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Evaluation of caffeine versus codeine for pain and swelling management after implant surgeries: A triple blind clinical trial☆,☆☆

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ABSTRACT

Introduction: There are controversies in recent studies over the application of NSAIDs for controlling pain and swelling after implant surgeries for osseointegration. The aim of this study was to compare caffeine-containing versus codeine-containing analgesics in relation to their anti-inflammatory and analgesic effects after dental implant surgeries.

Materials and methods: 80 patients (40 in each group) were selected as the final sample size. Forty drug packs, which were formulated and made by the consultant pharmacist, each containing 10 capsules of acetaminophen caffeine (consisting of 300 mg of acetaminophen and 20 mg of caffeine), and another 40 packs, each containing 10 capsules of acetaminophen codeine (consisting of 300 mg acetaminophen and 20 mg codeine) were prepared. These drugs were administered randomly to patients 1 h before surgery and every 6 h afterward until 48 h, according to the protocol. The patients' pain severities were determined at 30-min, 3-h, 6-h, 12-h, 1-day, 2-day, and 1-week intervals. In addition, the swelling was evaluated after 1-day, 2-days, 3-days, and 1-week. Data were analyzed with Mann–Whitney, student's *t*, and chi-squared tests, using SPSS 11.

Results: A total of 76 patients, including 38 males and 38 females, with a mean age of 41.06 ± 5 and an age range of 35–53 years, were studied. The pain severities in patients in the codeine group were significantly less than those in the caffeine group at 3-, 6-, and 12-h postoperative intervals ($p = 0.001$). However, the pain severities at the above intervals, even in caffeine group, were within the moderate pain severity range (VAS = 3–7). It is also interesting to note that the pain was at its maximum severity at the 6-h postoperative interval, and at its minimum at the 1-week interval. The severity of swelling was also evaluated in both groups, indicating that it was significantly less in the caffeine group at 1-, 2-, and 3-day postoperative intervals ($p = 0.018$).

Conclusion: According to this study, the codeine-containing analgesics are significantly more effective than caffeine-containing ones in reducing postoperative pain. It was also concluded that caffeine-containing analgesics are significantly more effective than codeine-containing ones in reducing postoperative swelling, which was reported to be significantly less within the first 3-days in the caffeine group. As a result, caffeine-containing analgesics are effective and acceptable in reducing both postoperative pain and swelling.

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1. Introduction

One of the surgeries that is routinely performed, especially by maxillofacial and periodontal surgeons, is dental implant surgery. It usually results in mild to moderate pain and swelling, sometimes exceeding the normal range. There are different reports on the severity of pain and swelling, depending on the operation complications, surgeon's skill, pain threshold, patient's immune system, and many other factors (Spin-Neto et al., 2014; Hashem et al., 2016; Gonzalez-Santana et al., 2005; Kim et al., 2013; Kuroi et al., 2015; Al-Khabbaz et al., 2007).

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, and naproxen, are effective in reducing inflammatory mediators that cause mild to moderate pain and postoperative swelling (Kalyvas & Tarenidou, 2008). Conflicting results have been reported in recent studies on indications of NSAIDs for controlling pain after implant surgeries, which is the result of the probable impairment of osseointegration of implants after long-term consumption of NSAIDs (over a week) (Raisian et al., 2012; Rashwan, 2009; Gomes et al., 2015; Cai et al., 2015; Alissa et al., 2009; Winnett et al., 2014; Sakka and Hanouneh, 2013; Jeffcoat et al., 1995).

Acetaminophen (paracetamol) is used to relieve pain and fever; it is usually combined with other drugs and is used for mild to moderate pain. It is believed that acetaminophen influences the central nervous system; some researchers have noted that it increases pain threshold by inhibition of cyclooxygenase-3 activity. Acetaminophen does not inhibit the enzyme COX-1 in tissues; therefore, it has no gastrointestinal side-effects. Combination of acetaminophen with nonsteroidal anti-inflammatory agents can be effective in the treatment of acute and chronic pain. Different studies have been conducted on this subject (Kalyvas & Tarenidou, 2008; Kjærsgaard-Andersen et al., 1990; Squires and Masson, 1981; Mitchell et al., 2012; Yoon et al., 2016).

Combining analgesics might increase the efficacy, but without decreasing the dose this might result in subsequent risks; therefore, caffeine or codeine supplements might be combined with acetaminophen to increase its efficacy (Chaturvedi et al., 2009).

Before addressing the role of caffeine in pain control, first we must be familiar with an endogenous compound called adenosine. Adenosine is an inhibitor of neuronal activity in the central nervous system (CNS) and peripheral nervous system (PNS). It has various modulatory effects in the central and peripheral nervous systems and its receptors have been known to be involved in antinociception. It has been shown that activation of A1 and A2A receptors leads to antinociception in neuropathic pain, nociceptive, and inflammatory models (Zylka, 2011, 2010; Sawynok, 2013). The structure of caffeine is similar to adenosine and therefore caffeine competes with adenosine for A2A receptors, causing their inhibition. Despite this, caffeine does not alter dopamine release and therefore does not have abuse potential like other adenosine-blocking agents, such as cocaine. Understanding these effects leads to renewed interest in caffeine as a novel option for pain control – it could reduce pain sensation through its effects on adenosine receptors (Sawynok, 1998, 2013; Latini and Pedata, 2001; Rogers and Dinges, 2005; Sollevi, 1997). Caffeine seems to express its direct effect via central blocking of adenosine receptors, which influence pain signaling, or by blocking of peripheral adenosine receptors on sensory afferents (Sawynok, 2011a,b, 2013; Sollevi, 1997; Astorino et al., 2011; Benowitz, 1990).

There are other studies showing evidence of caffeine decreasing pain by influencing adenosine receptors in the central nervous system. Promising results were gained by researchers in combination therapy with acetaminophen for controlling postoperative pain. Caffeine has vasoconstrictor effects on the cerebral and peripheral vascular system, reducing tension headaches and migraine attacks (Karabuda et al., 2007; Macedo et al., 2015; Forbes et al., 1994).

There is limited information in scientific papers regarding pain associated with dental implant surgery and only one study has indicated positive effects of the administration of caffeine in osseointegration (Al-Khabbaz et al., 2007; Macedo et al., 2011). Macedo showed that administration of caffeine enhances osseointegration of autogenous bone grafts in rats (Barasch et al., 2011).

Considering the conflicting results reported about the deleterious effect of NSAIDs on implant osseointegration (Raisian et al., 2012; Rashwan, 2009; Gomes et al., 2015; Cai et al., 2015; Alissa et al., 2009; Winnett et al., 2014; Sakka and Hanouneh, 2013; Jeffcoat et al., 1995), and regarding the importance of osseointegration in stabilization of dental implants, it seems absolutely necessary to conduct a clinical trial to find a suitable analgesic protocol, with sufficient analgesic and anti-inflammatory effects, that does not stimulate bleeding.

Therefore, we decided to design a triple-blind clinical trial and investigate the administration of caffeine in comparison with codeine, to assess the severity of pain and swelling after surgical placement of implants.

2. Materials and methods

Our study included 80 adult patients who were edentulous in the posterior region of the mandible and were applicants for single implants. The protocol of this randomized, triple-blind study was approved by the Ethics and Research Committee of Mashhad University of Medical Sciences (IR.mums.sd.REC.1394.89), and the study was registered in IRCT under the code IRCT2015061322697N1R1.

The subjects were systemically healthy (ASA Class I or II for physical status classification) (Alissa et al., 2009) from any gender or race, with an age range of 35–55 years. All the patients had the same surgical difficulty, and proper width and height of bone in their records. Bone grafts (both width and height) and displacement of the mental nerve were not necessary. Surgeries were carried out or supervised by a surgeon using a single protocol and the same implant systems (Implantinum implant, Dentium, South Korea) in edentulous posterior mandibular sites.

Subjects with a serious medical or mental condition, risk of infectious endocarditis, an acute local infection, a bleeding disorder, known sensitivity to NSAIDs, codeine, caffeine, and/or acetaminophen, pregnancy or lactation, or a history of asthma, drug, or alcohol abuse, or of taking an investigational drug or making a blood donation within the previous months, were excluded. All subjects were free of any infectious symptoms like swelling, fever, pus drainage, or decreased mouth opening at the time of surgery.

After explanations and consent, the patients participating in the study were given a discount for surgery. They were divided into two groups, each including 40 individuals, in a stratified, randomized manner.

In line with Consort guidelines, random codes were applied according to the number of patients and drugs, and each patient was randomly categorized with a code. Then, according to that code, a drug package was delivered by the student. This procedure was executed randomly; therefore, neither the patient nor the surgeon and statistician were aware of the pharmaceutical packages involved, and the student was the only informed person (triple-blind, randomized clinical trial).

The aim of the study was explained to the patients at the start, but they were not told who would receive which drug. The patients were told not to use any additional medication for pain relief, unless stronger sedation was required for extreme pain, in which case

they would be excluded from the study afterward. Written consent was taken from the patients and they were free to leave the study if they wished to, at any stage of the study.

The medications, consisting of acetaminophen caffeine (acetaminophen, 300 mg plus anhydrous caffeine, 20 mg, prepared by the consultant pharmacist) and acetaminophen codeine (acetaminophen, 300 mg plus codeine, 20 mg (Jung et al., 2004), prepared by the consultant pharmacist), were packed separately by a third party for 80 patients. The packing involved putting ten acetaminophen caffeine tablets in 40 packages, and ten acetaminophen codeine tablets in another 40 packages with the same form and appearance.

All the packages were labeled and numbered randomly. Prior to the surgery each patient was given a package. The randomization code was concealed from the study investigators, nurses, and patients, and kept in a secure location until the end of the study.

The patients in group I ($n = 40$) were given acetaminophen caffeine and the patients in group II ($n = 40$) were given acetaminophen codeine. Preoperative analgesic drugs, based on the patient's group, and oral preoperative antibiotics (500 mg of amoxicillin every 8 h for 4 days), were administered to all the patients 30 min before and after surgery.

Preoperative pain was assessed using a visual analog scale (VAS), in such a way that pain was recorded from 0, representing no pain, to 10, representing severe pain. Patients marked their level of pain on the relevant line (Fig. 1).

Patients' pain was measured 30 min, 3 h, 6 h, and 12 h after the operation. In order to check swelling and inflammation, we used VAS criteria introduced by Pasqualini et al., in 2005 (Table 1). The researcher asked patients to define their pain on days 1, 2, 3, and 7 after surgery, in line with studies by Kim et al. (2013) and Costa et al. (2015), in a specific list.

Eventually, a form that included patient characteristics and drug codes, along with a check-list that included the severity of pain and swelling, was delivered to the patient and surgeon.

Data forms were filled out under the supervision of the surgeon (supervising teacher) not by the student (who knew which patient had received which drug).

The day after surgery, the patients returned for re-examination. The checklists were encoded and sent for analyses. In the next stage of data analysis, decoding was performed. Data were analyzed using SPSS for Windows (V. 11.5, SPSS Inc., Chicago, IL), with a Mann–Whitney test, student's t-test, and chi-squared test, at a significance level of $p < 0.05$.

3. Results

A total of 80 patients (40 males and 40 females) were included in this study. Two patients were excluded because of self-medication and two others refused to deliver answer sheets; therefore, we completed the evaluation with 76 patients. Computer-generated randomization was performed and the 76 patients were divided into two groups of 38, matched in terms of sex and age. In group I, 38 patients were given acetaminophen caffeine (acetaminophen, 300 mg plus anhydrous caffeine, 20 mg); in group II, 38 patients were given acetaminophen codeine (acetaminophen, 300 mg plus codeine, 20 mg).

The mean surgery durations were 14.27 ± 0.71 min in the caffeine group and 14.2 ± 0.69 min in the codeine group, with no significant differences between the two groups ($p = 0.76$).

The patients' mean ages were 40.50 ± 4.80 and 41.5 ± 5.3 years in the caffeine and codeine groups, respectively, with no significant differences ($p = 0.89$).

3.1. Comparison of pain and swelling in both groups

The pain severities at the 30-min and 1-, 2-, and 3-week postoperative intervals did not show any significant differences between the two groups, but at the 3-, 6-, and 12-h intervals in the codeine group pain severity was significantly lower than the caffeine group ($p = 0.001$). It is notable that pain severities during this period were moderate in both groups (VAS was between 3 and 7, $p = 0.001$) (Table 2).

The peak of pain severity was at the 6-h postoperative interval, reaching its lowest point after 1-week. The rate of swelling was also compared between the two groups and it was found that postoperative inflammation on the first, second, and third days in the caffeine group was significantly lower than that in the codeine group ($p = 0.018$).

Interestingly, the severity of inflammation in the caffeine group, in comparison with the codeine group, was not significantly different a week later. The severity of inflammation in both groups exhibited significant changes during the study ($p = 0.001$) (Table 3).

The pain decreased significantly from the beginning to the end of the research in both groups ($p = 0.001$).

A detailed comparison in the caffeine group found that the pain severity at the 30-min and 1-week intervals was significantly lower than at the 3-, 6-, and 12-h intervals, and at day 1. However, the 30-min and 1-week intervals were not significantly different from the

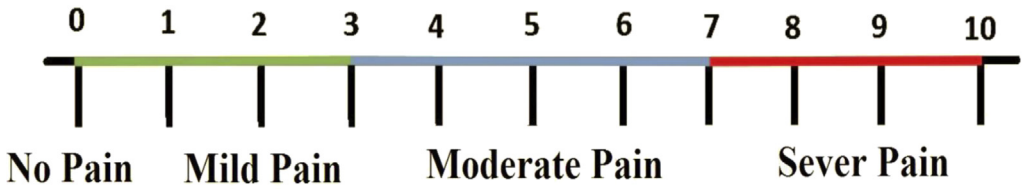

Fig. 1. VAS scale chart for pain measurement.

Table 1
Check list of swelling measurement based on the VAS criteria introduced by Pasqualini et al. (22).

VAS 0	Without swelling	The patient does not feel any swelling.
VAS 1	Mild swelling	The patient feels a little swelling, but does not attract attention.
VAS 2	Moderate swelling	Swelling is significant but does not interfere with chewing and swallowing.
VAS 3	Severe swelling	Swelling is remarkable and makes it difficult to chew.
VAS 4	Very severe swelling	Swelling has been severe and obvious, and makes it difficult to chew, but limited opening of the mouth (locking jaw) is not evident.
VAS 5	Extreme swelling	Swelling has been very severe and the patient has difficulty in chewing and opening mouth.

Table 2
Pain levels (VAS scales) for caffeine and codeine groups at different times.

Parameter	Group	*n*	Average VAS	SD	Min	Max	Mid	*p* value
Pain (30 min post-op)	Caffeine	38	0.44	0.616	0	2	0.00	0.592
	Codeine	38	0.56	0.616	0	2	0.50	
Pain (3 h post-op)	Caffeine	38	5.61	1.243	4	9	5.50	0.001
	Codeine	38	4.00	1.572	2	9	4.00	
Pain (6 h post-op)	Caffeine	38	6.06	1.259	4	10	6.00	0.001
	Codeine	38	4.39	1.614	2	10	4.00	
Pain (12 h post-op)	Caffeine	38	5.17	1.757	1	10	5.00	0.001
	Codeine	38	3.22	1.003	2	6	3.00	
Pain (24 h post-op)	Caffeine	38	2.94	0.735	2	4	3.00	0.071
	Codeine	38	2.39	1.037	1	5	2.00	
Pain (48 h post-op)	Caffeine	38	0.94	0.416	0	2	1.00	0.188
	Codeine	38	0.78	1.166	0	5	1.00	
Pain (72 h post-op)	Caffeine	38	0.67	0686	0	2	1.00	0.074
	Codeine	38	0.28	0.575	0	2	0.00	
Pain (1-week post-op)	Caffeine	38	0.17	0.383	0	1	0.00	0.083
	Codeine	38	0.00	0.000	0	0	0.00	

Table 3
Swelling levels (VAS scales) for caffeine and codeine groups at different times.

Parameter	Group	*n*	Average VAS	SD	Min	Max	Mid	*p* value
1st day swelling	Caffeine	38	1.11	0.583	0	3	1.00	0.018
	Codeine	38	1.39	0.916	0	4	1.00	
2nd day swelling	Caffeine	38	1.89	0.758	1	4	2.00	0.007
	Codeine	38	2.89	0.583	1	2	2.00	
3rd day swelling	Caffeine	38	1.78	0.808	0	3	2.00	0.001
	Codeine	38	2.50	0.786	2	4	3.00	
Swelling after 1-week	Caffeine	38	0.00	0.000	0	0	0.00	0.65
	Codeine	38	0.44	0.511	0	1	0.00	

2-day, 3-day, and 1-week intervals. Pain severity did not exhibit any significant differences at the 3-, 6-, and 12-h intervals. However, pain was significantly less severe on the second and third days compared with the 3-, 6-, and 12-h intervals.

In the codeine group, pain severity at the 1-week and 3-day intervals was significantly lower than that at the 3-, 6-, and 12-h intervals. The severity of pain at the 30-min and 2-day intervals was significantly less than that at 3-, 6-, and 12-h intervals. No significant differences were noted among the other time intervals. Chart 1 shows pain severity at the various study intervals for each group.

The severity of swelling during this study showed significant changes in both groups; swelling after surgery peaked on the second day and then, from the third day onwards, inflammation decreased until 1-week after surgery, when both groups exhibited the lowest inflammation severity. Inflammation in the caffeine group was significantly less than that in the codeine group during the first 3-days, but the difference was not significant on the seventh day.

In comparisons made within each group, the severity of swelling in the caffeine group on the seventh day was significantly lower than that on the first, second, and third days. There were no

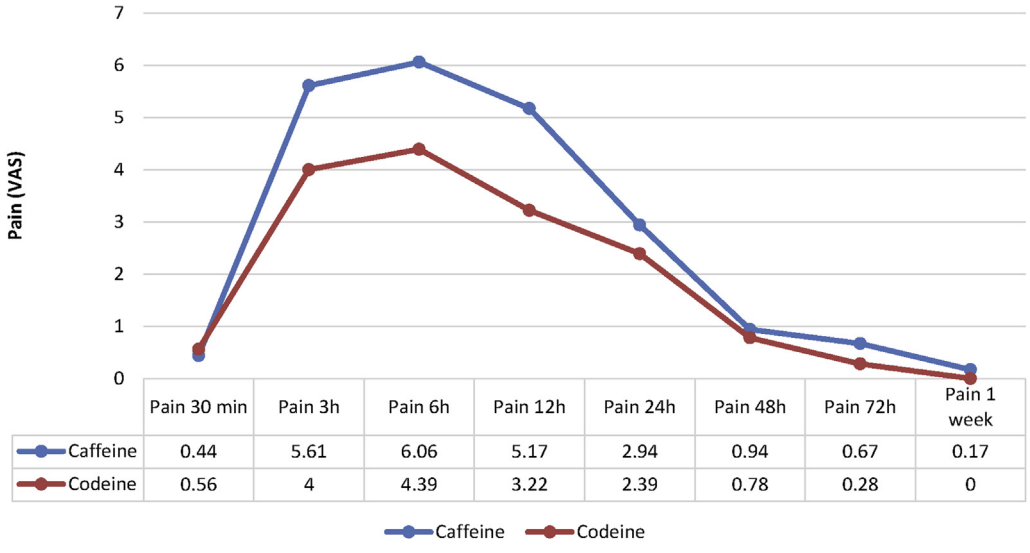

Chart 1. Evaluation of pain between caffeine and codeine groups at different times.

significant differences among the first, second, and third days. Significant changes during the study were also reported in the codeine group.

Chart 2 shows the trend for inflammation during this study for each group.

The patients were followed up for 3 and 6 months post-operatively to determine the odds of failure in implant surgery and peri-implantitis. The clinical and radiographic evaluations did not show any osseointegration complications in the two groups.

4. Discussion

In this triple-blind study, it was observed that the mean pain severity reported by patients in the codeine group was significantly lower than that in the caffeine group up to 12 h after implant surgeries. However, from the first day after the surgery up to 1-week, the difference was not significant. It was also observed at all time intervals that the severity of swelling after surgery in the caffeine group was significantly lower than that in the codeine group.

Implant surgery usually causes mild to moderate, and rarely severe, pain and swelling, depending on the time and difficulty of surgery, bone quality, amount of trauma to the bone and soft tissues, tissue responsiveness of the patient, the amount of trauma to the bone, local anesthetic effect, and removal time (Spin-Neto et al., 2014; Hashem et al., 2016; Gonzalez-Santana et al., 2005; Kim et al., 2013; Goiato et al., 2016). Therefore, it is necessary to prescribe the appropriate analgesic and anti-inflammatory drugs for implant surgery patients.

Studies have shown that use of NSAIDs to control implant surgery complications can impair implant osseointegration (Kalyvas & Tarenidou, 2008; Gomes et al., 2015; Cai et al., 2015; Alissa et al., 2009; Winnett et al., 2014; Sakka and Hanouneh, 2013; Jeffcoat et al., 1995; Karabuda et al., 2007). It seems that NSAIDs have negative effects on bone formation postoperatively through inhibition of Cox-2 enzyme (Gomes et al., 2015). However, it has been shown that this negative effect is temporary and does not affect the final bone formation. Some other studies suggest that this effect might be more destructive, so there is still need for further research in this area (Gomes et al., 2015; Cai et al., 2015; Alissa et al., 2009). New studies regarding the indications of NSAIDs for managing pain after implant surgery have shown conflicting results too, in some cases suggesting that long-term use of NSAIDs (over a week) might impair osseointegration of implants (Gomes et al., 2015; Cai et al., 2015; Alissa et al., 2009; Winnett et al., 2014; Sakka and Hanouneh, 2013; Jeffcoat et al., 1995; Karabuda et al., 2007). On the other hand, Macedo et al. reported in 2015 that caffeine has antioxidant, anti-mutation, angiogenic, and anti-inflammatory properties (Macedo et al., 2015), which is useful for osseointegration. It also has vasoconstrictor effects on peripheral vessels.

Therefore, performing a clinical trial in order to find a suitable protocol seems essential in selecting appropriate analgesics and anti-inflammatory drugs that do not interfere with osseointegration after dental implant surgery.

Studies have shown that analgesics containing an opioid, like codeine, are effective in decreasing average pain after surgery (Raisian et al., 2012; Forbes et al., 1994; Barasch et al., 2011; Moore et al., 2011; Nauta et al., 2009). Evidence and some studies have also shown that caffeine affects adenosine receptors in the central nervous system, which could decrease pain (Tavares & Sakata, 2012; Sawynok, 2011a,b). However, the differences between caffeine and codeine supplements in controlling pain and inflammation have not been examined specifically in previous studies.

Kuroi et al. reported in 2015 that factors associated with post-operative pain after dental implant surgery include the presence of underlying diseases such as hypertension and diabetes, duration of surgery, premedication, bone quality, the levels of preoperative anxiety and postoperative swelling, and the number of implants. Factors associated with simultaneous pain and swelling after surgery include bone quality, blood pressure, and diabetes (Kuroi et al., 2015).

Our study ensured the same surgical protocol and also the same health conditions for both patient groups; therefore, we excluded patients who had systemic problems. We used the same anesthetic technique for all the patients, while the degree of trauma and surgery time were equalized as far as possible by selecting an equal number of implants and the same anatomic sites, with sufficient bone width and height. The Implantium system was used for both groups, and every procedure was performed by one surgeon.

The number of cases used for this research was sufficient, and more than some other studies (for example, Spin-Neto, Gonzalez-Santana, Kuroiand Hashem et al.), which investigated pain, swelling, or anxiety after implant surgeries (Hashem et al., 2016; Gonzalez-Santana et al., 2005; Kuroi et al., 2015; Spin-Neto et al., 2014).

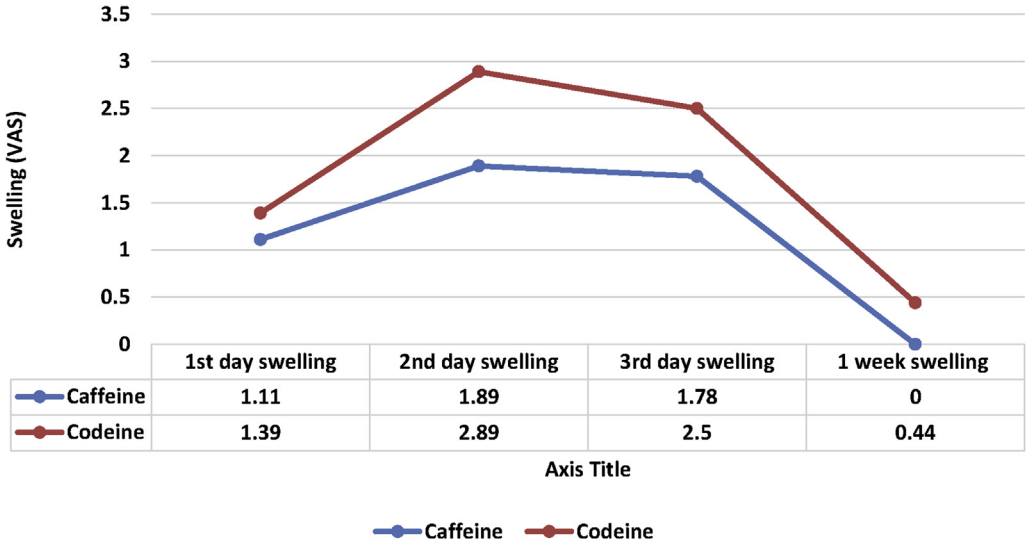

Chart 2. Evaluation of swelling between caffeine and codeine groups at different times.

Not prescribing analgesic in such cases is unethical, because bone drilling in implant surgery is a painful procedure. Recent studies (Raisian et al., 2012; Merry et al., 2010) showed that acetaminophen is more powerful than placebo in decreasing postoperative pain, so we prescribed either acetaminophen codeine or acetaminophen caffeine for our cases. Placebo was not used in this study. Furthermore, the dose of 20 mg of caffeine or codeine is acceptable from a pharmacodynamic viewpoint, and can reinforce the analgesic effect of acetaminophen (Raisian et al., 2012; Merry et al., 2010).

Postoperative pain severities at 30-min, 3-h, 6-h, 12-h, 1-day, 2-day, and 1-week intervals were measured. We observed that patients' pain during this period (from the beginning to the end of the study) decreased significantly over time. It is noteworthy that pain reached a peak in both groups at the 6-h postoperative interval.

Most of the patients had little or no pain 30 min after surgery, due to a successful local anesthesia effect; however, pain began 3 h postoperatively in both groups, in line with the anesthetic agent's half-life, and decreased over time until the 1-week interval. Studies by Urban et al. and González-Santana et al. also showed the highest pain levels 6 h after implant surgery (Gonzalez-Santana et al., 2005; Urban and Wenzel, 2010).

It was observed that pain severities in the codeine group at 3- and 12-h intervals postoperatively were significantly lower than those in the caffeine group. However, at other intervals, pain experience was not significantly different between the two groups. Even at 3-, 6-, and 12-h postoperative intervals, the level of pain across the two groups was recorded as moderate (VAS was between 3 and 7). In other words, the analgesic effects of caffeine, with a little delay, were close to those of codeine at all intervals.

The explanation for this finding relates to the effects of codeine on μ-receptors in the brain (Yoon et al., 2016). This action is relatively stronger and faster than the blocking of adenosine receptors by caffeine (Baratloo et al., 2016a,b). Codeine is also metabolized in the liver, where it is converted into morphine, causing more analgesic potential. Usually 5–10 per cent of codeine is converted into morphine (through the process of demethylation), so 30 mg of codeine is considered equivalent to 3 mg of morphine. The capacity for codeine metabolism can vary in different individuals (Straube et al., 2014). Some side-effects, such as constipation and nausea – as with most narcotics – have been attributed to codeine metabolism (Straube et al., 2014; Baratloo et al., 2016a,b).

It should be noted that the severity of pain expressed was approximately the same (in the majority of cases it was mild to moderate) in both groups. Generally, the analgesic effect of caffeine was close to that of codeine. In addition, caffeine does not have the side-effects of opioids derived from codeine (Baratloo et al., 2016a,b). According to a study by Raisian et al., in 2012, caffeine can be used as an analgesic in combination with acetaminophen and aspirin, and their combination also could raise the analgesic effect without increasing the dose (Raisian et al., 2012). Caffeine has an adenosine-like structure; therefore, it competes for A2A receptors and may inhibit these receptors and thus decrease pain (Nauta et al., 2009; Tavares & Sakata, 2012; Sawynok, 2011a,b). Hypnic headaches and migraine headaches can be controlled by caffeine (Nauta et al., 2009; Sawynok, 2011a,b).

In our study, inflammation in the caffeine group was significantly lower than that in the codeine group on the first, second, and third days. However, after 1-week no significant differences were seen between codeine and caffeine. The severity of swelling in both groups changed significantly over time. This peaked in both groups on the second day postoperatively and from the third day until a week after surgery it decreased. Both groups exhibited the lowest amount of swelling after a week.

Factors such as trauma during surgery, bone grafting, sinus lifting, mental nerve repositioning, increasing the number of implants, and duration of surgery can cause premature swelling after surgery (Spin-Neto et al., 2014;; Gonzalez-Santana et al., 2005; Kim et al., 2013; Kuroi et al., 2015; Goiato et al., 2016). Since the authors performed single-unit implant surgery in the posterior mandible, with minimum trauma and without bone grafting, inflammation and swelling were not seen in patients on the first postoperative day. Furthermore, swelling increased on the second day after surgery and reached a peak in our study, consistent with research by Gonzalez-Santana et al. (2005).

Severity of swelling in the caffeine group was less than that in the codeine group, so it was concluded the anti-inflammatory effect of caffeine was significantly stronger than that of codeine, which might be attributed to the vasoconstrictor mechanism of caffeine in blood vessels of the maxillofacial area by affecting the A1 receptors and stimulating the sympathetic nervous system. This process would increase the release of catecholamines and stimulate the renin-angiotensin-aldosterone axis. Published articles support this idea of the vasoconstrictor nature of caffeine resulting in a significant decrease in inflammation compared with codeine (Chaturvedi et al., 2009; Baratloo et al., 2016a,b; Echeverri et al., 2010; Robertson et al., 1978, 1984).

The severity of inflammation after oral surgeries, especially in the absence of an infectious process, decreases on the third day until the first week postoperatively (Raisian et al., 2012; Pasqualini et al., 2005; Costa et al., 2015; Pouchain et al., 2015). The results of our study confirm this trend in both groups.

As an opioid, codeine is a slightly stronger painkiller. Opioid painkillers work by mimicking the action of natural pain-reducing chemicals called endorphins that are produced in the brain and spinal cord. Codeine acts on the same opioid receptors as natural endorphins, and this blocks the transmission of pain signals sent by the nerves to the brain. This means that even though the cause of the pain may remain, less pain is actually felt. Solpadeine Plus capsules, tablets, and soluble tablets contain 8 mg of codeine, which in combination with the paracetamol is effective at relieving mild to moderate pain.

Caffeine is a weak stimulant that may enhance the painkilling effects of paracetamol. It may also counteract any drowsiness caused by the codeine.

Effective pain management must take these mechanisms into consideration when choosing medication to prevent and alleviate postoperative pain. We can simplify the process by classifying drug options into two broad categories: non-opioids and opioids (Bryce et al., 2014). Opioid medications carry a risk of abuse or addiction by either the patient or non-medical users. For these reasons, consideration of non-opioid strategies for pain management can be beneficial (Sinatra et al., 2005).

Our study showed that non-opioid alternatives are an acceptable way to control postoperative pain. Therefore, it is important to recognize the efficacy of non-opioid treatment options, such as acetaminophen and NSAIDs for postoperative pain management.

Finally, it should be remembered that complying with general rules and methods for postoperative care can be effective in reducing pain and swelling after surgery. Use of cold compresses, avoiding the use of tobacco, proper rest, and protecting the target area are non-pharmaceutical, but effective, ways to reduce pain and swelling (Goiato et al., 2016; Dejkam et al., 2015).

5. Conclusion

According to this study, codeine-containing analgesics are significantly more efficient than caffeine-containing ones in reducing postoperative pain. It was also concluded that caffeine-

containing analgesics are significantly more efficient than codeine-containing ones in reducing postoperative swelling, within the first 3-days. As a result, caffeine-containing analgesics are effective and acceptable in reducing both postoperative pain and swelling. Therefore, non-opioid analgesics can be used effectively in pain management.

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Conflict of interest

None.

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