Editorial Commentary

Adjuvants add up: "ABCD" for post-procedural dental analgesia

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Dental procedure fear is prevalent worldwide and can be triggered by prior adverse events (including pain) surrounding a dental visit (1). Therefore, making patients comfortable throughout the process is important in dental, oral, and temporomandibular procedures. Postoperative pain can be debilitating, interfering with quality of life and rehabilitation. In addition, due to the current opioid epidemic, methods to address pain management that minimize the need for opioid prescriptions are preferred. This is particularly true in the United States where dental opioid prescriptions for pain management are sometimes considered excessive of need (2). Nerve blocks and wound infiltration with local anesthetics (LA), have been demonstrated (I) to provide analgesia postoperatively and (II) to decrease the use of opioids. Adjuvants such as buprenorphine, clonidine and dexamethasone (BCD), can increase the duration of the nerve block, further reducing the need for oral or intravenous (IV) opioids. In this editorial, we will consider a pilot study presented in "Efficacy of Local Anesthetic Wound Infiltration in Temporomandibular Joint Ankylosis Surgery for Control of Postoperative Pain: A Prospective, Randomized Controlled, and Double-Blinded Trial" (3), published in the *Journal of Oral and Maxillofacial Surgery* in March, 2021 and suggest two considerations for future studies: nerve blocks versus wound infiltration and LA adjuvants.

In the pilot study, Rao *et al.* (3) investigated the analgesic benefits of clonidine and dexamethasone, independently, as adjuvants to ropivacaine wound infiltration for temporomandibular joint ankylosis (TMJA) surgery. This pilot study included 45 patients, American Society of Anesthesiologists Physical Status (ASA PS) I and II, who presented to the All India Institute of Medical Science for bilateral TMJA evaluation. Two surgeons performed 3 types of surgeries. Intraoperative anesthesia was induced with sevoflurane or IV propofol. All patients were intubated and received 2 µg/kg fentanyl and 0.5 mg/kg atracurium, then anesthesia was maintained with desflurane. Patients received 100 µg/kg ondansetron upon emergence and were extubated. In addition, 15 mg/kg paracetamol (acetaminophen) was administered every 6 h.

Patients were randomly assigned to one of three wound infiltration groups: 0.25% ropivacaine; 0.25% ropivacaine supplemented with 0.5 µg/kg clonidine; and 0.25% ropivacaine supplemented with 0.1 mg/kg dexamethasone. At the end of surgery, wound infiltration was performed with a total volume of 0.2 mL/kg of the respective LA solutions and distributed in a 50:25:25 ratio to the subcutaneous tissue, masseter, and joint, respectively. The primary outcomes were cumulative fentanyl consumption and pain scores 24 h postoperatively. Pain scores were assessed both at rest and with movement using a 0–10 visual analog scale (VAS). Secondary outcomes included time to first rescue pain medication, patient satisfaction score at 24 h,

and postoperative nausea and vomiting (PONV).

Total postoperative fentanyl consumption was not significantly different between the intervention groups and did not correlate with age, weight, or duration of surgery. VAS pain scores, both at rest and with movement, were similar among the three groups as was the time to first rescue medication. Patient satisfaction score was significantly higher in the ropivacaine with clonidine group as compared to the other two groups. Finally, PONV, (a yes-no dichotomous variable) was statistically less in the ropivacaine with dexamethasone and the ropivacaine with clonidine groups as compared with ropivacaine only group. Decreased PONV is not surprising, as both dexamethasone and clonidine have documented antiemetic effects when given intravenously (4). Therefore, as the authors suggest, this antiemetic benefit may be a result of systemic absorption of these drugs.

The authors recognized that a major limitation of this study was the sample size for the proposed study with 3 different treatment groups. Therefore, it is difficult to ascertain the benefits of dexamethasone or clonidine as adjuvants to ropivacaine for wound infiltration in TMJA surgery. With this pilot study however, a more refined randomized controlled trial (RCT) can be designed with the correct power analysis.

As future studies are designed to address postoperative pain management after dental, oral/maxillofacial, and TMJA surgeries, it is important to consider the benefits of nerve blocks versus wound infiltration. Nerve blocks have been key analgesic tools for lower extremity joint (e.g., knee and hip) arthroplasty, but the sacrifice for adequate analgesia has included motor weakness, delaying joint mobilization. The analgesic benefits of wound infiltration over oral or IV opioids has had mixed results, but motor weakness is minimized (5). In a RCT comparing mandibular infiltration and mandibular nerve block for surgery, the nerve block was found to provide more profound anesthesia, as expected (6). However, postoperative pain management likely does not require such a dense LA block; wound infiltration may be adequate. Wound infiltration is convenient because it does not require accessing a proximal location of the primary nerve innervating the wound. However, during inflammation, LA used during wound infiltration may not be efficacious due to focal tissue acidosis whereas a proximal nerve block may be more appropriate. With either nerve blocks or wound infiltration, appropriate techniques need to be employed and an understanding of anatomy and normal variations may necessitate supplemental blocks to cover the entire surgical area (7).

It is important to consider both the LA and its concentration in wound infiltration. A high LA concentration is usually preferred however, one study in total knee arthroplasty (TKA) found that the total dose may be more important than concentration, as neither high concentration nor high volume provided superior analgesia (8). There may be concerns of toxicity with high LA doses, but multiple studies have demonstrated that standard LA concentrations used are not harmful to wound healing (9). A variety of LA can be used depending on the goal (7). If return of motor function is necessary, then a short-acting LA, like lidocaine, may be an appropriate choice. If longer analgesia with minimal motor block is preferred, a lower concentration of a long-acting LA, such as bupivacaine, is likely a better choice. In recent years, liposomal bupivacaine wound infiltration has gained popularity, theoretically decreasing the need for nerve blocks, with or without catheters, while ideally providing extended analgesia. However, in a meta-analysis by Singh *et al.* (10), the use of liposomal bupivacaine in TKA did not provide analgesic benefits over femoral nerve blocks, although they both provided analgesic benefits over oral and IV medication.

One method to improve the analgesic efficacy of LA is with adjuvants, which Rao *et al.* (3) attempted to do in this study. Epinephrine has been added to LA in order to cause focal vasoconstriction and theoretically slow systemic absorption thereby extending analgesic duration. Epinephrine has been reportedly used at 1:80,000 to 1:400,000 without tissue ischemia or cardiac complications in patients. However, epinephrine has not definitively been demonstrated to provide analgesic benefit (11). Ropivacaine is beneficial in that it provides some vasoconstriction without the epinephrine adjuvant.

Clonidine is an alpha-2 adrenergic agonist, blocking catecholamine release from presynaptic nerve endings when used as an adjuvant to LA. The addition of 30 µg of clonidine to 2 mL of 2% lidocaine for pain management in lower third molar surgery provided enhanced analgesia, compared to lidocaine supplemented with epinephrine as measured by lower pain scores and less need for rescue medication (12). A meta-analysis of RCTs of perineural clonidine as an LA adjuvant in nerve blocks demonstrated prolonged analgesia as compared to plain LA (13). Another alpha-2 adrenergic agonist that may provide analgesic benefit is dexmedetomidine. It has been demonstrated to prolong analgesia in wound infiltration in maxillofacial procedures (14). Of note, dexmedetomidine with wound

infiltration may provide better hemodynamic stability as compared to clonidine; this is important to consider, especially in outpatient procedures (11).

Dexamethasone has also been demonstrated to prolong the analgesic effects of LA. When dexamethasone was added to 2% lidocaine with epinephrine (1:200,000) in dental blocks for third molar surgery, analgesic duration increased by 60–110 min (15). A meta-analysis demonstrated that dexamethasone is beneficial in perineural administration for nerve blocks (16). A review on LA adjuvants for wound infiltration suggested that dexamethasone (8–16 mg) modestly improve pain scores after abdominal surgeries, for example (11).

Opioids are another class of analgesic adjuvants used in wound infiltration. The addition of buprenorphine at 30 µg to 2% lidocaine with epinephrine for inferior alveolar nerve blocks improved postoperative pain scores and extended analgesia from 3.5 to 12 h, as compared to plain LA or LA with intramuscular buprenorphine (12). The addition of 300 µg of buprenorphine to 0.5% bupivacaine and epinephrine resulted in prolonged analgesia by 20 to 36 h (17,18). There may be concerns regarding use of opioids due to the risk of respiratory depression after systemic absorption of the opioid. However, perineural administration requires less overall opioid than oral or IV administration, therefore, decreasing the risk of respiratory depression. If opioids are included, buprenorphine (which also exhibits anti-hyperalgesic properties) may be the best choice. Because it is an agonist-antagonist of the mu opioid receptor, it provides analgesia without euphoria (19). More importantly, there is a limit to the respiratory depression caused by buprenorphine. However, it is more resistant to naloxone reversal (20,21).

At the Veterans Administration Pittsburgh Healthcare System, we have used a multimodal three-drug combination with LA that has been demonstrated to synergistically prolong analgesic time after TKAs and total hip arthroplasty (THA) (22). We use a local anesthetic (A, usually 0.25 or 0.5% bupivacaine), buprenorphine (B, usually 300 µg/plexus), clonidine (C, usually 20 µg/plexus), and dexamethasone (D, usually 1 mg/plexus; this combination henceforth will be called ABCD). Analgesia provided by ABCD solutions can last twice to four times as long as compared to plain LA (23). While some of these components independently have been demonstrated to cause nerve damage at higher (i.e., supraclinical) concentrations, when combined at lower concentrations, they are less toxic (24) and provide superior analgesic effects (23). We have not used ABCD for wound infiltration but each of these components at higher concentration has been used and has provided prolonged analgesia with wound infiltration.

Management of postoperative pain after oral, dental and temporomandibular surgeries is challenging but provides many opportunities for research. Facial anatomy and variations thereof in the normal population may be more conducive to wound infiltration as compared to nerve blocks. In addition, liposomal bupivacaine for wound infiltration (if it were dispensed in small enough aliquots to minimize product waste, due to expense) may prove beneficial in the dental setting. Meanwhile a variety of LA can be used, but the inclusion of adjuvants with LA has not been well studied. In addition to individual adjuvants, we have found that a multimodal combination of adjuvants to LA, with the latter at a lower concentration than when used alone, not only decreases potential toxicity but also provides a synergistic increase in analgesic duration. This may provide overall benefit in oral and temporomandibular surgeries. This multimodal approach to wound infiltration for postoperative pain management may ultimately be as simple as A-B-C-D!

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Footnote

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