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A Multimodal Analgesic Regimen Including Liposomal Bupivacaine Moderated Acute Pain Levels After Third Molar Surgery

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Abstract

This prospective, observational study was designed to moderate post-surgerical acute pain with a multimodal analgesic regimen including liposomal bupivacaine implemented for patients having third molar surgery. We hypothesized that acute pain would be reported no higher than 50% of the maximum possible.

Patients and methods: Inclusion criteria: ASA risk classification I or II, age 18-35 years, and at least two mandibular third molars below the occlusal plane. All subject-patients were enrolled after consent for surgery and treated with the multimodal analgesic regimen. Data at surgery were completed by patient and surgeon. Acute pain data were derived from a 14-day diary completed by subject-patients each Post-Surgical Day (PSD) for the past 24 hours. The primary outcome variable was subjects experiencing "worst pain" which was defined as the three highest values on a 7 point Likert scale. Secondary outcome variables were the time in number of days until "little or no pain" were recorded. This was defined as the two lowest values on the same Likert scale. We used descriptive statistics to report outcomes.

Results: Data were from 50 subjects. Thirty-two (64%) were female, median age was 22 years (IQR 19y, 26y), 48% were Caucasian, 25% Latino, 17% African-American, 10% other ethnicity. Surgeons' median estimate of degree of difficulty was 9 out of 28 (IQR 5,15). Median surgery time was 32min (IQR 20,40). Thirty-nine patients had maxillary third molars removed; 86%, were vertical or distoangular. Bone

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was removed from 35%. All had both mandibular third molars removed; 54% were mesioangular or horizontal. Bone was removed from 95%. Eleven (23%) patients reported worst pain on PSD1, 17 (35%) on PSD2, 18 (37.5%) on PSD3, and 12 (25%) on PSD4. By PSD6, half of the subject-patients reported little or no pain.

Conclusions: Outcomes for pain after third molar surgery were moderated by the multimodal analgesic regimen including liposomal bupivacaine, but the goal of all reporting pain 50% of the maximum possible was not achieved.

Introduction

The Joint Commission on Accreditation of Healthcare Organizations at the end of the last century challenged clinicians to better moderate acute pain, introducing a scale of 1 to 10 to measure pain levels in clinical settings. This designation was adopted widely as a "a fifth vital sign" [1]. Clinicians including oral and maxillofacial surgeons were challenged to do more to reduce acute pain. Prescribing immediate acting opioid drugs was a common component of an analgesic regimen to reduce post-procedure pain. However in the last decade, prescription (Rx) opioid drugs have been linked to opioid abuse and addiction, leading to increasingly larger numbers of deaths per year from drug overdose [2]. More recently, consuming opioid Rx after third molar removal has been associated with higher odds of persistent opioid use among young, opioid-naïve patients [3].

It would be ideal to eliminate opioid drugs entirely for acute pain management and their potential for misuse. This may be unrealistic after many procedures including third molar removal because many patients experience high levels of acute pain post-surgery. Current professional guidelines differ, and no consensus exists as to recommended maximum opioid Rx dosage [4]. To remedy this issue, the University of North Carolina (UNC) Oral and Maxillofacial Surgery (OMS) faculty adopted a multimodal analgesic regimen to limit opioid use in patients having third molar surgery in 2017. The multi-modal drug concept was suggested by the American Society of Anesthesiologists Task Force on Acute Pain Management in 2012, and the concept was expanded specifically to reduce opioid Rx use by Saverese and Tabler [5,6]. As a component of the UNC analgesic regimen, patients were given the option to fill two opioid Rx of four doses each; one Rx could be filled on the day of surgery, the other Rx on any post-surgery day. Both opioid Rx were to be filled electively if needed to moderate acute pain, with the opioid drugs taken along with the prescribed drugs in the analgesic regimen.

We reported some success in reducing the number of opioid doses in circulation with the analgesic regimen. Magraw et al in a retrospective pilot study reported 42% patients filled no opioid Rx [7]. Pham et al in a prospective observational study reported 60% subject-patients filled no opioid Rx [8]. By comparison as recently as 2018 Harbough et al accessing insurance data from 70,000+ patients having 3rd molar surgery, reported that 80% filled an opioid Rx [9].

Although the data we reported suggested clinicians could reduce the number of opioid Rx and opioid doses in circulation as a first step towards combating the potential for opioid addiction, we did not document levels of acute post-surgical pain. Patients could have endured higher pain levels to avoid taking opioid drugs.

The primary aim of this prospective, exploratory study was to assess acute pain levels experienced by patients for the 14 days after third molar surgery, all of whom were treated with the analgesic regimen as reported by Magraw et al. and Pham et al [7,8]. We hypothesized that a multimodal analgesic regimen including liposomal bupivacaine could not only limit opioid use, but also eliminate patients' reported highest levels of acute pain after third molar surgery.

Patients and methods

Study design/sample

We designed this prospective, observational study to assess data derived both at surgery and from a 14-day post-surgery diary. The study followed the Declaration of Helsinki on medical protocol and ethics and was approved by the UNC Institutional Review Board. We recruited and consented subject-patients for the study after they were given an appointment for third molar surgery following consultation. Surgery was conducted with a departmental adopted multimodal analgesic regimen, aimed at reducing inflammation sufficiently to reduce overall the number of opioid doses available to patients having 3rd molar surgery. All patients were treated by a senior level OMS resident supervised by the same OMS faculty attending surgeon (BK). We compensated patients for participation with an incentive fee if the diary was returned. For this prospective, exploratory study we sought participation from 50 subject-patients limited by the available departmental funds in 2018.

Inclusion criteria for the 50 subject-patients studied included being American Society of Anesthesiologists risk classification I or II, age 18-35 years, and having at least two mandibular third molars sited below the occlusal plane to be removed. Exclusion criteria were patients being treated for opioid addiction/abuse including those prescribed Suboxone or Methadone or allergy to any of the drugs in the multi-modal analgesic regimen.

All subject-patients had both mandibular 3rd molars and indicated maxillary third molars removed under intravenous (IV) sedation with midazolam and propofol in doses appropriate for the patient to maintain deep sedation. Each patient also received IV fentanyl 100 mcg.

The multi-modal analgesic regimen to reduce inflammation and the incidence of nausea post-surgery was identical to that reported by Magraw et al [7]. All patients received IV antibiotic prophylaxis with ampicillin 1.0gm or clindamycin 300mg. Dexamethasone 8 mg. and ketorolac 30 mg. were administered IV at the start of the procedure. We achieved local anesthesia with 2% lidocaine and 0.5% bupivacaine both with epinephrine as needed by field block in the maxilla and nerve block in the mandible. We placed topical minocycline 1 mg in each of the mandibular extraction sites for the drugs' anti-inflammatory and anti-microbial properties. We then infiltrated bupivacaine liposome suspension 1.3% buccal to each third molar site. Multiple injections were made into all tissue layers using a moving injection technique. This technique aimed to maximally cover an affected anatomic area. We injected 4 mL (53.2 mg) each side in the mandible and 1 mL (13.3 mg) each side in the maxilla (total of 10 mL or 133 mg for the removal of four 3rd molars). IV Ondansetron 4 mg to minimize post-surgery nausea was administered at completion of surgery just before discontinuing IV access.

We included cold therapy in the analgesic regimen. All patients were fitted with a head wrap containing bilateral frozen

gel packs and instructed to keep this in place for 24 hours, alternating the gel packs in place and refreezing at 30-minute intervals as often as possible. Patients were also given ibuprofen 800 mg to be taken on a scheduled basis at 8-hour intervals for the first 48-hours post-surgery.

Patients were given two Rx, each for four doses of hydrocodone 5 mg/acetaminophen 325 mg, one dated to be filled on the day of surgery and the other dated to be filled on any post-surgery day. Patients were counseled that opioid Rx could be filled at their discretion if pain was not adequately moderated. If requests were made for additional opioid doses beyond two opioid Rx, patients had to return for clinical evaluation. Additional doses of opioid Rx were given then at the clinician's discretion. Post-surgery antibiotics were prescribed only if there was a clinical indication to do so.

Data collection

We recorded demographic data (age, gender, ethnicity-race), prior 3rd molar symptoms, and clinical data at the time of the 3rd molar surgery. Clinical data recorded included: Third molar angulation as vertical/distoangular or mesial/horizontal, bone removal each surgery site, duration of surgery in minutes, and the surgeon's perceived difficulty of the surgery for each tooth with a 7pt Likert-type scale anchored with descriptors "least" and "most" difficult. The minimum difficulty score was 4 out of a possible 28.

Prior to being discharged, patients were given a 14-day post-surgery diary identical to the one reported by White et al that charted the patient's average and worst pain levels each day over the previous 24 hours on a 7-point Likert type scale anchored with associated descriptors, "no pain" to "worst pain imaginable"[10]. Other data recorded were responses to the Gracely pain scales with descriptive phrases for the unpleasantness and sensory domains, and number of opioid and other analgesic medication doses taken. Diaries were mailed back to the UNC data center via addressed-stamped envelopes.

Variables

The primary outcome variables were the subjects reported highest worst and average pain levels, 5 or greater out of 7 on a Likert-type scale, and responses to Gracely scale highest sensory phrases; "intense", "very intense", or "extremely intense" and Gracely scale highest unpleasantness phrases; "very distressing", "intolerable", or "very intolerable". Secondary outcome variables were the reported median number of days until "little" or "no" pain, 1 or 2 out of 7, and Gracely scale lowest sensory phrases; "faint" or "nothing", and Gracely scale lowest unpleasantness phrases; "slightly unpleasant" or "neutral". The primary predictor variable was the multimodal analgesic protocol.

Analyses

We scanned data from surgery and the 14-day diary directly with Teleform into an ACCESS database.

For this observational study we used descriptive statistics for reporting outcomes to describe demographic and clinical data. We reported subject-patients' pain levels each post-surgery day as reported in the diary.

Results

Day of surgery data from 50 consecutive, eligible patients treated in 2018 were available. Forty-eight completed diaries were returned including all who filled at least one opioid Rx. Of the 50 patients, 32 (64%) were females. The median age was 22 years (IQR 19y, 26y). Forty-eight percent were Caucasian, 25% Latino, 17% African-American, 8% Asian and 2% other ethnicity. Only one patient reported having pain from the 3rd molar region at the highest levels, 5 to 7 out of 7, in the week prior to surgery.

Thirty-nine patients had maxillary third molars removed; 86%, were vertical or distoangular. Bone was removed from 35%. All had mandibular third molars removed; 54% were mesioangular or horizontal. Bone was removed from 95%. Surgeons' median estimate of degree of difficulty for the surgery was 9 out of a possible 28 (IQR 5,15). Median surgery time was 32 min (IQR 20,40).

Sixty percent, 30 subject-patients, did not fill an opioid Rx, 8 filled one opioid Rx, and 12 filled two opioid Rx (Figure 1). Over 65% subject-patients reported taking at least 3 ibuprofen doses on PSD 1 and 2 suggesting reasonable compliance with this component of the analgesic regimen.

Eleven (23%) patients reported worst pain levels on PSD one, 17 (35%) on PSD two, 18 (37.5%) on PSD three, and 12 (25%) on PSD four (Figure 2). The median time until little or no pain was 5 days.

Five (10%) patients reported average pain levels 5-7/7 on PSD one, 8 (17%) on PSD two, 9 (19%) on PSD three, and 7 (15%) on PSD four. The median time until "little" or "no" average pain was 3.5 days.

Six patients (13%) reported Gracely scale highest sensory phrases: "intense", "very intense", or "extremely intense" on PSD one, 8 (17%) on PSD two, 9 (19%) on PSD three, and 5 (10%) on PSD four. The median time to lowest sensory phrases; "faint" or "nothing" was 9 days.

Two patients (4%) reported Gracely scale highest affective phrases: "very distressing", "intolerable", or "very intolerable" on PSD one, 4 (8%) on PSD two, 5 (10%) on PSD three, and 3 (6%) on PSD four.

The median time to lowest unpleasantness phrases; "slightly unpleasant" or "neutral" was 7 days.

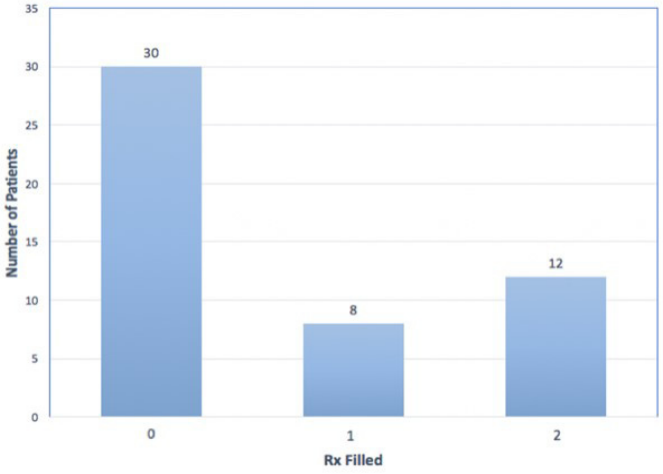

Figure 1: Number of patients who filled none, one, or two opioid prescriptions, each for four doses of hydrocodone 5 mg.

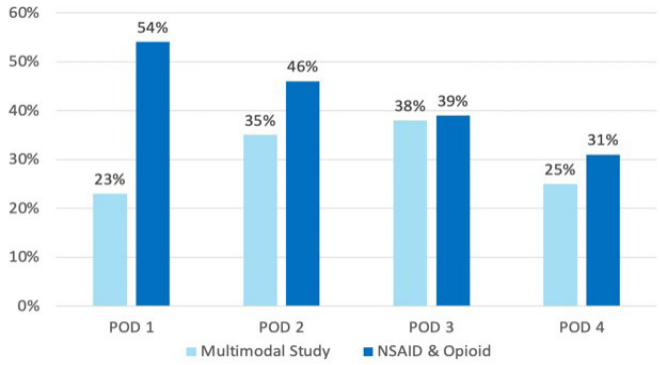

Figure 1: Comparison of subjects who reported worst pain 5-7/7 on Likert type scale by post-op day with report by White et al whose subjects reported using only an NSAID and an opioid.

Discussion

Data from this prospective, observational study suggested that a multimodal analgesic regimen designed to moderate acute pain after third molar surgery was effective, particularly if compared to a prior report by White et al of recovery with identical post-surgery data collection methods from 630 patients having third molar surgery in community practice and academic clinical centers [9]. However, we failed to eliminate all patients' reporting highest levels of acute pain, defined as the three highest values on a 7 point Likert scale.

The first two PSD encompass the time period when we would expect the highest acute pain levels and the maximum impact on moderating acute pain from our multimodal analgesic regimen. By comparison to earlier reported studies our data appear to support this expectation. For example, White et al reported worst pain levels as 54% on PSD one and 46% on PSD two even though over 90% of patients studied were taking combinations of NSAIDS and opioid drugs [9]. We report better outcomes by comparison for worst pain levels: 23% on PSD one and 35% on PSD two. White et al reported average pain levels 5-7/7 as 20% on PSD one and 19% on PSD two [9]. We report better outcomes for average pain levels 5-7/7: 10% on PSD one and 17% on PSD two.

Also, recovery to "little" or "no" worst pain, defined as the two lowest levels on a 7 point Likert scale, was shorter in our study, median 5 days as compared to White et al of 9 days [9]. Similarly, recovery to "little" or "no" average pain was shorter in our study, median 3.5 days as compared to White et al of 8 days [9].

Clinicians may wonder why data from our study suggested acute pain was not moderated as well on PSD two as compared to PSD one. The targeted time frame of the multi-modal analgesic regimen was the early post-surgery period, the first 24-36 hours. For example, Grant et al showed the median durations of analgesia after 1.0 and 2.0% liposomal bupivacaine to be 38 and 48 hrs [10]. Our 1.3% liposomal-bupivicaine was intermediate between the 1% and 2% dosages. Perhaps the expected duration of the liposomal bupivacaine and the 48 hour limited schedule advised for the NSAID, ibuprofen, explains these outcomes in our study. However, by measures with the 7 pt. Likert scale, acute pain was better moderated across the first few PSD in our observational study than was the case in the comparison report by White et al from 630 patients [9].

Establishing an acceptable target for moderating post-surgical acute pain by clinicians for patients must be a judgement since pain tolerance differs for each patient. Moore et al used a 50% reduction from maximum pain as criteria for rating effectiveness of combinations of analgesic drugs; opioids, NSAIDS, and actetaminophen [11]. Similarly, Martin et al studied clinically important changes in pain intensity after third molar surgery, reporting that successful pain reduction was 50% from a maximum possible [12]. If this target is translated to Likert scale pain levels 5-7/7, we did achieve this goal for two-thirds of our study patients but not all in the first days after surgery. This makes establishing a goal for clinicians' moderating acute pain after third molar surgery possible, while reserving opioid drugs for patients expected to have the highest pain levels post-surgery.

The data reported in this study has limitations. Even though the subject-patients included were diverse, the total number studied in this exploratory study was low, limited by available funds. Though clinicians could assume patients filled opioid Rx to achieve adequate pain control, we do not know what motivated them to fill opioid Rx or not. The public's increased awareness of the "opioid crisis" may have discouraged patients filling any opioid Rx, while tolerating higher levels of acute pain. The inconvenience of a trip to a pharmacy could also have discouraged filling a second opioid Rx. Also, it is not possible from our studies with the multi-modal analgesic regimen to determine which individual components was the most effective in reducing acute pain levels post-surgery. If a randomization of the component drugs in a future study is attempted, ethical considerations suggest that the study design must minimize the risk for subjects' having higher levels of acute pain.

Clinicians continue to face a challenge attempting to achieve adequate acute pain control while also decreasing opioid use and mis-use after procedures including third molar surgery. A multimodal analgesic regimen is suggested as effective current option in attaining both goals.

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This study #18-0047 was approved by the UNC IRB. The Clinical Trials.gov identifier for this study is: NCT03456141.

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