A comprehensive meta-analysis using strict inclusion criteria examined 8 studies comparing the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) and codeine-based oral analgesics for treating moderate to severe oral surgery pain. The studies involved 1,163 patients, drawn from a literature search of more than 300 studies published since 1990. Of the 8, 5 showed significantly better outcomes (P < .05) with NSAIDs, while 3 showed no differences in outcomes (P > .05). Adverse reactions were greater in the opiate group (P < .001).

Data from the 8 studies were subjected to standardized data transformation and analysis procedures using preselected pain measurement inventories. An oral surgery pain model was used because it is relatively free of confounding variables, thereby leading to clearer results.

Results of the meta-analysis revealed that NSAIDs were either as effective or more effective than codeine-based analgesics for treating the moderate to severe pain associated with oral surgery. NSAIDs also were associated with fewer complications. Based on this analysis, NSAIDs should be considered for the control of postoperative oral surgery pain. Generalizability to other forms of postoperative pain remains speculative.

Key words: Analgesic efficacy, nonsteroidal anti-inflammatory drugs, oral surgery, pain.

Meta-analysis of the effectiveness of nonsteroidal anti-inflammatory drugs in a standardized pain model

Postoperative pain occurring as a result of noxious thermal, mechanical, or chemical events activating free nerve endings is a major concern to the patient undergoing anesthesia and surgery. This complex human response manifests with psychological, behavioral, and autonomic reactions. The study of pain and its treatment is challenging as many patient, provider, procedural, and pharmacological factors interplay in an often bewildering manner.

The enlarging family of nonsteroidal anti-inflammatory drugs (NSAIDs) provides alternatives to managing postoperative discomfort beyond traditional opioid-based interventions, but their clinical use must be founded on evidence-based practice. By using meta-analytical techniques, this study addressed the effectiveness of NSAIDs in treating an oral pain model free of many of the confounding factors often plaguing pain-related research.

Methods

The meta-analytical techniques used in this study are well described and were meticulously followed.13 In order to avoid confounding variables, a simple pain model (third molar extraction) was selected for the following reasons: it is associated with moderate to severe pain based on standardized scales; it is performed electively on generally fit, ambulatory subjects; and the surgical intervention is consistent, and involves only one area of the body.

MEDLINE and BIOSIS were searched using the key words “oral surgery,” “pain,” and “analgesics,” spanning the time period January 1990 to July 2000 and including all English-language studies that met the criteria in Table 1. The initial search identified nearly 300

<table>
<thead>
<tr>
<th>Table 1. Study entry criteria</th>
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<tr>
<td>Of the many published studies, only the most methodologically superior were included to ensure high internal validity. Many studies of questionable merit exist in the literature that compare analgesic efficacy. Entry criteria were decided on a priori and rigidly followed to guarantee scientific excellence.</td>
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<tr>
<td>• Nonpilot nature with appropriate statistical power (authors indicated that a power analysis was performed and that the sample size was sufficient)</td>
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<td>• Randomized, double-blind controlled trial</td>
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<td>• Both sexes represented</td>
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<td>• Subjects provided informed consent</td>
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<td>• Minimum of 2 treatment arms; 1 opioid-based, 1 nonsteroidal anti-inflammatory drug (NSAID)-based</td>
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<tr>
<td>• Consistently applied pain inventories that were psychometrically valid, standardized tools assessing pain experience and therapeutic response for at least 6 h</td>
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<tr>
<td>• Same-day surgical procedure in fit subjects</td>
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<tr>
<td>• Presumed analgesic equivalency of groups based on the following:3,11,13,14</td>
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<tr>
<td>30 mg of codeine + NSAID = 30 mg of morphine by mouth = 10 mg of parenteral morphine; acetaminophen, 1,000 mg = diclofenac, 100 mg = zomepirac, 100 mg = flurbiprofen, 100 mg = ketorolac, 20 mg = ibuprofen, 400 mg = naproxen, 500 mg = naproxen, 1,000 mg = meclofenamate, 100 mg = tenoxicam, 40 mg</td>
</tr>
<tr>
<td>• Reporting of all adverse effects</td>
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studies that were subsequently narrowed to 8 that met the full criteria for inclusion in the meta-analysis (Table 2). Data were transcribed from these studies onto standardized forms that allowed for transformation to a common numeric for both outcome measures and pain scores (before and during treatment). For example, for purposes of comparing studies and facilitating statistical analysis, data were converted to frequency (percentage) level data using a standardized, valid approach that was meticulously followed.

The rationale for including only studies that assessed postoperative pain for at least 6 hours was based on the assumption that this was a clinically relevant time frame and because pain scores were commonly reported to at least 6 hours in the research literature.

The following are representative standardized pain assessment inventories (outcome measures universally used and accepted in this literature) that were encountered in the included trials:

1. **Pain relief (PAR)** = amount that pain has decreased compared with baseline value recorded at regular, predetermined intervals

2. **Total pain relief (TOTPAR)** = the weighted sum of the PAR scores

3. **Peak pain relief (PPAR)** = the maximum PAR value

4. **Pain intensity difference (PID)** = the difference between the baseline pain score minus the pain intensity score at each time interval

5. **Summed pain intensity difference (SPID)** = the weighted sum of each PID

6. **Peak pain intensity difference (PPID)** = the maximum PID difference observed

For purposes of this meta-analysis, TOTPAR and PPID were recorded, transformed to a common frequency numeric, and analyzed.

To put these outcomes in a clinical framework, increasing scores of TOTPAR and PPID indicate increasing analgesic effectiveness. Satisfaction inventories (on the part of either patient or care provider) were not incorporated into the analysis because they were not uniformly reported or were derived inconsistently, often using unstandardized tools.

Sample size–weighted mean effect (N-weighted mean) was computed so that the effect of an intervention could be valued from each study according to its sample size. This was again accomplished for the analgesic outcome measures (pain relief efficacy measures) of PPID and TOTPAR. In order to determine (calculate) whether NSAIDs or opiates had greater therapeutic value within each of the 8 study groups, a standard statistical technique (random effects model, see Appendix) was used that eliminated the impact of extraneous factors occurring as a random effect. Accordingly, the percentage of relative difference for each interventional outcome measure was compared using 95% confidence intervals. Because study inclusion criteria were rigidly followed, no statistical test for homogeneity was undertaken.

### Results

The 8 studies included 1,163 patients receiving oral analgesic interventions. No placebo group comparisons were performed in this meta-analysis because NSAIDs and opioid-based interventions are well...
known to have statistically (and clinically) significant rates of analgesia compared with placebo intervention for this type of oral pain.\textsuperscript{3,14}

Overall there was a significant difference favoring the NSAID in the outcome measures of PPID or TOTPAR when the NSAID regimens (naproxen, ketorolac, flurbiprofen, ibuprofen, or diflunisal) and opioid (codeine) regimens were compared. Table 3 details the statistical comparisons. Five trials observed significantly better outcomes with the NSAID interventions, 3 trials observed no difference in outcome measures; surprisingly, no trial found a statistically significant effect that favored the opioid-based regimen. Adverse reactions, including both gastroemetic (nausea and vomiting) and central nervous system (sedation, dizziness, blurred vision, headache) phenomena were greater in the opioid group ($P < .001$, $\chi^2$).

**Discussion**

Meta-analysis, introduced in the 1970s, is a method to achieve a quantitative synthesis of the results of different studies focused on similar questions or hypotheses. Despite acknowledged limitations (eg, publication bias favoring positive findings, analyst bias, assumptions of internal and external validity\textsuperscript{15}), the technique is widely used in the social and biomedical sciences. Essentially the approach involves combining empirical evidence from studies conducted in a similar way by transforming the findings into a common numeric and then using statistical reasoning to assemble a single “best” estimate. Because the quality of the meta-analysis depends on the quality of the studies evaluated,\textsuperscript{16,17} only the most scientifically rigorous and clinically relevant work was included. Subject to the discipline of mathematical reasoning, general intuition provides firm common sense guides concerning the use of random effects models—calculations give us insight into the size of fluctuations or error that might result from unexplained variation in sampled units. The random effects analysis informs us about true differences in treatment means across all groups, which is intuitively obvious. The strength of the random effects analysis emerges when there are several treatment options/groups, in which case we can get a rough estimate of the treatment interaction variance. An inherent limitation in this model is that though it would be best to sample treatment effects randomly, we must be concerned about generalizability since in addition to random error, there may be selection bias in what is studied.

The use of the random effects model is a popular way to model Gaussian longitudinal data where, $Y_i = X_i \beta + Z_i \alpha + e_i$ $i = 1, \ldots, n$. The actual data analysis is accomplished as:

**Appendix: The random effects model**

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The use of the random effects model is a popular way to model Gaussian longitudinal data where, $Y_i = X_i \beta + Z_i \alpha + e_i$ $i = 1, \ldots, n$. The actual data analysis is accomplished as:

**Computation of the sums of squares over all observations.** $SS_{\text{total}} = \sum (X_i - X..)^2$

**Sum of squares of the first-level unit measures ($\alpha - 1$ df).** $SS_{\alpha} = \sum \sum (X_{ij} - X_i)^2$

**Total of within-unit sums of squares (an – a df).** $SS_{\text{within}} = \sum \sum (X_{ij} - X_i)^2$

Note that $SS_{\alpha}$ is algebraically equivalent to $SS_{\text{treatment}}$ from fixed-effects ANOVA (analysis of variance).

When there are repeated subsamples or measurements on sampled units, we are interested in both the overall mean and the contributions of various levels of sampling to the overall variability. The random effects model captures both of these interests.

**Table 3. Statistical analysis of included randomized trials**

| Reference | N  | Analgesic score † | Relative difference ‡ | 95% CI $§$ | Side effects $||$ |
|-----------|----|-------------------|-----------------------|------------|-------------------|
| **Studies favoring ($P < .05$) a codeine-based intervention over the NSAID** | | | | |
| None | — | — | — | — | — |
| **Studies favoring ($P < .05$) an NSAID over the codeine-based intervention** | | | | |
| 3, 5, 6, 9, 10 | 621 | 25/14 (PPID) | 11 | 7/13 Cod |
| 48/36 (TOTPAR) | 12 | $-20/-3$ | |
| **Studies showing equivalence ($P > .05$) between codeine-based or NSAID intervention** | | | | |
| 4, 7, 8 | 551 | 35/34 (PPID) | 1 | $-9/7$ Cod |
| 44/39 (TOTPAR) | 5 | $-11/4$ | |

*CI indicates confidence interval; NSAID, nonsteroidal anti-inflammatory drug; Cod, codeine-based intervention; PPID, peak pain intensity difference score (NSAID score/Cod score); TOTPAR, total pain relief score (NSAID score/Cod score).
† Percentage improvement for NSAID/Cod on the pain assessment inventory.
‡ Calculated percentage difference between the interventions.
§ Upper and lower 95% confidence interval.
$||$ Group with highest side effects ($P < .05$ for sedation, nausea/vomiting, dizziness).
included in this analysis. The outcome tools used in the enclosed studies are universally used and accepted in this clinical research domain.5,11,13,14

In this meta-analysis, it was found that NSAIDs were as effective or more effective than codeine-based interventions in the relief of moderate to severe pain associated with the oral pain model. The nature, intensity, and experience of oral surgery pain differ in many ways from the discomfort experienced by patients we usually encounter in the operating room. It also should be noted that there is not consensus that oral surgery pain is a relevant model for comparing opiates and NSAIDs due to the fact that oral pain is generally prostaglandin-mediated (Scot Reuben, MD, personal communication, December 2000). However, the opportunity to compare the regimens in terms of analgesic efficacy using a study design/pain model relatively free of confounding variables is a valuable exercise in establishing evidence-based practice.

Recent work has revealed that there may be sex-oriented differences to painful stimuli and in the response to analgesics, including NSAIDs.18,19 Future trials of analgesic efficacy should consider sex as a key methodological issue in both the design and analysis of the trial. Because of absent or incomplete reporting in the included trials, sex could not be considered as an independent variable in this meta-analysis.

Based on this analysis, it is recommended that NSAIDs be considered for the control of postoperative analgesia in the domain of oral surgery due to (1) similar or better efficacy compared with codeine-based interventions, and (2) fewer side effects such as constipation, dizziness, sedation, headache, and nausea. Its generalizability to patients experiencing other types of postoperative pain is entirely speculative at this time.

A future randomized clinical trial using a standardized pain tool, independent observers, and well-defined, commonly used analgesic interventions should be applied to a surgical population undergoing a procedure more akin to that traditionally encountered in an ambulatory surgical setting. Age, sex, psychosocial factors, medication use, and operative site factors should be considered in the analysis.

REFERENCES


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