A Preliminary Study on the Effects of Self-Reported Dietary Caffeine on Pain Experience and Postoperative Analgesia

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Background: Caffeine reduces the amount of analgesic medications necessary to provide postoperative pain (POP) relief and augments treatments for headaches and dental pain. Despite considerable evidence of its beneficial effects, little is understood about the role of dietary caffeine consumption on baseline pain sensitivity or POP following oral surgery.

Method: Baseline experimental pain testing (quantitative sensory testing [QST]) using four stimulus modalities was conducted on 30 healthy adults (53% females) before surgical extraction of four third molars. Self-reported caffeine ingestion was reported before QST, and on the day of surgery, preoperative and postoperative caffeine plasma concentrations (CPC) were measured by mass spectrometry. POP ratings were obtained at timed intervals.

Results: In QST, compared to subjects who self-reported no caffeine intake, those who self-reported caffeine ingestion demonstrated a higher pain sensitivity, particularly, on ramp and hold sustained heat at 44°C and 46°C, as well as a lower heat pain threshold and tolerance ($p=0.05$). Differences approached significance ($p=0.06$) in POP between subjects with CPC above 300 ng/mL and those with CPC below 300 ng/mL. Specifically, those with >300 ng/mL CPC had a slightly lower POP (mean 2.43, range 0–5) compared to those with <300 ng/mL CPC whose POP ratings were slightly higher (mean 2.89) with a greater variability (range 0–9.5).

Conclusions: Self-reported, dietary caffeine intake was associated with higher QST ratings with lower threshold and tolerance particularly on heat pain modalities. External factors (i.e., analgesic dosage) may have played a role in the analgesic effects of caffeine on POP in oral surgery, especially in individuals with CPC exceeding 300 ng/mL who reported lower pain.

Introduction

CAFFEINE IS A commonly used psychoactive drug in the world. It is remarkably prevalent in common dietary substances ranging from coffee and tea to chocolates; the quantity of caffeine consumed varies widely between cultures.¹ Caffeine is commonly coformulated in medications because of its analgesic adjuvant effects and can be found combined with medications, such as aspirin, acetaminophen, and ibuprofen.^{1–3} There are no studies examining the effects of dietary intake of caffeine on human pain experience.³

Baseline pain sensitivity, also termed experimental pain or quantitative sensory testing (QST), can be useful to evaluate pain perception in different populations and predict postoperative pain (POP).^{4,5} Examining baseline pain sensitivity

might lend important information to predict acute pain following invasive procedures and might inform clinicians on better pre-, intra-, and POP management. Recent studies suggest a varied response to caffeine in human experimental settings, preclinical studies, and in human treatment venues. For example, caffeine has been shown to lower the threshold and increase tolerance in human experimental pain.^{6,7} Even though caffeine is known for its analgesic effects, how dietary caffeine influences pain is not well understood. Thus, human QST coupled with examination of caffeine intake can provide insight regarding how caffeine might influence pain responses.

Caffeine acts as an antagonist to both adenosine A_{2A} and A_{2B} receptors and its analgesic activity in animals and humans is reportedly due to blockade of the peripheral

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pronociceptive action of adenosine.³ Also, caffeine's analgesic activity activates central noradrenergic pathway, which is a regulatory pain-suppressing mechanism.⁸ The half-life of caffeine ranges 3–5 hours, but factors, such as genetics and other concurrent drugs, can increase or decrease caffeine half-life.⁹ Preclinical studies have shown that caffeine's effects vary by supplementing, inhibiting, or having no effect on analgesia depending on the caffeine dose and route of administration.^{3,9–11} A recent review found that caffeine doses below 50 mg/kg are often inactive, while caffeine doses between 35–100 mg/kg usually produce antinociceptive effects.³

Clinically, caffeine is used as an adjuvant analgesic to treat headaches,^{2,12} and postpartum,^{2,12} dental,^{2,12} and cancer pain.^{12,13} The analgesic effects of psychotropic medications (i.e., amitriptyline) can be inhibited by caffeine, while the antinociceptive effects of aspirin and ibuprofen are increased.³ One could surmise that the dietary intake of caffeine could affect analgesic efficacy as well. In fact, for certain medical conditions with pain, patients are advised to avoid ingestion of caffeine, while in others (e.g., migraine), caffeine can be pain-relieving and is formulated in over-the-counter medications (e.g., Excedrin).¹⁴

Third molar surgery provides an excellent model for studying acute pain in humans for several reasons. These surgeries are commonly performed in dentistry,^{15–17} and have very standardized protocols that facilitate comparison across settings.^{16–18} Hence, using a third molar model to assess dietary caffeine in conjunction with standard medications used during surgery can be beneficial to learn about potential influences of dietary caffeine on acute pain.

This research explores the influence of caffeine on two types of pain via two aims. First, it explored the effect of self-reported dietary caffeine on baseline pain sensitivity using four QST modalities. It was hypothesized that there would be an inverse relationship between an individual's baseline/experimental pain perception and their self-reported caffeine consumption as caffeine is known to en-

hance pain relief, especially in certain clinical treatments. The second type of pain to be examined was acute POP by observing associations between caffeine plasma concentrations (CPC) and individual self-reported POP following a third molar surgery. A subhypothesis sought to prove that subjects with higher postoperative CPC would report lower POP. Outcomes obtained from the study could be useful in uncovering whether dietary caffeine is beneficial or might mitigate pain relief after an oral surgery.

Methods

Subjects

Thirty young, healthy individuals representing four ethnic groups were recruited. For inclusion, all participants had a negative health history (ASA Classification I) and were not using herbal or prescription medications. All subjects had to undergo extraction of all four third molars, with a minimum of two impacted teeth to ensure POP. Subjects were recruited through the Oral and Maxillofacial Surgery Clinic at the University of Florida (UF). This study was approved by the UF Institutional Review Board.

Baseline QST session

Between 2 to 9 days before surgery, subjects were assessed on four QST modalities that lasted for ~90 minutes (described below; Fig. 1A). Standard QST modalities were counter balanced. Additionally, all subjects were naïve to QST. Body weight was measured on a calibrated scale and subjects were verbally asked to report any caffeine intake within 4 hours before testing.

Baseline/QST pain modalities

Thermal pain. Contact heat stimuli were delivered on the volar side of the subject's forearm beginning at 2 cm inferior to the elbow joint and moved 4 cm distal toward the wrist

FIG. 1. Timeline for baseline quantitative sensory testing and same-day surgery assessments. The top box (A) indicates the timing and protocol procedures for the baseline experimental testing session and related procedures, which were conducted 2–9 days before the day of surgery. The numbers below the line represent approximate time in minutes for the various components of the testing. The bidirectional arrow pointing to thermal pain and pressure pain indicate that these pain tasks were counter balanced. The bottom box (B) indicates an approximate timeline and protocol procedures conducted on the day of surgery.

for each subsequent trial. Intratrial stimuli were separated by 1 minute each and intertrial testing employed a 5-minute rest between tests. This pattern of testing is standardized to avoid habituation.¹⁹ A computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001) was used to assess heat pain threshold (HPTh) and tolerance (HPTo). Four trials of HPTh were obtained when the subject first determined the stimulus to be painful and pressed a button that automatically recorded the temperature. Four trials of HPTo were determined when subjects reached their maximum tolerance, at which time they pressed a button to stop the stimulus. The average temperature for each of the four trials when the stimulus was stopped comprised the scores for HPTh and HPTo.

Subjects also rated suprathreshold pain ratings of a "ramp and hold" (R&H) sustained thermal stimulus that administered 30 seconds of sustained thermal stimuli at 44°C, 46°C, and 48°C on the dorsal side of the forearm. When the target temperature was achieved, subjects rated the intensity every 10, 20, and 30 seconds using a 0–100 standardized scale. The averages of the three timed pain ratings at each designated temperature were used for the analyses.

Temporal summation of heat pain. Temporal summation (TS) was assessed by applying the thermode to the volar side of the forearm and administering a series of 10 trials of rapid, brief heat pulses, which were <3 seconds apart. Trials were conducted at two target temperatures, 49°C and 52°C. Subjects were instructed to provide intensity ratings on a 0–100 scale at the peak of each pulse. The averages of the pain ratings for each of the 10 trials at 49°C and 52°C were used as the TS ratings in the analyses.

Pressure pain. A handheld pressure algometer (Wagner Instruments) was used to assess pressure pain (PP) thresholds at three different body sites (masseter, trapezius, and ulna) bilaterally and randomly selected. The algometer was placed over a site and pressure was gradually increased by a constant rate of 1 kg/s for three trials. Subjects were instructed to respond when they first felt pain at which time the pressure rating was recorded. The average amounts of pressure for each trial at each of the sites were used in the analyses.

Cold pressor pain. To replicate deep pain, a cold 5°C circulating refrigerated water bath (Neslab) was used as subjects immersed their hand up to the wrist for up to 5 minutes. Cold pain (CP) threshold was assessed as subjects reported when they first felt pain and CP tolerance was determined when they could no longer tolerate the pain. Subjects rated intensity (CPInt) and unpleasantness (CPUnpl) every 15 seconds using 0–100 scales. The averages of the subject-reported pain ratings for CPInt and CPUnpl were used in the analyses.

Day of surgery

One attending surgeon performed all surgeries. According to recommended guidelines for intravenous sedation, subjects did not eat or drink 8 hours before surgery. Pursuant to routine sedation techniques, subjects received a continuous infusion of 0.9% sodium chloride and intravenous doses of midazolam and fentanyl; most patients received comparable doses of dexamethasone and ketoralac (see Results section). Before incision, local anesthesia was obtained using 2% lido-

caine with 1:100,000 epinephrine and 0.5% bupivacaine with 1:200,000 epinephrine at each extraction site.

Postoperative assessment

After surgery and immediately before discharge, subjects reported pain and side effects using a standard rating scale of 0–10. Beginning 6 hours after the surgery and then 4 times per day for 3 days at multiple timed intervals, subjects completed daily diaries of common symptoms that included pain and side effects (i.e., nausea), and also recorded medications (e.g., time, dose). Since electronic monitoring was not feasible, research staff spoke directly by telephone with subject postdischarge to ensure compliance with self-reports of postoperative data. The subject self-reports were used to determine levels of POP and analgesic use.

Blood plasma collection

Approximately, 5–10 mL of blood was collected into an EDTA tube via the intravenous line immediately before surgery. The postoperative blood draw was obtained within 45 minutes after the first fentanyl administration (Fig. 1B). Blood samples were placed on ice and then centrifuged within 30 minutes at 5000 rpm for 15 minutes at 5°C. Plasma aliquots were stored at –80°C until analysis.

CPC measurements

Caffeine concentrations were determined by a sensitive liquid chromatographic tandem mass spectrometric assay procedure. Plasma samples were processed as described previously.²⁰ Ammonium sulfate (60 mg) and internal standard (β -hydroxyethyltheophylline) were added to plasma samples (100 μ L), which were then acidified by addition of 100 μ L of 0.2 M sodium acetate (pH 4.5). Samples were briefly vortex mixed and then extracted with methylene chloride (1 mL) by high-speed shaking for 10 minutes, then centrifuged for 10 minutes at 2660 rpm. The upper aqueous layer was aspirated and discarded and the organic layer was evaporated to dryness under a stream of nitrogen. The remaining residue was reconstituted in 300 μ L mobile phase, transferred to vials, and 20 μ L were injected into the system. Chromatography was performed on a C18 column using a mobile phase consisting of 90% 10 mM ammonium acetate pH 4.5, 9% methanol, 1% tetrahydrofuran, and 0.05% formic acid. Caffeine was detected by single reaction monitoring with positive ion mode electrospray. The limit of quantitation was 50 ng/mL and the accuracy and precision were within 6%, which is below the 15% required by the FDA for assay validation.

Statistical analysis

Statistical analyses were run with SPSS 20.0. For pain ratings on QST, averages of multiple trials for each modality were calculated and comprised continuous variables in the analyses. POP ratings were continuous variables on a 0–10 scale. For associations, Pearson product moment correlations were conducted. Baseline caffeine was self-reported as a nominal variable of having consumed or not consumed caffeine within 4 hours of the testing. Nonparametric analyses were conducted to compare "with" versus "without" caffeine groups across QST modalities. Regarding POP and actual

CPC, the General Linear Model in SPSS was used to analyze differences between subjects with measurable CPC outcomes, accounting for a level of surgical difficulty, duration, recovery time, number of impacted molars, and body weight. Linear regression was used to test for predicting the caffeine amount and level of postoperative analgesia with sex, ethnicity, and age as covariates.

Results

Demographic and surgical factors

Thirty healthy individuals (53.3% females; 46.7% males) 18–29 years (mean 22.0 years, SD 3.5 years) without any premorbid conditions participated in the study. Four ethnic groups were represented: 20.0% Asians, 6.7% African Americans, 70.0% non-Hispanic whites, and 3.3% Pacific Islanders. Table 1 shows demographics. There were no significant group differences on demographic factors related to self-reported caffeine levels. The mean body weight among the study participants was 72.9 kg (range 53.3–119.5; SD 15.9).

All 30 participants had all four third molars extracted with the average surgery duration of 22:34 minutes (range 9:45–39:40; SD 8:22). Table 2 shows preoperative, perioperative, and surgical factors in relation to preoperative CPC. The number of impacted teeth, surgery extraction time, level of surgeon-rated difficulty, surgery duration, or recovery time in relation to preoperative CPC were not different.

QST/experimental pain modalities

Significant group differences were found between those who self-reported caffeine consumption and those who did not; whereby, the “with caffeine” group demonstrated significantly lower HPTh [$F(1,28)=4.865$, $p=0.04$] and tolerance [HPTo, $F(1,28)=12.164$, $p=0.002$] (Fig. 2). Compared to those “without caffeine,” the “with caffeine” group appeared more pain sensitive on virtually all other baseline QST modalities, which resulted in higher pain ratings on CPInt and CPUnt, TS at 49°C and 52°C, and sustained heat R&H at 44°C [$F(1,26)=4.797$, $p=0.04$], 46°C [$F(1,26)=4.598$, $p=0.04$], and 48°C, with two of the latter showing significant differences (Fig. 3). Thus, those with self-reported caffeine demonstrated higher pain ratings with lower threshold and

tolerance on most QST modalities compared to those who self-reported no caffeine consumption.

For PP, threshold was lower at the ulna and masseter sites among subjects who self-reported caffeine ingestion, but was slightly higher at the trapezius site. Since PP is reported in kilograms per seconds, it is shown separately (Table 3). The slight differences in mean pressure ratings were not found to be statistically significant between subjects who self-reported caffeine and those who did not. However, these may be clinically relevant as this modality is considered analogous to palpation utilized in clinical care⁵ and in revealing trigger points for certain pain conditions. This might prove to be useful prospectively as a screen for potential risk of increased pain sensitivity.

Preoperative and postoperative medications

As a part of standard sedation and pain management procedures, the medications utilized during surgery included fentanyl (mean 113.1 µg; SD 24.8), midazolam (mean 5.8 mg; SD 1.5), ketorolac (mean 26.0 mg; SD 10.4), and dexamethasone (mean 7.6 mg; SD 1.6). Dosages for each medication were within the standard limits and there were no statistically significant differences based on body weight, age, sex, or ethnicity. Based on patient reports, standard postoperative medication included acetaminophen/hydrocodone ($n=10.0\%$), hydrocodone ($n=40.0\%$), and oxycodone ($n=23.0\%$). They also recorded measures taken to alleviate symptoms, such as applying ice ($n=70.0\%$).

Preoperative and postoperative CPC in relation to POP

The first postoperative blood draw occurred within 11:41 minutes (range 9:14–15:21; SD 2:25) following surgery. Mean preoperative CPC was 324.2 ng/mL (range 0–1503.2, SD 455.3); postoperative CPC mean was 251.5 ng/mL (range 0–1877.8, SD 429.3). Body weight was not correlated with preoperative or postoperative CPC or analgesics. However, there was a significant correlation between body weight and POP at 6 hours ($r=-0.393$, $p=0.04$), but not with CPC.

POP ratings at 6 hours varied between individuals depending on CPC (Fig. 4). Based on plotted POP scores, patterns seemed to change at caffeine levels of 300 ng/mL. While that is the level at which there seemed to be less variability

TABLE 1. DEMOGRAPHICS GROUP DIFFERENCES OF THE STUDY SAMPLE

	Percentage of subjects in sample (n=30)	Self-reported caffeine before experimental testing ^a		Significance level
		With caffeine (n=5)	Without caffeine (n=25)	
Sex				
Male	46.7% (n=14)	14.3% (n=2)	85.7% (n=12)	$\chi^2=0.107$ ($p=0.743$)
Female	53.3% (n=16)	18.8% (n=3)	81.3% (n=13)	
Ethnicity				
African American	6.7% (n=2)	0.0% (n=0)	100.0% (n=2)	$\chi^2=0.686$ ($p=0.877$)
Asian	20.0% (n=6)	16.7% (n=1)	83.3% (n=5)	
Non-Hispanic White	70.0% (n=21)	19.0% (n=4)	81.0% (n=17)	
Pacific Islander	3.3% (n=1)	0.0% (n=0)	100.0% (n=1)	
Age				
Years, mean (range)	22.0 (18–29)	22.8 (19–29)	21.9 (18–28)	$p=0.489$

^aExperimental pain testing occurred 2–9 days prior to surgery.

TABLE 2. THIRD MOLAR SURGERY INFORMATION AND CAFFEINE PLASMA CONCENTRATION BY SURGICAL FACTORS

	Preoperative CPC		Significance
	Mean CPC caffeine ≤ 300 ng/mL (range, SD) (n = 23)	Mean CPC caffeine > 300 ng/mL (range, SD) (n = 7)	
Total sample (n = 30)	104.37 (0–283.77; 93.98)	1046.27 (300.79–1503.20; 419.34)	F(1,28) = 106.70, $p < 0.001$
Means (range; SD)			
Number of impacted teeth	2.96 (2.0–4.0; SD 1.0)	3.14 (2.0–4.0; SD 1.07)	$\chi^2 = 0.307$, $p = 0.580$
Total surgery duration (minutes)	22:34 (9:45–39:40; SD 8:22)	18:22 (10:40–26:27; SD 5:30)	F(1,28) = 2.394, $p = 0.133$
Individual molar extraction time (minutes)			
Molar 1	12:20 (0:30–27:30; SD 9:08)	12:52 (0:30–22:51; SD 8:01)	F(1,28) = 0.059, $p = 0.809$
Molar 16	1:39 (0:14–4:36; SD 1:08)	1:52 (0:30–4:36; SD 1:48)	F(1,28) = 0.122, $p = 0.730$
Molar 17	7:56 (1:23–18:46; SD 4:23)	5:49 (1:23–13:09; SD 4:18)	F(1,28) = 2.28, $p = 0.142$
Molar 32	13:05 (2:35–29:35; SD 7:02)	11:05 (2:35–18:09; SD 5:51)	F(1,28) = 0.829, $p = 0.370$
Surgeon's rating of extraction difficulty (1–5 scale)			
Molar 1	1.87 (1.0–4.0; SD 0.94)	2.43 (1.0–4.0; SD 1.13)	$\chi^2 = 5.845$, $p = 0.119$
Molar 16	2.07 (1.0–5.0; SD 1.17)	2.43 (1.0–5.0; SD 1.51)	$\chi^2 = 7.553$, $p = 0.104$
Molar 17	3.27 (2.0–5.0; SD 0.83)	2.57 (2.0–3.0; SD 0.54)	$\chi^2 = 9.547$, $p = 0.023$
Molar 32	3.30 (1.0–5.0; SD 1.12)	2.57 (1.0–3.0; SD 0.79)	$\chi^2 = 9.024$, $p = 0.060$

CPC, caffeine plasma concentrations.

FIG. 2. Group differences in baseline experimental heat pain threshold and tolerance between participants with self-reported caffeine versus without self-reported caffeine. * $p < 0.05$; ** $p < 0.01$. HPTH, heat pain threshold; HPTO, heat pain tolerance. Self-report was based on ingestion of caffeine within 4 hours before baseline experimental testing. With self-reported caffeine ($n = 5$; 16.67%); without self-reported caffeine ($n = 25$; 83.33%).

in pain scores, it is also an amount comparable to CPC observed with 0.5 mg/kg dose of caffeine after 8 hours of ingestion.²¹ In this sample, among individuals with > 300 ng/mL postoperative CPC, POP results appeared lower. Mean pain rating for this group was 2.4 out of 10 (range 0–5.0; SD 1.6). In contrast, among subjects with CPC < 300 ng/mL, POP ratings were more variable. While the mean was 2.9 out of 10, indeed, quite similar to the > 300 ng/mL group, the range was greater, from 0 to 9.5 (SD 2.7). Differences between

FIG. 3. Group differences in baseline experimental pain modalities and ratings between participants with self-reported caffeine versus without self-reported caffeine. * $p < 0.05$. Experimental pain modalities: RH, “ramp and hold” (sustained heat) at 44°C, 46°C, 48°C; TS, temporal summation at 49°C and 52°C; CP_INT, cold pressor intensity; CP_UNPL, cold pressor unpleasantness. Caffeine ingested and self-reported within 4 hours before baseline experimental testing. With self-reported caffeine ($n = 5$; 16.67%); without self-reported caffeine ($n = 25$; 83.33%).

TABLE 3. MEANS OF PRESSURE PAIN TESTS

Testing sites	With caffeine	Without caffeine	Significance
Trapezius (kg/s) (range; SD)	6.55 (3.45–12.06; 3.27)	5.99 (3.01–13.87; 2.75)	F(1,29)=0.169, $p=0.684$
Masseter (kg/s) (range; SD)	2.62 (1.71–4.14; 0.97)	2.72 (1.68–5.41; 1.04)	F(1,28)=0.037, $p=0.850$
Ulna (kg/s) (range; SD)	4.50 (2.41–7.79; 2.18)	4.97 (2.21–11.15; 2.35)	F(1,29)=0.161, $p=0.692$

those with <300 ng/mL compared >300 ng/mL CPC and POP at 6 hours approached statistical significance (Adjusted $R^2=0.505$, $p=0.06$) even though no baseline differences were shown on sex, ethnicity, and age, they were covariates in the test. No significance was found between the two groups on pain ratings at bedtime on day of surgery or at days 1–3 postoperatively (data not shown).

Discussion

These results lend new evidence regarding the effects of caffeine on baseline pain/QST and shed further insight on postoperative analgesic effects among healthy young adults undergoing oral surgery. This study revealed significant differences and consistent patterns in QST ratings, depending on subjects' self-reported caffeine consumption. Individuals who self-reported caffeine ingestion showed increased pain sensitivity, including lower threshold and tolerance. Juhl *et al.*²² showed that a minor orofacial surgical procedure (i.e., third molar extraction) could lead to both central and peripheral sensitization. Using QST procedures of pinprick and electrical stimulation, they detected central sensitization that lasted for about 1 week even with local anesthetics and analgesics. This current study varied slightly by employing different stimulus modalities (e.g., HP, PP, CP, and TS) to show increased pain sensitivity among individuals in response to caffeine consumption.

Notably, a plasma caffeine concentration of 300 ng/mL corresponds to the value observed after a 0.5 mg/kg dose of

caffeine after 8 hours of ingestion, which approximates the amount of caffeine in a soft drink.²¹ This study results approached significance in revealing an association between postoperative CPC and POP, showing a slight inverse relationship between caffeine levels >300 ng/mL and lower POP ratings. Previous research also supports that caffeine enhances pain relief in some subjects, but not all.² A possible explanation for this variability could be the actual dose of caffeine ingested preoperatively, variations in metabolism rates, and the half-life affecting analgesic effects of caffeine. Caffeine doses that are either too low or high may diminish analgesic enhancement.³ Derry *et al.*² concluded that caffeine doses higher than 100 mg are usually effective as an analgesic adjuvant. Based on that study, the caffeine levels detected in this present investigation were much lower than what would be considered effective and may be the reason that the current findings did not show a distinctive trend between caffeine and POP. However, these current findings lend information regarding sensitivity to caffeine among individuals with levels >300 ng/mL, who reported overall lower POP, suggesting even minimal levels might be antinociceptive in select patients. Hence, caffeine could potentially be clinically beneficial especially in acute surgical procedures, but may be dose dependent and medication dependent.

An inverse relationship between an individual's baseline/experimental pain perception and their self-reported caffeine consumption was expected. However, this study found that baseline pain sensitivity was higher among individuals who self-reported caffeine consumption before baseline testing. This increased sensitivity could be a result of the stimulating properties of caffeine,²³ which could elicit heightened somatic attention and augmented response to painful stimuli. It might also be that caffeine's influence on pain relief is effective mostly as an adjuvant when administered with other medications. Since this population had no medication at the time of experimental testing, only caffeine's stimulating properties were pronounced with no synergistic effects with pain relieving or other medications (as in the postoperative setting).

Our secondary aim sought to show a decrease in pain perception in subjects with higher postoperative CPC compared to subjects with lower concentrations, and that was partially supported, but mainly in individuals with CPC >300 ng/mL; below that, patterns were not detected. As such, this study did not find a distinct dose-dependent response. It is evident that a number of factors influence the analgesic effects of caffeine and further research, with more controlled parameters might yield more evident associations between CPC and POP.

For example, a preferred study design would include a larger sample size and detailed information regarding caffeine habits, including withdrawal experiences, ascertained at baseline. Next, it would be optimal to ensure all subjects are caffeine free for 4 hours before testing to obtain baseline

FIG. 4. Individual postoperative caffeine plasma concentrations and postoperative pain levels 6 hours after Surgery. ◆ represents 1 subject rating. ■ represents 2 subjects' ratings. ● represents 3 subjects' ratings. $R^2=0.505$; $p=0.064$.

CPC. After initial baseline QST, a 100 mg caffeine dose would be administered as that has generally shown to produce analgesic effects. To account for metabolism variations, subjects would then complete questionnaires for a waiting period of 1 hour, followed by a postcaffeine repeat QST session. Three days before surgery and 3 days postoperatively, participants would record detailed caffeine consumption. On the day of surgery, as participants have ingested nothing for 8 hours, a preoperative CPC would be obtained, and then a 100 mg caffeine dose would be administered before any other medication administration. Timed blood draws would occur within 45 minutes of the first medication administration, and then every 30 minutes for up to 4 hours as part of a larger postoperative session. These data would allow more objective measures for comparing differences of caffeine effects on baseline/experimental pain. Such a design also allows for analyzing variations in caffeine metabolism and synergistic effects with other medications via pharmacokinetic/pharmacodynamic measures from timed blood draws over time from pre- to postsurgery. All these data could be used in a predictive model to conclude how dietary caffeine can affect baseline pain sensitivity and POP after oral surgery.

This study is unique in that dietary caffeine was studied with the intention of examining its analgesic effects in third molar surgery. Even though a few studies have been conducted with caffeine and oral surgery,^{2,9,12} they examine caffeine as an adjuvant rather than considering how dietary intake of caffeine could affect POP. This preliminary study begins to uncover whether dietary caffeine is useful in POP control after oral surgery. Another point to note is that most published studies that examine caffeine and POP are preclinical or experimental studies where caffeine administration is combined with other medications. This study provides new findings regarding the relationship with circulating caffeine and baseline pain sensitivity in the laboratory as measured with four QST modalities.

Limitations observed during the QST session include that baseline caffeine intake was obtained by self-report from the subjects and information about subjects' daily dietary use of caffeine was not obtained. If caffeine was administered to the subjects, then there would have been more control over caffeine intake among subjects. More extensive details about daily use of caffeine can also lend more information about how dietary caffeine might influence baseline/experimental pain in humans. This study also did not assess chronic caffeine intake among subjects. This may have been an important factor since studies have shown that pain receptors, such as adenosine A1 and cannabinoid CB1, can be altered by chronic caffeine use.²⁴ However, such findings have been primarily in preclinical samples and it is not known how long-term dietary caffeine intake in humans might influence this antinociceptive action.

An additional drawback observed when obtaining CPC from the day of surgery is that all subjects had nothing to eat or drink for 8 hours. Thus, the majority of participants had very low amounts of caffeine in their system. This might explain the great variance observed with caffeine levels (especially <300 ng/mL) and POP. Notably, in a regular caffeine user, a substance withdrawal effect can be seen if the person refrains from consumption for 12–24 hours. Some symptoms of caffeine withdrawal are muscle pain, nausea, and vomiting, which can be also seen after third

molar surgery.²⁵ Since the current surgery protocol required subjects to refrain from ingesting anything for 8 hours preoperatively plus considering the time undergoing surgery, it is likely that some subjects experienced caffeine abstinence. Due to this acute absence of caffeine consumption, it is conceivable that some subjects may have been experiencing caffeine withdrawal increased pain sensitization,²⁵ which could be reflected in the lower CPC (especially <300 ng/mL) seen in those subjects who also reported higher POP. While this current study did not record regular caffeine use, it should be considered in future investigations to better understand the influence of acute caffeine abstinence and substance withdrawal on POP.

Besides caffeine, other factors may influence pain perception. For example, there are reported sex-dependent influences on pain.²⁶ While this study found no sex differences in caffeine influence on baseline or POP, including sex-specific factors in future studies might offer improved insight into differential effects of gender and caffeine on POP. Since this is a preliminary study, our results should be interpreted with caution, and needs to be replicated in a larger sample with more carefully controlled baseline, preoperative and postoperative measures, including additional timed measures and more longitudinal recordings of caffeine consumption.

In conclusion, self-reported caffeine ingestion was consistently related to increased baseline pain sensitivity across multiple stimulus modalities (e.g., heat, cold, TS) with increased pain ratings and decreased threshold and tolerance (except PP modality). This suggested an interesting role of caffeine on heightened pain sensitivity in an experimental setting. Conversely, for acute POP following third molar surgery, caffeine seemed to have an antinociceptive effect with individuals with CPC >300 ng/mL reporting relatively less variable and lower POP. While it is tempting to conclude that caffeine has a dose-dependent effect in analgesia, indeed, there are a number of other factors that can influence caffeine metabolism in humans, such as the dosage, time of administration, concomitant medication, and caffeine tolerance (or withdrawal), all of which can influence whether caffeine increases or decreases pain. Yet, in general, caffeine seemed to show lower pain ratings postoperatively in an oral surgery population among individuals with a dietary caffeine concentration >300 ng/mL.

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