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Research Article

The Efficacy of Preemptive Analgesia Using a Non-Opioid Alternative Therapy Regimen on Postoperative Analgesia Following Block Bone Graft Surgery of the Mandible: A Prospective Pilot Study in Pain Management in Response to the Opioid Epidemic

Cameron Y.S. Lee, DMD, MD, PHD, MPH[1], and Jon B. Suzuki, DDS, PHD, MBA[2]*

[1]*Private Practice in Oral, Maxillofacial and Reconstructive Surgery, Aiea, Hawaii 96701; Clinical Professor of Periodontology and Oral Implantology; Kornberg School of Dentistry, Temple University, Philadelphia, PA 19140, USA*

[2]*Professor (Emeritus) of Microbiology and Immunology (School of Medicine); Professor (Emeritus) of Periodontology and Oral Implantology (School of Dentistry); Kornberg School of Dentistry, Temple University, Philadelphia, PA 19140, USA*

Abstract

Purpose: The authors examined whether a novel alternative treatment regimen that is opioid-free administered preemptively 3 days prior to block bone graft surgery of the mandible has a preemptive analgesic effect on the intensity of pain at the graft harvest site during the 72-hour postoperative period.

Materials and methods: This qualitative prospective pilot study was conducted in a single office in 2018. Thirty-four patients were randomly divided into two groups: Group A (14 patients) were provided the opioid-free regimen three days prior to surgery; Group B (20 patients) were not provided the opioid-free regimen, but only opioid analgesics. The primary outcome variable was pain intensity measured at the bone graft harvest site by each patient using a 10-point pain intensity scale (PIS) from 0 (no pain) to 10 (worst pain possible). Secondary outcome variables measured were the total number of opioid rescue analgesics used over a 72-hour postoperative period and the time interval to initial use of opioid analgesics to relieve the postoperative pain in both cohort groups. A P value less than .05 was statistically significant.

Results: Patients in Group A recorded lower pain intensity scores at all time intervals. The median time interval to use of the first opioid rescue analgesic after surgery in Group A was 4.3-hours compared with 1.9 hours for patients in Group B. The average postoperative pain intensity score for Group A patients was 5.6 on the 0 to 10 PIS. The average number of opioid rescue analgesics consumed was 2.3 tablets per day over the 72-hour postoperative period. For Group B patients, the average postoperative pain intensity score was 7.1 on the PIS and average number of opioid analgesics used was 3.8 tablets per day over the 72-hour postoperative period.

Conclusions: The results of the study illustrate that postoperative pain intensity was lower in the group of patients with the opioid-free regimen when used preemptively compared to the group of patients that did not receive the opioid-free regimen. Further, use of this novel treatment alternative in managing postoperative pain resulted in less consumption of opioid analgesic medication and increased the time interval to first use of an opioid analgesic. The results of this pilot study support the need for novel alternative and complementary analgesic strategies.

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***Corresponding author:** Cameron Y.S. Lee, DMD, MD, PHD, MPH, Oral, Maxillofacial and Reconstructive Surgery, Department of Periodontology/Oral Implantology, Kornberg School of Dentistry. Temple University, 98-1247 Kaahumanu Street. Suite 314. Aiea, Hawaii 96701, USA, Tel: 808-484-2288; E-mail: CLee555294@aol.com

Introduction

The opioid abuse, addiction, and overdose epidemic in the United States is at a public health crisis and has caught the attention of the Food and Drug Administration (FDA), National Institute of Drug Abuse (NIDA), National Institutes of Health (NIH), Drug Enforcement Agency (DEA), the Centers for Disease Control (CDC), and medical and dental organizations such as the American Medical Association (AMA), American Dental Association (ADA), and the American Association of Oral and Maxillofacial Surgeons (AAOMS) [1-5]. On October 26, 2017, President Donald Trump declared the opioid crisis a national public health emergency under the federal Public Health Services Act [6].

Opioid analgesics (synthetic variants of opium) have always been important in the management of acute and chronic pain. But when used by patients improperly the consequences can be unforgiving. After marijuana, prescription painkillers are the second most abused drug [7]. In 2016, greater than 11 million Americans misused

opioid drug prescriptions. Since 1994, deaths from opioid use more than quadrupled and parallels the increased number of opioid prescriptions [8-10]. In 2015, there were over 33,00 deaths reported involving opioids.[10] Further, over 2 million citizens are addicted to opioids, In 2015, greater than 12 million reported misusing opioids.[11] Such increased morbidity and mortality can also be attributed to injudicious prescribing and has increased the spread of HIV and hepatitis C infections and heroin use [11,12].

While in office, former President Barrack Obama and his administration did address the opioid epidemic as millions of dollars were invested in drug treatment and monitoring programs. As part of this call to action, the Centers for Disease Control developed guidelines for clinicians in the prescribing of opioids [13]. However, the opioid epidemic cannot be solved completely by our federal government. Clinicians must also be held accountable [14]. In the American Association of Oral and Maxillofacial Surgeons White Paper on opioid prescribing for acute and postsurgical management, clinicians should decrease the number of opioid drug prescriptions to control the post-operative pain to reduce opioid misuse and abuse [15]. Most important, clinicians can elect to prescribe non-opioid medications as a safer alternative to opioid drugs to manage postsurgical pain and avoid prescribing long-acting and extended release opioids.

Preemptive analgesia has received considerable attention in the past few years. The goal of preemptive analgesia is to control and decrease postsurgical pain when it is most intense prior to exposing the patient to the surgical procedure [15]. This will reduce the reliance of opioid analgesics to control the postoperative pain, lead to a faster return to daily life activities and reduce the cost of overall patient care [16,17]. Several clinical trials established that direct links with preemptive analgesia decreases postsurgical pain resulting in less dependence on pain medication and increased patient comfort and satisfaction [18-23]. Acute pain is due to an inflammatory cascade that occurs in the tissues and results in chemical, mechanical and thermal nociceptive stimuli from the surgical procedure [18,24]. Preemptive analgesia attempts to inhibit nociceptive signals from peripheral and central pain pathways that prevents release of chemical mediators, such as histamine, substance P, bradykinin and prostaglandins that results in primary hyperalgesia at the site of tissue injury and may last for several hours after tissue injury [15,18,25]. Hyperalgesia during surgery in the oral cavity is due to peripheral sensitization of periosteal and mucosal receptors from large amounts of prostaglandin release that appears one hour after the surgical procedure. This facilitates peripheral and central sensitization before tissue trauma and injury from the surgical procedure [26-28]. A reduction in sensitization is believed to reduce postsurgical hyperalgesia, allodynia and the magnitude and duration of postsurgical pain that could influence the need for rescue analgesics, post-surgically [18,25,27].

Although controversial regarding its effectiveness in controlling postsurgical pain, preemptive analgesia has been studied in the surgical removal of impacted third molars with different pharmacologic agents because of the moderate to severe patient response to pain that occurs 6 to 8 hours, postsurgery [16,17,19-21,23]. However, the severity of postsurgical pain after harvesting monocortical blocks of bone from the posterior mandible and ramus in preparation for placement of dental implants in the jaws has not been studied. The painful stimuli of soft tissues due to periosteal and muscle dissection and ultimately, the osteotomy to harvest the block of bone from the posterior mandible will cause moderate to severe postoperative pain and swelling.

Interestingly, current research with opioids in preemptive analgesia has revealed minimal clinical efficacy in controlling postsurgical pain [25,28]. Because of the opioid epidemic, the authors evaluated a novel opioid-free alternative treatment regimen during the preemptive analgesic stage to control postoperative pain at the bone graft harvest site at the ascending ramus and posterior mandible in preparation for dental implant surgery. Like removal of impacted mandibular third molar teeth and orthognathic surgery that requires advanced surgical skill and can be challenging even for experienced surgeons, the postoperative recovery observed in the maxillofacial region from harvesting bone from the mandible is associated with an acute inflammatory response that includes pain, bleeding, soft tissue edema and ecchymosis [29,30]. For the surgical patient who completes any of these surgical procedures, the first 24 hours after surgery are considered the most excruciating. As an anesthesia strategy, preemptive analgesia may decrease the pain intensity associated with block bone graft surgery and decrease the number of opioid analgesics during the postoperative recovery period.

The VEGA Oral Care Recovery Kit evaluated in this study is opioid-free and has been shown to accelerate wound healing, decrease pain, edema and ecchymosis [31]. It consist of 16 active ingredients that are monographed in the Homeopathic Pharmacopeia of United States (HPUS) and recognized for their accelerated healing properties. However, there are no published articles in the peer-reviewed medical and dental literature as a preemptive analgesic for controlling postoperative pain. The hypothesis of this study is that preemptively managing pain before its onset with this non-opioid alternative regimen may effectively reduce the pain intensity and number of opioid rescue analgesics consumed in the postoperative period. Specific goals of this study are to evaluate if the VEGA Oral Care Recovery Kit administered 3 days prior to block bone graft surgery of the mandible would produce a preemptive analgesic effect compared with no treatment with patients who underwent harvesting of monocortical blocks of bone from the posterior mandible and ramus with local anesthesia. The primary outcome variable is pain intensity measured at the bone graft harvest site. Secondary outcome variables measured are the total number of opioid rescue analgesics used over the 72-hour postoperative period and the time interval to use of the first opioid rescue analgesic.

Materials and Methods

Study Design and Participants

This prospective qualitative pilot study was conducted on a group of 34 patients in a single office (CYSL) in 2018. Demographic characteristics for both groups are summarized in Table 1. Gender was measured as a binary variable, while race was measured as a categorical variable. The primary outcome variable was pain intensity measured at the bone graft harvest site using a 10-point pain intensity scale (PIS) from 0 (no pain) to 10 (worst pain possible). Secondary outcome variables measured are the total number of rescue opioid analgesics used over a 72-hour postoperative period (Table 2 and 3) and the time interval to initial use of an opioid rescue analgesic (Table 4). A P value less than .05 was statistically significant.

Patients included in the study were over 18 years of age and diagnosed with either atrophy in the vertical or horizontal dimension of the maxilla or mandible and referred for bone graft reconstructive surgery in preparation for dental implant surgery. All patients were identified as either physical status class I or II according to the American Society of Anesthesiologists for this elective surgical

procedure in an office-based setting under local anesthesia. Excluded from this study were patients with a history of opioid or alcohol misuse, recreational drug abuse, chronic pain and past medical history of treatment for chronic pain. A total of 42 monocortical blocks of bone were harvested from the twenty-nine patients from the ramus and posterior mandible as described by Pikos [32]. Every patient included in this study was informed of the primary diagnosis, treatment options, surgical procedure and goals of this prospective pilot study. Written and verbal informed consent from each patient and ethical approval was obtained prior to initiation of this study.

Patients were randomly divided into 2 groups. Group A patients (14 in preemptive treatment group) received the opioid-free regimen prior to surgery and the instructions on it use. In addition, each patient was prescribed five tablets of an opioid rescue analgesic (5mg hydrocodone/325mg acetaminophen). Group B patients (20 in control group) only received a prescription of opioid analgesic (total of 15), 5mg hydrocodone/acetaminophen 325mg after the surgery to control the postsurgical pain. All patients were prescribed chlorhexidine gluconate 0.12% mouthwash that was to be used twice per day for a period of seven days.

Study Protocol

All 34 patients completed bone graft surgery under local anesthesia with vasoconstrictor. To harvest the monocortical block grafts, local anesthetic consisting of 2% lidocaine with 1:100,000 epinephrine was administered for nerve block of the inferior alveolar nerve and buccal soft tissue infiltration at the bone graft harvest site. The average dose used at the bone graft harvest site was 7.2 ml. At the recipient bone graft site, the average dose of local anesthesia was 5.4 ml. The operation time was recorded from initial mucosal incision to placement of the last suture.

Monocortical blocks of bone harvested from the buccal posterior and ascending ramus of the mandible were used to increase the vertical and horizontal dimensions of the future implant sites (Figure 1-3). Bone graft average size harvested from the mandible was width 3-4mm; length 10-20mm and height 8-12mm. Of the 14 patients in Group A, five patients had two monocortical blocks of bone harvested from the bilateral posterior mandible to reconstruct implant sites in the anterior maxilla. Eight patients in Group B had two monocortical blocks of bone harvested from the bilateral posterior mandible to reconstruct the anterior or posterior maxilla in preparation for future implant surgery.

Study Variables

Primary Outcome Variable: To evaluate postoperative pain, immediately after the completion of the surgical procedure all patients began to complete the pain scale as instructed. Patients were instructed on how to complete the 10-point pain intensity scale (PIS) regarding postoperative pain intensity that recorded pain from 0 (no pain) to 10 (worst pain experienced). The primary outcome variable is the postoperative pain intensity recorded from the results of the intensity scale (PIS). All participants were instructed to record their pain intensity scores at 4, 8, 12, 16, 24-time intervals over the next 72 hours after surgery. An assumption could be made that the recording of low pain intensity scores correlates with an increased time interval to use of opioid rescue analgesics and in a reduction in the amount of rescue analgesic used. Such an assumption is based on the hypothesis that the opioid -free alternative regiment has a preemptive analgesic effect.

Table1: Patient Demographics.

	Group 1 (n=14)	Group 2 (n=20)
Female	13	16
Male	1	4
Ethnicity		
asian	13	17
white		2
other	1	1
ASA Classification		
1	2	4
2	12	16
3		

Group 1: VEGA Oral Care Kit
Group 2: Control Group

Table 2: Group 1 Opioid Rescue Analgesics Consumed over 72 Hours.

	POD 1	POD 2	POD 3
Average Postoperative Pain Intensity	6.3	5.5	5
*Average Number of Opioids	3.5	2	1.5

POD: Postoperative Day
*Average number of opioids used per 24 hours

Table 3: Group 2 Average Opioid Consumption Over 72 Hours.

	POD 1	POD 2	POD 3
Average Postoperative Pain Intensity	8.5	7.5	5.5
*Average Number of Opioids	5.5	4	2.5

*Average number of opioids used Per 24 hours.

Table 4: Time Interval to Use of First Opioid Analgesic.

	Group 1	Group 2
Time Interval (hr)	4.3	1.9

Group 1: VEGA Oral Care Kit
Group 2: Control Group

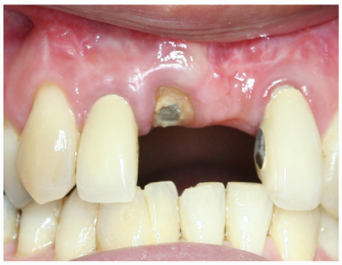

Figure 1: Clinical photograph of 42-year old Asian female missing two anterior maxillary incisor teeth causing psychological embarrassment and anxiety.

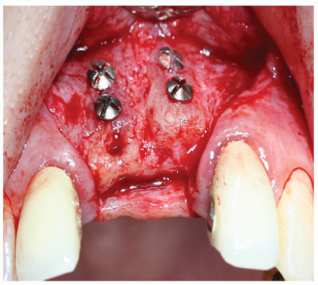

Figure 2: Two monocortical blocks of bone harvested from bilateral posterior ascending ramus of mandible four months ago rigidly fixated to maxilla using micro screws now successfully incorporated with maxilla and ready for implant placement. Post-operative pain is most intense at harvest site during first 24-48 hours after surgery.

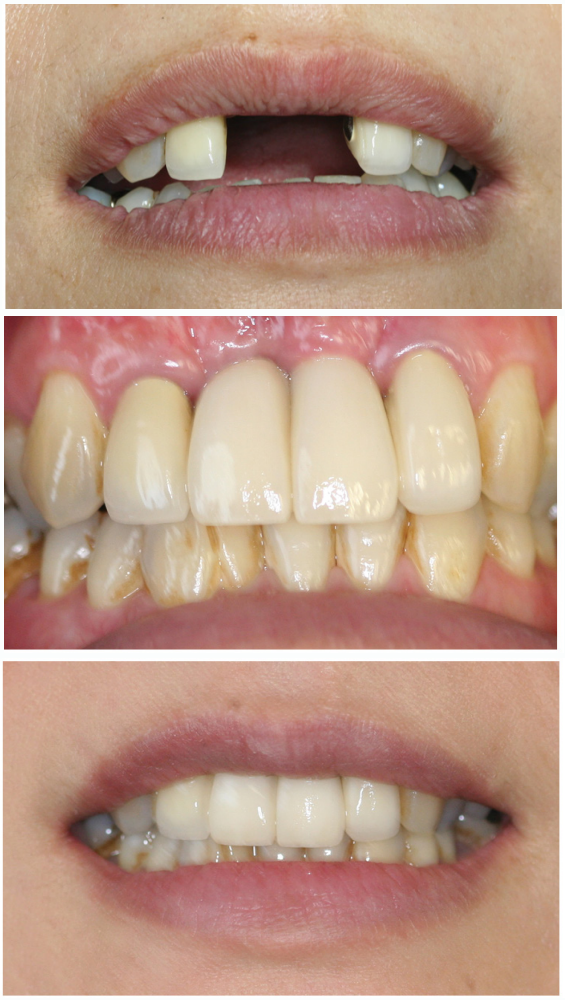

Figure 3: (A) Clinical photograph of patient without teeth. (B and C) Intraoral view of anterior maxilla restored with implants and zirconia teeth.

Secondary Outcome Variable: Secondary outcome variables evaluated were the total amount of opioid rescue analgesics consumed to relieve the postoperative pain over the 72-hour observation period and the time interval to administration of the first opioid rescue analgesic. Time interval is the time from the end of the surgical procedure to use of the opioid rescue analgesic.

Statistical Analysis

Data collected from this pilot study was entered into a statistical database and conducted using the Statistical Package for Social Sciences (SPSS for Windows, version 25; SPSS, Chicago, IL). The level of significance for all statistical evaluations was set at $P < .05$. Data are presented as a mean +/- standard deviation. Descriptive statistics were used to describe the data obtained for each clinical outcome. Unpaired student t test with a 95% confidence interval was used to compare mean postoperative pain intensity scores and use of rescue opioid analgesics. The Wilcoxon rank sum test was used to evaluate the time interval to use of opioid analgesics for both groups.

Results

A total of 40 adult patients were initially enrolled in the project. However, only 34 completed this study as 6 patients were removed from the research group due to lack of instructional compliance. Patients in Group A (14 in preemptive treatment) reported lower cumulative pain intensity scores throughout the 72-hour postoperative observation period compared to patients in Group B (20 in control group) (Table 2 and 3). The average postoperative pain intensity score for patients in Group A using the PIS was 5.6 over the 72-hour observational period (range 2 to 8.5). The average rescue opioid analgesic consumption over the 72-hour observational period was 2.3 tablets per day. For patients in Group B, the average postoperative pain intensity score was 7.1 (range 4.0 to 9.5) on the PIS. The average number of opioid analgesics consumed to relieve postoperative pain over the 72-hour observational period was 3.8 tablets per day. The median time interval to use of the first opioid rescue analgesic was 4.3 hours for patients in Group A. For patients in Group B, the median time interval to initial use of opioid pain medication was 1.9 hours.

Discussion

The intensity of postoperative pain is directly correlated with the type of surgical procedure the patient completes. Harvesting monocortical blocks of bone is similar to orthopedic and orthognathic surgery. All three types of surgical procedures commonly involve sharp dissection of the periosteum and muscles and surgical osteotomies with a high-speed cutting device such as a saw or fissure bur that result in moderate to severe postoperative pain and the need for opioid analgesics to control the pain. In surgery, strategies utilizing medications have been developed to decrease the postoperative pain response, including the use of opioids [25,28,33-40]. Opioid analgesics such as hydrocodone and oxycodone are commonly prescribed to reduce postoperative pain with or without non-steroidal anti-inflammatory drugs (NSAIDS) to provide pain relief. The dental profession is the third highest prescribers of opioid analgesics in the United States [41]. In a study by Denisco and colleagues [42] greater than 3 million patients each month are exposed to opioid analgesics from oral and maxillofacial surgeons. Opioids provide excellent pain relief, but are associated with drug tolerance, abuse and risk of addiction. This is the driving force for the search for an efficacious opioid-free alternative treatment regimen in the management of postoperative pain [43].

In a third molar study by Ong evaluating the efficacy of ketorolac on postoperative pain, the cohort of patients receiving the pain medication prior to surgery reported significantly lower levels of pain 12 hours post-surgery compared to the cohort who received ketorolac after surgery. In another study by Ong on rofecoxib, the group of patients who received the medication prior to surgery also reported decreased levels of pain over the first 12 hours post-surgery, compared to the group of patients who received rofecoxib after surgery. Studies by Presser-Lima and Fontanella and Zor also showed that preemptive analgesia administered to their patients resulted in less pain postoperatively. However, some studies failed to show the benefits of preemptive analgesia in the post-surgical, but rather a reduction in the amount of rescue drug used to control the postoperative pain, or in a delay in the time for the onset of pain experienced by the patient. Although the mechanism of action is not entirely known, a reduction or delay in the use of an opioid rescue analgesic may be due to the preemptive effect of the alternative therapy in our study. Stimulation of free nerve endings at the bone harvest site causes nociceptive pain.

As the VEGA Oral Care Recovery Kit is provided as an oral rinse, sublingual spray and topical gel, we hypothesize that all three routes of product administration contribute to the preemptive effects due to peripheral and possibly, central sensitization by blockade of nociception when applied three days prior to the date of the surgical

procedure and during the 72-hour postoperative period. The cohort group that used the opioid-free regimen preemptively experienced less postoperative pain (average pain intensity of 5.6 over the 72-hour observation period) than the control group based on the results of the pain intensity scale (average pain intensity of 7.1 over 72 hours, postoperatively). This observation was most significant at the 2 to 4-hour time interval after surgery when the reported pain was most severe for patients who were not treated preemptively. When used preemptively, onset of postoperative pain by a mean time of 4.3 hours before having to resort to use of any opioid rescue analgesic was observed. Such a preemptive analgesic affect may be due to inhibition of peripheral nociceptor input. For the surgical patient, a prolonged pain-free period from the end of surgery to the first use of an opioid analgesic to control the onset of postoperative pain is clinically significant. Like third molar surgery where the postoperative pain is most intense 2 to 4 hours after surgery, it has been the authors experience that the postoperative pain from harvesting monocortical blocks of bone at the osteotomy site is also most intense during this time interval.

This pilot study did have limitations, such as not being blinded and its small sample size. Studies that are not blinded can result in research bias, as both the research investigators and the patient know which treatment they were assigned to. As the study included only 34 patients, its small sample size may affect statistical power. As clinicians are well-aware of, postoperative pain is subjective, difficult to measure and perceived differently among different age groups, races and cultures. Such self-reporting by patients is another limitation of any study and could be influenced by several different factors. In both groups, over 90% of the patients in this qualitative study were Asian, female and older in age. Many of the participants in both groups limited their opioid consumption to control the postoperative pain. With advanced age, there may be a "blunting effect" on peripheral nociceptive function that decreases pain perception and the need for less analgesic medication [44,45].

Conclusion

This novel, opioid-free alternative form of therapy administered preemptively prior to block bone graft surgery resulted in decreased postoperative pain, less reliance of opioid analgesics and increased the time interval to use of an opioid analgesic. The authors believe that there is a definite role in the use of this novel opioid-free alternative therapy in managing postoperative pain. As the opioid-abuse epidemic is now at a national public health crisis with no end in sight, the use of a non-opioid product should be considered by every clinician who manages postoperative pain in their daily practice. Because of the paucity of studies in this area of pain management, long-term randomized clinical studies are needed as alternative and complementary treatment regimens do have a role in pain management in oral and maxillofacial surgery and implant dentistry.

References

1. Califf RM, Woodcock J, Ostroff S. A Proactive Response to Prescription Opioid Abuse. N Engl J Med. 2016;374(15):1480-5.
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain- United States, 2016. JAMA. 2016;65(1):1624-45.
3. Centers for Disease Control and Prevention. Opioid overdose: understanding the epidemic. August 30, 2017.
4. ADA announces new policy to combat opioid epidemic. American Dental Association News (03/26/18).
5. Opioid prescribing: acute and postoperative pain management. American Association of Oral and Maxillofacial Surgeons White Paper.
6. Rutkow L, Vernick JS. Emergency Legal Authority and the Opioid Crisis. N Engl J Med. 2017;377(26):2512-2514.
7. Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med. 2010;363(21):1981-5.
8. Paulozzi L, Jones C, Mack K. Vital signs: overdoses of prescription opioid pain relievers- United States, 1999-2008. MMWR;2011:60(43):1487-92.
9. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths--United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2016;64(50-51):1378-82.
10. National Institute on Drug Abuse, National Institutes of Health. Overdose death rates.
11. Prescription drug use and misuse in the United States: results from the 2015 National Survey on Drug Use and Health.
12. Comerci G Jr, Katzman J, Duhigg D. Controlling the Swing of the Opioid Pendulum. N Engl J Med. 2018;378(8):691-3.
13. Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical and prescription-opioid use and heroin use. N Engl J Med, 2016;374:154-63.
14. Murthy VH. Ending the Opioid Epidemic - A Call to Action. N Engl J Med. 2016;375(25):2413-2415.
15. Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. Am Fam Physician. 2001;63(10):1979-84.
16. Costa FW, Esses DF, de Barros Silva PG, Carvalho FS, Sá CD, Albuquerque AF, et al. Does the preemptive use of oral nonsteroidal anti-inflammatory drugs reduce postoperative pain in surgical removal of third molars? A meta-analysis of randomized clinical trials. Anesth Prog. 2015;62(2):57-63.
17. Alcântara CE, Falci SG, Oliveira-Ferreira F, Santos CR, Pinheiro ML. Pre-emptive effect of dexamethasone and methylprednisolone on pain, swelling, and trismus after third molar surgery: a split mouth randomized triple-blind clinical trial. Int J Oral Maxillofac Surg. 2014;43(1):93-8.
18. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg. 2005;100(3):757-73.
19. Gutta R, Koebn CR, James LE. Does ketorolac have a preemptive analgesic effect? A randomized, double-blind, control study. J Oral Maxillofac Surg. 2013;71(12):2029-34.
20. Bauer HC, Duarte FL, Horliana AC, Tortamano IP, Perez FE, Simone JL, et al. Assessment of preemptive analgesia with ibuprofen coadministered or not with dexamethasone in third molar surgery: a randomized double-blind controlled clinical trial. Oral Maxillofac Surg. 2013;17(3):165-71.
21. Moore PA, Brar P, Smiga ER, Costello BJ. Preemptive rofecoxib and dexamethasone for prevention of pain and trismus following third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod . 2005;99(2):E1-7.
22. Kim JH, Seo MY, Hong SD, Lee J, Chung SK, Kim HY, et al. The efficacy of preemptive analgesia with pregabalin in septoplasty. Clin Exp Otorhinolaryngol. 2014;7(2):102-5.
23. Mojsa IM, Stypulkowska J, Novak P, Lipczynski K, Szczeklik K, Zaleska M. Pre-emptive analgesic effect of lornoxicam in mandibular third molar surgery: a prospective, randomized, double-blind clinical trial. Int J Oral Maxillofac Surg. 2017;46(5):614-20.
24. Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. Curr Opin Anaesthesiol. 2006;19(5):551-5.
25. Kissin I. Preemptive analgesia. Anesthesiology. 2000;93(4):1138-43.
26. Savage MG, Henry MA. Preoperative nonsteroidal anti-inflammatory agents: review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98(2):146-53.
27. Woolf CJ, Chong MS. Preemptive analgesia- treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993;77(2):362-79.

28. Kelly DJ, Ahmed M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth. 2001;48(10):1000-10.

29. Savin J, Ogden GR. Third molar surgery- a preliminary report on aspects affecting quality of life in the early postoperative period. Br J Oral Maxillofac Surg. 1997;35(4):246-53.

30. Bortoluzzi MC, Guollo A, Capella DL. Pain levels after third molar surgical removal: an evaluation of predictive variables. J Contemp Dental Prac. 2011;12(4):239-44.

31. VEGA Oral Care Recovery Kit. StellaLife. Glenview, IL, 2016.

32. Pikos M. Block autografts for localized ridge augmentation. Part II. The posterior mandible. Implant Dent. 2000;9(1):67-73.

33. Dahl JB, Mřiniche S. Pre-emptive analgesia. Br Med Bull. 2004;71:13-27.

34. Lebrun T, Van Elstraete AC, Sandefo I, Polin B, Pierre-Louis L. Lack of a pre-emptive effect of low-dose ketamine on postoperative pain following oral surgery. Can J Anaesth. 2006;53(2):146-52.

35. Pozos-Guillen A, Martinez-Rider R, Aguirre-Banuelos P, Perez-Urizar J. Pre-emptive analgesic effect of tramadol after mandibular third molar extraction: a pilot study. J Oral Maxillofac Surg. 2007;65(7):1315-20.

36. Ong KS, Seymour RA, Chen FG, Ho VC. Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. Int J Oral Maxillofac Surg. 2004;33(8):771-6.

37. Ong KS, Seymour RA, Yeo JF, Ho KH, Lirk P. The efficacy of preoperative versus postoperative rofecoxib for preventing acute postoperative dental pain: a prospective randomized crossover study using bilateral symmetrical oral surgery. Clin J Pain. 2005;21(6):536-42.

38. Presser Lima PV, Fontanella V. Analgesic efficacy of aceclofenac after surgical extraction of impacted lower third molars. Int J Oral Maxillofac Surg. 2006;35(6):518-21.

39. Zor ZF, Isik B, Cetiner S. Efficacy of preemptive lornoxicam on postoperative analgesia after surgical removal of mandibular third molars. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(1):27-31.

40. Becker DE. Pain management: Part 1: Managing acute and postoperative dental pain. Anesth Prog. 2010;57(2):67-78.

41. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. JAMA. 2011;305(13):1299-301.

42. Janssen SA, Arntz A. Anxiety and pain: attentional and endorphinergic influences. Pain. 1996;66(2-3):145-50.

43. Cigerim L, Eroglu CN. Comparison of clinical efficacies of preoperatively initiated naproxen sodium-codeine phosphate in combination, diclofenac potassium, and benzylamine hydrochloride for pain, edema, and trismus after extraction of impacted lower third molar: a randomized double-blind study. J Oral Maxillofac Surg. 2018;76(3):495-502.

44. Gagliese L, Gauthier LR, Macpherson AK, Jovellanos M, Chan VW. Correlates of postoperative pain and intravenous patient-controlled analgesia use in younger and older surgical patients. Pain Med. 2006;9(3):299-303.

45. De Cosmo G, Congedo E, Lai C, Primieri P, Dottarelli A, Aceto P. Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. Clin J Pain. 2008;24(5):399-406.