Nonnarcotic Analgesic Use in Acute and Cancer Pain: Results of Selected Meta-analyses

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Introduction

Meta-analysis is a statistical tool used for analyzing the combined data from multiple trials, both randomized, controlled trials (RCTs) and other trials. The pooling of data from several trials that is part of the methodology of meta-analysis increases the number of patients available for statistical analysis. This may, in turn, increase the statistical power of certain findings. Alternately, a meta-analysis that is conducted in an area in which several trials have produced conflicting results may help summarize overall trends in findings. Meta-analysis is valuable not only because the process forces a systematic evaluation of existing trials, but also because it can expose deficiencies in existing data, contribute to the planning process for new research, and promote standardized data reporting. However, the techniques of meta-analysis cannot be universally applied. Even though large numbers of clinical trials may have been completed in a certain area, it may not be possible to produce valid meta-analyses if data are not reported in a standardized fashion. Moreover, there are pitfalls in meta-analysis that, if ignored, lessen its value and destroy its credibility.1-10 Pitfalls include failure to eliminate publication and individual study bias, failure to identify duplicate publications, and heavy reliance on statistical tools. Meta-analysis is not a panacea; it cannot provide new evidence and is not a substitute for new research or for mega-trials.

How can meta-analysis help to assess the utility of nonnarcotic analgesics in acute and cancer pain? The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in mild acute pain is well established.6-8 Countless RCTs confirm the efficacy of NSAID treatment for this indication, the most common pain model in these trials being the postoperative dental pain model.9,10 Despite this surfeit of trials, no meta-analysis has been performed that simply assesses the analgesic efficacy of NSAIDs. With so many trials clearly demonstrating efficacy, a meta-analysis is probably not even necessary. At the same time, lack of standardization of methodology among the thousands of studies conducted on the subject means that producing valid meta-analyses with comparative analgesic efficacy as the end-point is difficult. However, there are other important questions relevant to the use of nonnarcotic analgesics for the management of acute pain for which meta-analysis should be able to provide valid answers, and a limited number of meta-analyses have been undertaken. In the field of cancer pain, there is actually a paucity of RCTs, so that the scope for meta-analysis is limited.11

This article discusses the only two published systematic reviews on the role of non-opioid analgesics in the management of acute pain, and the only two published systematic reviews on the role of these drugs in the management of cancer pain. The article also addresses relevant information on the toxicity of these agents provided by meta-analyses on the management of chronic pain in other disease states, predominantly arthritis.

On acute pain relief, the Agency for Health Care Policy and Research (AHCPR) commissioned for its guideline on acute pain management a meta-analysis on the opioid-sparing effect of NSAIDs.12 The author led the team that completed this task. The only other systematic review on the management of acute pain was conducted by Henry McQuay of Oxford University,13 who evaluated the preemptive effect of various types of analgesia, including NSAIDs.

The two systematic reviews on the management of cancer pain were performed by Eisenberg and colleagues at Harvard14 and by Jadad and Brownman of McMaster University15 in Canada. The systematic review assembled by Jadad and Brownman is not a formal meta-analysis, the studies available being simply case series and not controlled trials. Both meta-analyses assess the utility of the World Health Organization (WHO) analgesic stepladder.16

Meta-analyses of NSAID Use in Acute Pain

We can identify four major questions that potentially meta-analysis could help elucidate, each of which has been examined in multiple research trials: (1) What is the relative efficacy of available NSAIDs, in comparison with placebo and in comparison with other drugs, particularly opioids? (2) What are the opioid-sparing properties of nonnarcotic analgesics, and to what extent are these associated with avoidance of serious side effects associated with opioid drugs? (3) What is the optimum timing of doses of nonnarcotic analgesics? In the management of postoperative pain, for example, should each drug be administered preoperatively, intraoperatively, or postoperatively? (4) What side effects are associated with each drug, and how can the clinician gain optimal benefit from each drug while minimizing the potential for doing harm? The two published meta-analyses address our second and third major questions.

The AHCPR meta-analysis on the opioid-sparing effect of NSAIDs for acute pain was completed in 1990. Six trials were identified that were suitable for inclusion. The meta-analysis demonstrated clearly the opioid-sparing effects of NSAIDs, which are associated with an estimated mean reduction in opioid consumption. An overall reduction in morphine consumption of 8.3 mg per patient was achieved with NSAID use, and this reduction is highly significant (P=0.0028). Further, respiratory depression was determined to be less frequent with combined therapy than with treatment using opioids alone. Two of the three studies that included data on respiratory depression found a statistically significant decrease in the incidence of respiratory depression in those patients who were receiving adjunctive NSAIDs.

McQuay’s meta-analysis looks at the preemptive effect of NSAIDs. The preemptive effect of an analgesic is its ability to decrease acute pain more if given before rather than after injury or surgery. Only four RCTs were identified for inclusion in this systematic review. The four studies provided consistent results, i.e., no measurable difference was found between the same dose given preoperatively vs postoperatively. The balance of the evidence is that at normal therapeutic oral doses of NSAIDs, no pre-emptive effect was demonstrable.

Until toxicity risks associated with the use of NSAIDs in patients with surgical or other acute pain have been better studied, it may be valuable to consult meta-analyses of NSAID use in patients suffering from other sorts of pain. In meta-analyses,16-25 patients with chronic arthritis pain have been found to be at increased risk of peptic ulceration and gastrointestinal hemorrhage with (1) age over 60 years, (2) a history of gastrointestinal complaints, and (3) concomitant corticosteroid use. Gender had no effect on
prevalence of side effects. Risks increase with duration of therapy, with minimal risk during short-term therapy, suggesting that when acute pain is being treated for a period of 24 hours, the patient is at little danger from side effects. Risk also increases with larger doses. Our experience with ketorolac in postoperative patients is a case in point. When the drug was launched as the first injectable NSAID with Food and Drug Administration approval for use in acute pain, the recommended dose was 60 mg. It was widely and enthusiastically used, but there were problems with side effects, some catastrophic. The recommended dose was later reduced to 30 mg, and the incidence of side effects has diminished significantly. Thus, the evidence from these meta-analyses in chronic arthritis patients leads us to apply caution when treating elderly patients, patients with pre-existent peptic ulcer disease, patients with coagulopathy, and patients on corticosteroid therapy. At the same time, we often restrict the use of these drugs (particularly potent NSAIDs such as ketorolac) to the first one or two postoperative days, and we avoid high doses.

Meta-analyses of NSAID Use in Cancer Pain

In their meta-analysis of the use of NSAIDs in cancer pain, Eisenberg and colleagues15 examined 25 RCTs. It should be noted that these studies made use of diverse end-points and multiple analyses were undertaken; therefore, each has less power than if all 25 RCTs had been combinable. The conclusions of these meta-analyses are the following. The efficacy of single-dose NSAIDs is greater than placebo and is approximately equivalent to 5 to 10 mg of parenteral morphine. The analgesic efficacy achieved with single and multiple doses of weak opioids is no greater than that achieved with NSAIDs alone. Neither single or multiple doses of weak opioid/NSAID combinations produce greater analgesia than NSAIDs alone. A dose-response relationship is suggested but is not statistically significant. There is no improvement with supramaximal doses as compared with standard doses.

Common side effects of NSAIDs are found to be upper gastrointestinal symptoms, dizziness, and drowsiness. Single-dose side effects are greater for opioid/NSAID combinations than for NSAIDs alone, although this difference disappears with multiple doses.

The results of these meta-analyses put into question the validity of the WHO analgesic ladder. NSAIDs alone were found to be as effective as opioid/NSAID combinations and as weak as opioids alone. However, the WHO analgesic ladder positions a non-opioid on its own as the first step in treatment. To move a patient to the second step of the ladder is to add an opioid, either with or without concomitant administration of a non-opioid. The authors of the meta-analysis question whether trial data support the conclusion that clinicians should move from the first step to the second when they wish to find more effective treatment for patients or, perhaps, to make different use of NSAIDs themselves.

However, a note of caution is necessary in the interpretation of this meta-analysis. The studies available for inclusion in the meta-analysis of NSAID vs weak opioid or weak opioid/NSAID combination form a heterogeneous group. While one study compared aspirin (a weak analgesic) with aspirin-opioid combinations, another two studies compared ketorolac (an extremely potent NSAID that is associated with potent side effects and is probably unsuitable for long-term use) with a weak opioid/NSAID combination and with a weak opioid alone. Note also that only single-dose studies were available in sufficient numbers for inclusion in the meta-analysis. Yet, what we are really interested in is not the efficacy of single doses but the efficacy of multiple doses, which would be used in clinical practice. The only studies that present data from multiple dose evaluations demonstrate negative findings. Have the authors of these meta-analyses fallen into the trap of mistakenly combining heterogeneous data and ignoring important clinical information (viz., the negative results of multidose studies) because it cannot be included in the analyses? We need to critically evaluate the conclusions of this paper before the concept of building analgesic strength on the WHO stepladder.

The systematic review assembled by Jadad and Browman identified eight studies that evaluated patients with cancer pain treated according to the WHO analgesic ladder. Studies selected for inclusion were of various methodological design but were included if they provided enough information to estimate the proportion of patients who achieved adequate analgesia with the use of the ladder. Formal meta-analysis was not performed because the studies were case series with no control groups. Analgesia was adequate in 86% to 96% of patients analyzed in the studies, depending on the study. Jadad and Browman concluded that although the studies available provide valuable information on the course of cancer pain and its treatment, the evidence from these studies is insufficient for confident assessment of the WHO analgesic ladder for managing cancer pain. The authors state that until results from carefully designed controlled trials are available, it would be inappropriate to judge the performance of clinicians, programs, institutions, or to design policies based on such evidence. In overall conclusion, both the Eisenberg and the Jadad studies advance the same question: Should the WHO analgesic ladder be reevaluated?

Conclusions

**Acute Pain:** Neither the efficacy nor the relative efficacy of nonnarcotic analgesics vs opioid analgesics for the management of acute pain have been examined by meta-analysis. However, the efficacy of NSAIDs in mild acute pain is well established and has been confirmed by countless randomized trials. The opioid-sparing effects of nonnarcotic analgesics is strongly supported by a meta-analysis. In patients with acute pain, nonnarcotic analgesics can significantly reduce concomitant opioid usage. There is also evidence of a decrease in the incidence of respiratory depression with combination therapy in which non-opioid and opioid analgesics are administered concomitantly. No support is found for a preemptive effect of these drugs following administration prior to surgery, although the data obtained thus far on this subject are not abundant and additional studies are needed. As to risks associated with the use of nonnarcotic analgesics, meta-analyses in patients with chronic arthritis have shown that important risk factors are age greater than 60 years, a history of gastrointestinal events, and corticosteroid use. They have also shown that increased risk can be expected with longer duration of therapy and with the use of high doses of medications.

**Cancer Pain:** The efficacy of nonnarcotic analgesics for management of cancer pain is supported both in comparison to placebo and in comparison to weak opioids and combinations of weak opioids and nonsteroidal agents. In single doses, the risk of side effects from nonnarcotic usage is comparable to that of placebo treatments and appears to be less than that of side effects associated with opioid/NSAID combinations. In contrast, in multiple doses the incidence of side effects is increased so that side effects associated with NSAID use is comparable to that of combination therapies comprised of weak opioids and NSAIDs. Common side effects include upper gastrointestinal symptoms, dizziness, and drowsiness.

**The Future:** In the future, meta-analysis may be applied to answering a variety of questions relevant to the treatment of acute and cancer pain. In postoperative patients, there are differences in outcome when NSAID usage results in an opioid-sparing effect; for example, is there an early return of bowel function or earlier hospital discharge? When during the perioperative course should NSAIDs be started, preoperatively, intraoperatively, or postoperatively? What are the risks of short-term NSAID usage in patients undergoing major surgery, both those sustaining blood loss and those not sustaining blood loss, particularly with regard to gastrointestinal bleeding, platelet effects, and renal effects? In cancer patients, should the WHO analgesic ladder be reevaluated?

An important benefit of the process of undertaking and publishing meta-analyses is to expose deficiencies not only in the scope of the literature but also in the way in which clinical findings are reported. Exactly how standardization in reporting may be achieved is open to assessment, but organizations such as the Cochrane Collaboration, the American Pain Society, and the International Association for the Study of Pain are making progress toward this goal and in disseminating the existing evidence syntheses.

References

Additional Reading and General References


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