ANALGESICS

Evidence-based dental pain relief

BACKGROUND

The opioid addiction crisis in North America can be traced back to inappropriate prescribing of opioid analgesics to manage pain. In the 1990s advocacy groups lobbied the medical community to improve the management of chronic pain in the United States. This led to an increased use of opioid analgesics, especially those with delayed-release formulations, for pain relief. From 2000 to 2016, opioid prescriptions increased 10-fold, which resulted in increased availability and misuse of these addictive pain medications. The increase in emergency department visits for opioid overdoses was the ultimate outcome of this trend. Another contributing factor was a letter to the editor of the *New England Journal of Medicine,* which produced statements that were misrepresented to imply that addiction and dependence on opioid analgesics was rare. The safety and efficacy of oral analgesics have been further studied to develop better recommendations based on higher levels of evidence.

PAIN ASSESSMENT AND RELIEF STUDIES

Randomized Controlled Clinical Trials

A significant contribution to the knowledge of safe and efficacious oral analgesia was related to an outpatient methodology described in the 1970s. A pair of clinical pharmacologists developed and validated a method to assess the efficacy of analgesics for pain relief after outpatient third-molar extraction. The postoperative pain model showed sensitivity in distinguishing oral analgesics from placebos and other drugs. The usefulness of the clinical pain model was enhanced by the availability of a large potential population who required postoperative pain management. An estimated 3.5 million young adults undergo third-molar extraction annually.

This efficient pain assessment model was often used to evaluate newer nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen. It has been used for almost all of the analgesics marketed in North America.

In the study protocol, subjects require at least 1 tooth impacted in the lower jaw bone and are given local anesthesia and often intravenous sedation for this outpatient procedure. After surgery, the local anesthesia wears off, with pain intensity reaching moderate to severe levels. Subjects are then provided with one of the treatment options, usually in a parallel design. The options include a placebo and one of the medications being evaluated. A rescue medication is provided if the patient's pain is not adequately controlled. Pain is assessed before the drugs are administered and hourly as severe, moderate, slight, or none. Relief is judged to be complete, a lot, some, a little, or none. Measures include pain intensity difference (PID) from baseline, the sum of all hourly PIDs weighted over time (SPIDs), and the sum of hourly pain relief scores weighted over time (TOTPARs). Sometimes additional measures are also obtained, such as when pain is reduced by 50% of the initial pain (Pain Half-Gone) or visual analog scale (VAS) pain ratings. Findings from randomized controlled clinical trials indicate that placebo is the least effective in relieving pain and ibuprofen 400 mg is the most effective.

Systematic Reviews and Meta-analyses

Because of the many similarities in these clinical trials, which include patient population, outcome pain, and pain relief measures, multiple clinical research studies investigating the same analgesic can be combined in systematic reviews. With these combinations, a meta-analysis can be performed.

Cochrane Reviews

Using the meta-analyses of individual quantitative reviews, Cochrane Collaborative investigators have created a probability statistic common to all of the studies. The number-needed-to-treat (NNT) can be used to compare all the analgesic medications used to relieve third-molar extraction pain. NNT refers to the number of people who must be treated using a specific dose of a pain medication to have 1 person achieve clinically meaningful relief of pain. The lower the NNT, the better is the analgesic in relieving pain.

For oral pain medications, an NNT of 1.5 is considered excellent, 2.5 would be very good, and 10 would be ineffective. When the analgesics commonly prescribed in North America are considered, 2 500-mg tablets of acetyl para-aminophenol

Table 1. Relative Analgesic Efficacy of Oral Analgesics

Drug Formulation	Trials/Subjects	NNT (95% CI)
Aspirin 600/650 mg	45/3581	4.5 (4.0–5.2)
APAP 1000 mg	19/2157	3.2 (2.9–3.6)
Celecoxib 400 mg	4/620	2.5 (2.2–2.9)
Ibuprofen 400 mg	49/5428	2.3 (2.2–2.4)
Oxycodone 10 mg plus APAP 650 mg	6/673	2.3 (2.0–6.4)
Naproxen 500/550 mg	5/402	1.8 (1.6–2.1)
Ibuprofen 200 mg plus APAP 500 mg	2/280	1.6 (1.4–1.8)

(Courtesy of Moore PA, Hersh EV: Analgesic therapy in dentistry: From a letter to the editor to an evidence-base review. *Dent Clin N Am* 63:35-44, 2019.)

(APAP) or acetaminophen have an NNT of 3.2, 2 400-mg ibuprofen tablets have an NNT of 2.3, and 2 tablets of oxycodone 10 mg plus APAP 650 mg have an NNT of 2.3 (Table 1). The combination of ibuprofen 200 mg and APAP 500 mg has an NNT of 1.6, making this the most effective pain relief after third-molar surgery.

An additional consideration is the risk for adverse effects with these medications. The NNT statistic is used to determine the number-needed-to-treat-to-benefit (NNTB) and the number-needed-to-treat-to-harm (NNTH). Comparisons indicate that opioid combinations are more likely to have side effects, usually consisting of nausea/vomiting and dizziness.

DEVELOPING THERAPEUTIC GUIDELINES AND TREATMENT STRATEGIES

Having evidence-based knowledge concerning the efficacy and safety of oral analgesics allows the creation of recommendations for treating postoperative pain. NSAIDs are efficacious and not associated with the potential harm that accompanies the use of opioid analgesics. Understanding the additive analgesia available when an NSAID and APAP are combined provides support for the use of this combination as an alternative to using opioids (Table 2). The specific dose of ibuprofen and APAP should be tailored to the needs of the patient and the practitioner's expectations for postoperative pain.

Adverse drug reactions must also be considered. NSAIDs are contraindicated for patients such as those with a history of peptic ulcer, stomach bleeding, and uncontrolled hypertension and preexisting renal disease. An enhanced bleeding risk or lithium toxicity can complicate the use of NSAIDS for patients taking anticoagulant or lithium therapy. Excessive doses of acetaminophen are also linked to potential liver toxicity. Patients must be cautioned to follow dosing instructions and avoid taking other medications that contain APAP.

Table 2. Opioid-sparing Treatments for Acute Pain

Pain Severity	Analgesic Recommendation
Mild pain	Ibuprofen 200–400 mg q 4–6 h: as needed for pain
Mild-moderate pain	Ibuprofen 400–600 mg q 6 h: fixed interval for 24 h Then ibuprofen 400 mg q 4–6 h: as needed for pain
Moderate-severe pain	Ibuprofen 400–600 mg plus APAP 500 mg q 6 h: fixed interval for 24 h Then ibuprofen 400 mg plus APAP 500 mg q 6 h: as needed for pain
Severe pain	Ibuprofen 400–600 mg plus APAP 650/ hydrocodone 10 mg q 6 h: fixed interval for 24–48 h Then ibuprofen 400–600 mg plus APAP 650 mg q 6 h: as needed for pain

(Courtesy of Moore PA, Hersh EV: Analgesic therapy in dentistry: From a letter to the editor to an evidence-base review. *Dent Clin N Am* 63:35-44, 2019.)

Clinical Significance

The database on analgesic efficacy and safety permits the application of evidence-based methodologies to compare oral analgesics for dental pain relief. The efficacy of the ibuprofen-APAP combination offers a clinically acceptable alternative to opioid analgesics for many patients.

Moore PA, Hersh EV: Analgesic therapy in dentistry: From a letter to the editor to an evidence-base review. *Dent Clin N Am* 63:35-44, 2019

Reprints available from PA Moore, Pharmacology, Dental Public Health, Univ of Pittsburgh School of Dental Medicine, 386 Salk Hall, Pittsburgh, PA 15261; e-mail: pam7@pitt.edu