *et al*. in 1996 demonstrated that ibuprofen in conjunction with caffeine had greater analgesic efficacy for use after third molar surgery compared to ibuprofen alone (26).

Diamond *et al*. in 2000 concluded that combination of ibuprofen and caffeine had greater analgesic efficacy for neural headaches compared to ibuprofen, attributed to the analgesic potential of caffeine enhancing the analgesic effect of ibuprofen (27).

A study on rats showed that combination of caffeine and acetylsalicylic acid may decrease the drug side effects and enhance the analgesic efficacy (17). Another study showed significant analgesic effect of caffeine in combination with opioids (28). Our finding regarding the boosting effect of caffeine is in line with the results of afore mentioned studies.

In terms of age range, since the patients were in the age range of 20-60 years, patients were matched in terms of age in the three groups. On the other hand, in each group, subjects were divided into two subgroups of $\leq$30 and >30 years and then data were analyzed. The results showed that in patients $\leq$30 years, significant differences were noted in the mean pain score between celecoxib + caffeine and ibuprofen at 24 and 48 hours in favor of the former regimen. In those >30 years, at 1, 2 and 8 hours, the

difference in pain score between the celecoxib and celecoxib + caffeine groups was significant in favor of the latter regimen. Difference in pain at early hours post-operation in older age group indicates the lower pain threshold of older patients and the need for prescribing an analgesic with rapid absorption. Caffeine can accelerate the absorption of celecoxib and this may explain the obtained results.

In terms of gender, no significant difference was noted at any time point in males. However, significant differences might have been found if there had been a larger sample size.

The analgesic effect of caffeine is attributed to several factors such as the presence of caffeine in combination with analgesics and enhancing their efficacy by inhibiting the adenosine receptors and subsequently the synthesis of COX_2 enzyme and also its effects on the central nervous system leading to increased consciousness, and decreased pain and fatigue (3, 18, 28, 29).

In the current study, the highest pain reduction was seen in celecoxib + caffeine group. Such significant difference may be due to the caffeine pharmacokinetics because it inhibits phosphodiesterase enzyme and increases intracellular cAMP and subsequently increases the secretion of stomach acid and peristalsis and consequently, it acceleratesdrug absorption. The drug reaches the target organ and exerts its effect faster (18, 20, 30, 31).

Conclusion:

In long-term, celecoxib has less gastrointestinal side effects than ibuprofen. Also, it has longerdosing interval than ibuprofen(twice daily versus 4 times daily) making its use more convenient for patients. Caffeine enhanced the analgesic efficacy of celecoxib. Thus, to decrease dosage and avoid the side effects of other analgesics, celecoxib + caffeine is recommended to alleviate pain following crown lengthening surgery.

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Conflict of Interest: "None Declared"

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