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Michael A. Fiedler, PhD, CRNA

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Abstract

Purpose The purpose of this study was to evaluate the efficiency and patient satisfaction associated with three different sedation procedures: propofol only, propofol / midazolam / fentanyl, or midazolam / fentanyl only.

Background Propofol is generally accepted as producing better sedation for endoscopy than boluses of opioid and benzodiazepine. Propofol allows for faster recovery, higher physician satisfaction, and greater efficiency in the endoscopy suite. Combining fentanyl and midazolam with propofol has been purported to reduce the need for deep sedation, but, despite this, propofol is widely becoming the sole agent used for sedation during endoscopy.

Methodology This retrospective review included 951 patient records for endoscopies performed between 2007 and 2010. Procedures were either esophagastroduodenoscopy (EGD) or colonoscopy. All procedures were performed in an ambulatory endoscopy center.

Propofol sedation methods were administered by a CRNA and midazolam / fentanyl sedation was administered by an RN at the direction of the endoscopist. The goal of each sedation technique was to provide analgesia without significant physical signs of discomfort. Sedation was assessed with the Modified Observer’s Assessment of Alertness/Sedation instrument (MOAA/S). Patients also completed a satisfaction survey after the procedure.

Result Of the 951 patient records reviewed, 24% were EGDs and 56% were colonoscopies. The other 20% of cases were both EGD and colonoscopy and these were not included in the analysis.

Demographic variables were similar between sedation groups. The level of sedation achieved was similar for EGD cases and colonoscopies.

MOAA/S sedation scores were significantly lower in patients who received propofol only (P<0.05). Likewise, patients who received propofol / midazolam / fentanyl sedation had lower sedation scores than those who received only midazolam / fentanyl (P<0.05). The average level of sedation

Table 1: Three Methods of Sedation

1. **propofol only** - 50 mg bolus with follow up 20 mg boluses throughout procedure (n=330)

2. **propofol / midazolam / fentanyl** - 10 mg propofol, 50 µg fentanyl, 2 mg midazolam with follow up propofol 20 mg boluses throughout procedure (n=282)

3. **midazolam / fentanyl only** - 2 mg midazolam and 50 µg fentanyl with follow up 1 mg midazolam and 25 µg fentanyl throughout procedure (n=339)
during propofol only was 0.9. An MOAA/S of “1” signifies that the patient “does not respond to mild prodding/shaking.” In contrast, the average level of sedation in the propofol / midazolam / fentanyl and the midazolam / fentanyl only groups was about “4.” An MOAA/S of “4” signifies that the patient has a “lethargic response to [their] name [spoken] in normal tone.” Thus, the level of sedation was significantly “deeper” in the propofol only group. [Editor’s Note: a lower MOAA/S sedation score is deeper sedation; see note describing the entire scale following the abstract and comment.] No patient required assisted ventilation during sedation.

Patients in the propofol only group who received a 50 mg bolus were ready for the start of the procedure significantly more quickly than patients in the other groups (P <0.05). Depending upon the type of procedure, patients were ready for the start 2 to 3 minutes faster following the 50 mg propofol bolus. Likewise, propofol only patients recovered from sedation significantly more quickly than patients in the other groups (P<0.05) and patients in the propofol / midazolam / fentanyl group recovered more quickly than the midazolam / fentanyl only group (P=0.007). Propofol only patients recovered 9 to 10 minutes faster than midazolam / fentanyl only patients.

Patients in either of the groups that received propofol reported less discomfort during the procedure than those in the midazolam / fentanyl only group when interviewed at discharge (P<0.05). They were also more satisfied with their endoscopy experience and remembered less of what happened during the procedure. However, the differences in satisfaction were very small between groups. Patients from each sedation method rated their overall satisfaction 9.5 or higher on a scale of 1 to 10.

**Conclusion**

The use of propofol only for sedation during EGD or colonoscopy was associated with slightly less time in the procedure room and clinically significantly faster recovery from sedation compared to groups in which midazolam and fentanyl were administered. This, despite the fact that propofol only patients were more “deeply” sedated than patients in the other groups. Patients who received propofol only sedation reported less discomfort and remembered less during the procedure. The faster initiation and recovery times associated with the propofol only group may allow greater efficiency, especially in a busy endoscopy unit. This efficiency may at least partially offset the additional cost of having an anesthesia provider present to sedate the patient.

**Comment**

I feel certain the results of this study are no surprise to anyone who has done much sedation for endoscopies. It points out why propofol is becoming the drug of choice for sedation during endoscopy: 1) Patients are ready for the endoscope to be inserted faster. Two or three minutes faster may not sound like much to the uninitiated, but you and I know how much most physicians don’t like to wait to start their procedure. 2) Patients recover faster. The “system” likes this because patients move through the system faster and it costs...
less to provide the service. 3) Patients and physicians are highly satisfied and patients tend not to remember anything that would lead to dissatisfaction.

But I’d like to pull out another lesson from this study. Endoscopies would be quite uncomfortable without sedation and/or analgesia. Why were the propofol only patients sedated so much more deeply than the propofol / midazolam / fentanyl group? I believe it was probably because it takes a lot of sedation to overcome painful stimuli. Note that giving only 50 µg fentanyl made it possible to sedate the patient much more lightly and the only real disadvantage was a slower recovery. As we become aware of the aspiration risks associated with deep sedation (see the abstract and comment “COMPLICATIONS FOLLOWING COLONOSCOPY WITH ANESTHESIA ASSISTANCE” elsewhere in this issue) we need to think about providing adequate analgesia during sedation for endoscopies so that we don’t need sedation so deep that it boarders on, or is, general anesthesia. It may be that fentanyl can be used to provide this analgesia (without the midazolam) but there will be some additive respiratory depression and, perhaps, slower recovery. My recommendation is to use a combination of propofol and ketamine (1 to 2 mg ketamine per 10 mg propofol). Ketamine is a potent analgesic and amnestic but does not depress respirations like propofol. While we’d usually want to use some midazolam to protect against ketamine induced dysphoria, there are scores of studies in which propofol and ketamine were combined for infusion or TIVA without midazolam and without postop dysphoria. Neither does ketamine slow recovery. Adding ketamine should make lighter sedation possible while achieving the desired results. It will reduce the dose of propofol used and thus increase the margin of safety for respiratory depression. And, lighter sedation should reduce the risk of aspiration as well. Many anesthesia providers are already happily using this sedation technique during endoscopies.

Michael A. Fiedler, PhD, CRNA

MOAA/S sedation scoring:

6 = agitated
5 = responds to name in normal tone
4 = lethargic response to name in normal tone
3 = responds to name called loudly
2 = responds to mild prodding/shaking
1 = does not respond to mild prodding/shaking
0 = does not respond to deep-stimulus “sternal rub”
Pharmacology

**Intramuscular Dexmedetomidine Sedation for Pediatric MRI and CT**

Am J Roentgenol 2011;197:720-5
Mason K, Lubisch N, Robinson F, Roskos R

**Abstract**

**Purpose** The purpose of this study was to describe intramuscular dexmedetomidine sedation used in the pediatric population undergoing MRI and CT imaging studies.

**Background** Infants and young children often require sedation to ensure motionless conditions while undergoing imaging studies such as MRI and CT scans. More traditional, older sedative medications such as pentobarbital and chloral hydrate have numerous disadvantages; for example, an extremely long duration of action that has been linked to prolonged recovery and several sedation-related side effects. Dexmedetomidine is not labeled for pediatric use however literature is becoming abundant with clinical scenarios describing its effectiveness in the pediatric patient population. It has been administered to children using the IV, nasal, buccal, and subcutaneous routes however the intramuscular (IM) route has only been described in adults. Oftentimes children do not need an intravenous for MRI and CT imaging studies other than to receive sedation. Dexmedetomidine via the IM route has potential for a safe and high quality sedative agent.

**Methodology** This study was carried out as a retrospective analysis of an institutional dexmedetomidine sedation protocol. The goal was to assess the effectiveness of IM dexmedetomidine administered to pediatric patients when undergoing MRI and CT imaging studies. Children who were undergoing routine brain, seizure, and musculoskeletal imaging received:

1. 4% lidocaine topical lysosomal delivery 20 minutes before the planned IM dexmedetomidine injection (two separate sites)
2. An initial dose of 1-4 µg/kg of undiluted intramuscular dexmedetomidine (4 µg/mL solution) in the deltoid muscle (dose used dependent upon discretion of provider, child’s medical diagnosis, preexisting state of anxiety and agitation)
3. An assessment to determine whether a Ramsay sedation score of 4 was achieved
4. A second reduced dose of dexmedetomidine if a Ramsay score of 4 was not achieved and maintained after a minimum observation of 10 minutes

Quality assurance data entered into an electronic database at 5 minutes intervals included:

- Blood pressure
- Heart rate
- Pulse oximetry values

Additional data collected included the dose of dexmedetomidine administered, time required to achieve adequate sedation, duration of imaging study, time required to meet discharge criteria, total duration of sedation, and adverse events. An age-adjusted deviation beyond 20% of baseline vital signs was plotted for comparison.
Result  A total of 65 children received IM dexmedetomidine, completed the imaging studies, and were included in the final analysis. A total of 21 had an MRI and 44 had a CT scan. Nine children, 14%, had hypotension. Only one of those nine received a second dose of the study drug because of the inability to achieve the sedation score required. There was no association between hypotension and the total dose of the study drug. All nine patients exhibited a return to within 20% of baseline/normal vital signs without pharmacologic intervention. There were no other adverse effects noted. The average time to achieve sedation was about 13 minutes.

Conclusion  Intramuscular dexmedetomidine, administered in mean dose of between 2.4 - 2.9 µg/kg to children undergoing MRI and CT imaging studies produced adequate sedation with an average onset time of 13 minutes. These doses allowed successful completion of the study, and allowed for a recovery period on average of 30 minutes or less. No adverse events were noted. The study was underpowered for determining if a relationship existed between a child’s medical diagnosis and the incidence of hemodynamic variability.

Comment  Far too often the complexity of the anesthetic exceeds the complexity of the procedure requiring the anesthetic, especially in the pediatric population. That just doesn’t seem right but it is very true! Clearly the developmental behavioral patterns and stages of infants and younger children mandate a special way of caring for them by the anesthesia provider. This is the humane way of taking care of young people and is widely accepted. What is exciting about this novel IM dexmedetomidine sedation protocol, is that it meets the special needs of young children. Why start an intravenous line and cause trauma when a topical cream can be used to localize an area where an intramuscular injection is given? Why start an IV when the drug administered has very little potential to create respiratory depression or hemodynamic instability? It truly is a unique way to continue to promote a safe and high quality environment in a very special patient population.

Some may ask: what is the difference then of anesthetizing a young child for myringotomy tube placement using inhalational anesthesia and not placing an IV? The difference is obvious: dexmedetomidine is an alpha 2 adrenoreceptor agonist that pharmacokinetically and pharmacodynamically works in distinctly different ways than our inhalation agents. Unlike inhalation agents, it does not carry the risk of causing a loss of airway patency or of creating myocardial depression and tachycardia. Therefore, the risk of not placing on IV to treat effects of an anesthetic is very minimal in the case of dexmedetomidine. For minimally invasive diagnostic procedures where immobility is a necessity, such as imaging studies, it appears to be one of the most appropriate ways to sedate children without making the anesthesia risk and associated side effects greater than the procedure risk!

Mary A Golinski, PhD, CRNA
**The effects of preoperative intravenous acetaminophen in patients undergoing abdominal hysterectomy**

Arch Gynecol Obstet. 2011;284:1455-60
Moon Y, Lee Y, Lee J, Moon D

**Abstract**

**Purpose** The purpose of this study was to determine the post-operative analgesic efficacy of intravenous acetaminophen, when administered prior to incision, in females undergoing total abdominal hysterectomy.

**Background** The mechanisms involved in the post-operative pain response suggest that a multimodal approach may be efficacious by enhancing the quality of analgesia and diminishing the untoward effects of opioids. Non-steroidal anti-inflammatory drugs (NSAIDS), when co-administered with morphine, have been shown to reduce the side effects of morphine alone, however, there are contraindications that exist related to NSAIDS and many patients cannot take them. Acetaminophen has very few contraindications and is relatively free from side effects at therapeutic clinical doses. Very little is known about the pre-emptive effects of acetaminophen and how it may modulate post-operative pain when administered in combination with an opioid.

**Methodology** This research was carried out as a placebo-controlled, double blind, randomized study. A total of 76 women scheduled for elective abdominal hysterectomy under general anesthesia were randomized into one of two groups. Prior to the induction of anesthesia, the acetaminophen group received 2 grams of acetaminophen intravenously while the placebo group received normal saline in equal volume as the study drug. The anesthetic was standardized for all subjects and all operations were performed using the same incision type.

Thirty minutes prior to conclusion of surgery, 7 mg hydromorphone was administered to subjects in both groups. At the conclusion of the procedure, each subject was given a PCA device set to deliver 0.2 mg bolus of hydromorphone with a specified lock out interval. If subjects needed additional analgesia during the study period, ketorolac (Toradol) 30 mg intravenously was given; no other analgesics were used at any time period during the study. The primary outcome variable measured was PCA hydromorphone consumption for 24 hours post-operatively. The secondary outcome variables measured included pain scores via a VAS, both at rest and during activity, and any side effects, for 24 hours post-operatively.

**Result** A total of 71 patients were included in the study. There were no statistical differences in the demographic data between the groups. The following outcome variables were found to be significant:

- Total 24 hour hydromorphone consumption was lower in the acetaminophen group
• Overall hydromorphone consumption was reduced at all time points (1, 2, 6, 12, & 24 hours) (P = 0.013)
• The incidence of PONV was lower in the acetaminophen group (P = 0.044)

**Conclusion** The pre-operative administration of IV acetaminophen reduced hydromorphone consumption in patients undergoing abdominal hysterectomy as well as reduced the incidence of post-operative nausea and vomiting. The VAS scores for pain during rest and activity were similar in both groups; the number of patients needing ketorolac, however, did not differ. Sedation scores, a secondary outcome measure of untoward effects, were lower in the acetaminophen group (not statistically significant).

**Comment** Multimodal analgesia is becoming the norm, and should be, as we learn more and more about pain, pain receptors and pathways, and the various side effects of drugs within multiple classes. Our goal, of course, is a safe (non respiratory depressed and/or overly sedated) and highly satisfied patient experiencing positive outcomes. Combining different drug classes (opioids) with non-opioids (Cox-2 inhibitors, NSAIDS) delivered through various routes and even including neuraxial use of local anesthetics are showing extremely favorable results. Patients are more satisfied and the untoward effect of each respective drug can often be minimized when multimodal pain therapy is used. With the multimodal approach you do not need high or escalating doses of any one agent. As a result, side effects related to each drug class are reduced.

Acute post-operative pain remains a challenge, however a multimodal therapeutic approach enhances the efficacy of pain-control. Intravenous acetaminophen appears to represent another class of medications with a place in multimodal analgesia.

**Mary A. Golinski, PhD, CRNA**

**Intravenous Acetaminophen (Ofirmev)** was approved by the FDA in November 2010. Its exact mechanism of action for acute pain management is unknown and is theorized to be related to several entities: inhibition of cyclooxygenase isoenzymes, interaction with the endogenous opioid pathway, activation of the serotoninergic bulbospinal pathway, involvement of the nitric oxide pathway, and an increase in the cannabinoid/vanilloid tone. The package insert can be found at: [http://www.ofirmev.com/](http://www.ofirmev.com/)
A PROSPECTIVE SURVEY OF PATIENT-CONTROLLED EPIDURAL ANALGESIA WITH BUPIVACAINE AND CLONIDINE AFTER TOTAL HIP REPLACEMENT: A PRE- AND POSTCHANGE COMPARISON WITH BUPIVACAINE AND HYDROMORPHONE IN 1,000 PATIENTS

Anesth Analg 2011;113:1213-17
Liu S, Bae J, Bieltz M, Wukovits B, Ma Y

Abstract

Purpose The purpose of this study was to evaluate the difference in efficacy and side effects between epidural hydromorphone and epidural clonidine.

Background This prospective survey examined the use of epidural patient controlled analgesia (PCEA) after total hip replacement. A solution that is frequently used for this type of pain management contains bupivacaine and hydromorphone. This solution has been reported to cause a significant amount of nausea and pruritus (15-30%). The source of the side effects is almost certainly hydromorphone. This study replaced the hydromorphone with clonidine in half of the patients and hypothesized that the use of clonidine would provide similar pain relief with fewer side effects.

Methodology The study reviewed two groups. Each group contained 500 patients that were undergoing total hip replacement or hip resurfacing. The hydromorphone group received postoperative epidural analgesia with bupivacaine 0.06% and hydromorphone 10 µg/mL running at 4 mL/hr with a PCEA dose of 4 mL/10 min prn for pain. In both groups, the epidural was discontinued on the first postoperative day and patients were placed on Meloxicam 7.5 to 15 mg qd. Both groups had orders for nalbuphine 5mg IV prn itching and ondansetron 4mg IV prn nausea.

Each patient was evaluated for pain using a verbal pain score and side effects using the following definitions for three postoperative days. The primary variables compared between groups were pain, nausea, pruritus, and hypotension. Nausea was defined as the use of ondansetron while receiving PCEA. Pruritus was defined as the use of nalbuphine while receiving PCEA. Hypotension was defined as a systolic blood pressure <90 mm Hg. Variables were analyzed using a Student’s t test with unequal variance and a Fisher 2-tailed exact test. The study used a P<0.01 to determine significance.

Result Patient characteristics were similar between the two groups. The clonidine group had a lower verbal pain score at rest (2.3 vs 3.7, P=0.001) and a lower incidence of pruritus (1% vs 10%, P=0.01) than the hydromorphone group. The hydromorphone group had a lower incidence of hypotension (11% vs 20%, P=0.001). Rates of nausea...
were not significantly different between groups. Secondary findings revealed no incidence of sedation or respiratory depression in either group. A majority of physician and non-physician staff caring for the patients considered the clonidine PCEA to be a “worse” choice than the hydromorphone PCEA.

**Conclusion** Even though the clonidine group had statistically significant improvement over the hydromorphone group with respect to the verbal pain score and pruritus, the clinical appearance was similar. Both groups had relatively low verbal pain scores and a low incidences of pruritus and the hypotension associated with clonidine group was easily managed.

**Comment**
I thought this was a well done study in a reasonably controlled situation, with the exception of the lack of randomization. The parameters were simple, well controlled, and clinically relevant. Although I was interested in the outcome of this study in order to determine which drug combination might be superior, my main interest was in finding a drug that could replace preservative free morphine for postoperative pain management. The shortage of preservative free morphine and fentanyl has forced all of us to pursue alternatives. Preservative free morphine has been an extremely valuable drug when given by the intrathecal or epidural route and used to supplement pain management for a number of surgical procedures. Now that preservative free morphine is almost impossible to obtain, I have started to use hydromorphone for both routes. My initial impression of hydromorphone has been positive, but my experience is still limited. I continue to look for alternatives, and I feel clonidine may play a role in epidural pain management. This study has confirmed that assumption, and I will consider using it in the future.

We are being forced to consider what alternative drugs may be effective when our drugs of choice are no longer available. I don’t think this drug shortage situation will be improving in the near future so I am always looking for alternatives for all of my current drug plans.

**Steven R. Wooden, DNP, CRNA**
Pharmacology

Does Intraoperative Ketamine Attenuate Inflammatory Reactivity Following Surgery? A Systematic Review and Meta-analysis

Anesth Analg 2012;115:934-43
Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y

Abstract

Purpose The purpose of this systematic review was to evaluate the effect intraoperative ketamine had on interleukin-6, an inflammatory biomarker, in surgical patients.

Background Major surgery is associated with a systemic inflammatory response and the release of proinflammatory cytokines (interleukin-6 [IL-6], interleukin-1β [IL-1β], tumor necrosis factor α [TNFα]). Increased concentrations of inflammatory cytokines such as IL-6 have been associated with wall motion abnormalities and myocardial ischemia, perioperative complications, postoperative hyperdynamic instability, and have been correlated with postoperative morbidity and mortality in children undergoing open-heart surgery.

Several perioperative interventions have been attempted to reduce the inflammatory response and IL-6 concentrations. Multiple studies have examined the effects of opioids, inhaled anesthetics, local anesthetics, and ketamine. Most studies have mixed results; however, research results on local anesthetics consistently demonstrated an anti-inflammatory response. Ketamine has also been found to possess anti-inflammatory effects; however, the evidence has not been systematically evaluated to determine what effect intraoperative ketamine has on IL-6 concentrations.

Methodology This was a systematic review and metaanalysis of studies evaluating the effect intraoperative ketamine had on inflammation/immune modulation in surgical patients. The investigators were specifically interested in ketamine’s effect on IL-6 because this was the most consistently reported outcome. A standardized search strategy was used to identify and criteria used to grade the level of evidence of studies published up to October 13, 2011. Only randomized controlled studies were included. Metaanalysis statistics were used to evaluate the effect ketamine had on IL-6 concentrations measured within the first 6 hours postoperatively.

Result Fourteen studies including 684 patients were eligible for evaluation. Of these studies, 8 involved cardiopulmonary bypass operations (CABG), 4 abdominal surgery, 1 thoracic surgery, and 1 cataract surgery. Only 6 of these studies were included in the meta-analysis (N = 331 patients; Table 1). A majority of studies evaluated CABG patients (n = 4), the other 2 included patients undergoing abdominal surgery (gastroplasty and hysterectomy). The authors judged the level of evidence to be high for all six of these studies. Most of the studies
included a single bolus of ketamine ranging from 0.15-0.5 mg/kg [10.5 mg to 35 mg in a 70 Kg patient]. Only one study evaluated the effect of a ketamine-based technique as the sole anesthetic. That study compared ketamine 1-3 mg/kg at induction then 2-4 mg/kg/hr vs. sufentanil-based anesthesia with 0.25 to 1 µg/kg at induction then 0.5-2 µg/kg/h.

In all 6 studies, ketamine decreased IL-6 concentrations postoperatively. In general, ketamine had the greatest effect on IL-6 concentrations after cardiac surgery (Table 1 and Figure 1). In the two types of abdominal surgery included in the analysis, the authors of those studies found no significant difference in IL-6 concentrations postoperatively between ketamine or control groups. However, a significant effect of ketamine during abdominal surgery was seen when data was analyzed in this meta-analysis. No dose response effect was seen. There were no signs of publication bias in any of the reviewed studies.

### Conclusion
Intraoperatorily administered ketamine significantly inhibited the inflammatory response in the early postoperative period, based on decreased IL-6 concentrations, in patients undergoing major surgery.

### Comment
Use of ketamine perioperatively has seen a resurgence in recent years. Numerous studies have found it reduces postoperative pain and opioid consumption, and now we have some evidence after major surgery, that it also reduces the early postoperative inflammatory response as measured by IL-6 levels. In fact, one of the largest effects of ketamine on postoperative IL-6 levels was in a study which compared a sole ketamine anesthetic with a sufentanil-based anesthetic during cardiac surgery. These findings support the argument that ketamine has an anti-inflammatory effect. These are exciting findings and are sure to generate many studies in the future. The key “so what?” question we need to ask is,

#### Table 1. Studies Included in Metaanalysis

<table>
<thead>
<tr>
<th>Population/sample size</th>
<th>Intervention</th>
<th>IL-6 mean difference in pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CABG /n = 50</td>
<td>Induction: ketamine 0.25 or 0.5 mg/kg Control = saline</td>
<td>-96</td>
</tr>
<tr>
<td>2. CABG /n = 128</td>
<td>Ketamine-based anesthesia: 1-3 mg/kg induction then 2-4 mg/kg/hr Sufentanil-based anesthesia: 0.25 µg/kg induction then 0.5-2 µg/kg/h</td>
<td>-114</td>
</tr>
<tr>
<td>3. CABG /n = 50</td>
<td>Induction: ketamine 0.5 mg/kg Control = saline</td>
<td>-29</td>
</tr>
<tr>
<td>4. CABG /n = 31</td>
<td>Induction: ketamine 0.25 mg/kg Control = saline</td>
<td>-130</td>
</tr>
<tr>
<td>5. Abdominal /n = 22</td>
<td>Ketamine 0.15 mg/kg before incision Control = saline</td>
<td>-35</td>
</tr>
<tr>
<td>6. Abdominal /n = 36</td>
<td>Induction: ketamine 0.15 mg/kg Control = saline</td>
<td>-46</td>
</tr>
</tbody>
</table>
“does ketamine improve outcomes?” Theoretically it should, because a heightened inflammatory response has been associated with poorer outcomes, especially after major surgery.

It should be pointed out that the findings of this metaanalysis apply mainly to patients undergoing cardiac surgery. Only two studies examined patients having major abdominal surgery. I would be interested to see if a similar effect was seen after other less major surgery, and to find out what effect ketamine has on outcomes, such as wound infection, return of bowel function, cardiac morbidity, and chronic pain. Ketamine, even in subanesthetic doses, is not without side effects, and some patients may experience adverse psychomimetic effects or hyperdynamic responses. Therefore I think it is important we find out if ketamine does indeed improve outcomes.

From this analysis we cannot determine if there is a dose response with ketamine with regards to IL-6 levels. However, in most of the studies investigators used a subanesthetic dose of 0.15-0.25 mg/kg. Based on these findings, I would probably consider using the smallest possible dose, taking into consideration the patients comorbidities and the planned surgical procedure.

Dennis Spence, PhD, CRNA

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
The effects of oral ibuprofen and celecoxib in preventing pain, improving recovery outcomes and patient satisfaction after ambulatory surgery

White PF, Tang J, Wender RH, Zhao M, Time M, Zaentz A et al

Abstract

Purpose The purpose of this study was to evaluate the efficacy of ibuprofen and celecoxib on preventing pain, decreasing opiate consumption, and improving patient satisfaction and recovery outcomes after ambulatory surgery.

Background Non-steroidal anti-inflammatory drugs (NSAIDS) are effective in decreasing postoperative pain, opioid consumption, and improving recovery after ambulatory surgery. However, concern over gastrointestinal and operative site bleeding due to blockade of prostaglandin synthesis at the cyclooxygenase (COX)-1 enzyme limit there widespread use. COX-2 selective inhibitors, such as celecoxib, reduce postoperative pain and opioid consumption, have a lower risk of bleeding, and thus may be safe alternatives to COX-1 NSAIDS. Unfortunately, some studies suggest that celecoxib is associated with cardiovascular complications with short-term postoperative use. Furthermore, subsequently retracted COX-2 publications have called into question previous positive findings on these classes of drugs. This study sought to compare outcomes after ambulatory surgery in patients administered either maximum daily doses of ibuprofen 1,200 mg/day or celecoxib 400 mg/day for four days.

Methodology This was a prospective, randomized, double-blind, placebo controlled study of 180 ASA I to III patients undergoing superficial surgery, such as knee arthroscopy, inguinal hernia repair, breast lumpectomy, or lipoma excision. Patients were randomly assigned to one of three groups; ibuprofen 1,200 mg/day (400 mg TID), celecoxib 400 mg (200 mg BID), or placebo. All drugs were started 20 minutes after arrival in the PACU and continued for 3 days after surgery.

In the operating room anesthesia was induced with propofol and an LMA was placed. Anesthesia was maintained with a propofol infusion, and fentanyl 50-200 µg was titrated as needed. Surgical incisions were injected with 1% lidocaine and 0.25% bupivacaine. Prior to emergence, all patients received 4 mg ondansetron, 4 mg dexamethasone, and 10 mg metoclopramide. After completion of the surgery, patients were taken to the PACU. Twenty minutes after arrival patients in the ibuprofen group received ibuprofen 400 mg, those in the celecoxib group received 400 mg, and those in the placebo group received placebo capsules and tablet matching the treatment drugs. Patients were prescribed Vicodin (5 mg hydrocodone + acetaminophen 500 mg) for breakthrough pain in the PACU or at home.
Patients were contacted by telephone at 24, 48, and 72 hours after surgery by a trained interviewer who was unaware of group assignment. Outcome data included the following:

- opioid consumption (number of pills)
- maximum pain scores (0-10 scale)
- satisfaction with postoperative pain management (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent)
- quality of recovery (QoR; 9-item questionnaire, 0-18) (See Notes at end.)
- side effects
- time to return of bowel function
- incidence of constipation
- time to resumption of normal activities of daily living

At their 7 and 30 day follow-up evaluations patients were asked about the number of days it took to tolerate normal fluids and solid food, for return of normal bowel function, and resume normal activities of daily living. At the time of the initial post-surgical visit, and at 30 days, the presence of wound complications was recorded (i.e., bleeding, hematomas, and infections), as was the occurrence of any cardiovascular complications. The primary outcome for which the sample size was based was the time in days to return of normal activities of daily living. Descriptive and inferential statistics were used to analyze the results. A P value less than 0.05 was significant.

**Result** Sixty subjects were enrolled in each of the three groups. Patient demographic characteristics, duration of surgery and anesthesia, and anesthetic drug doses were similar between the three groups (P > 0.05). The majority of the patients were Caucasian, with a mean age of approximately 48 years. Most surgeries were hernia repairs. Time to return of bowel function was one day less in the ibuprofen and celecoxib groups (2 ± 2 days) compared to the placebo group (3 ± 2 days). However, this difference was not statistically significant. Likewise, the time to return of normal physical activities did not differ between groups (ibuprofen: 7 ± 5 d vs. celecoxib: 8 ± 6 d vs. placebo: 7 ± 4 d; P = ns).

Postoperative maximum pain scores at 24 and 48 hours were similar between the three groups (Figure 1). However, at 72 hours patients in the ibuprofen group had significantly less pain than those in the placebo group (P < 0.05; Figure 1). Overall, maximum pain scores for the 72 hour period were less in the ibuprofen and celecoxib groups (4 ± 3) compared to the placebo group (5 ± 3) (P < 0.05). Opioid requirements were significantly less in the ibuprofen and

![Figure 1. Comparison of Pain Scores](image-url)

**Note.** VNRS = verbal numeric rating scale.
celecoxib groups when compared to the placebo group at 24, 48, and 72 hours (P < 0.05; Figure 2).

Patient satisfaction with postoperative pain management was higher in the ibuprofen and celecoxib groups (3 ± 1) when compared to the placebo group (2 ± 2) (P = 0.02). Patients in the two treatment groups rated their pain management as very good compared to only good in the placebo group. Quality of recovery scores were significantly higher on all three postoperative days in the ibuprofen and celecoxib groups when compared to the placebo group (P < 0.01; Table 1). The incidence of postoperative emesis was similar in all groups.

However, the incidence of constipation was significantly higher in the control group with 18.3% complaining of constipation compared to only 5% in the ibuprofen and 3.3% in the celecoxib groups (P < 0.05). None of the patients in the two treatment groups experienced postoperative bleeding, wound infection or cardiovascular complications during the follow-up evaluations at 7 or 30 days.

**Figure 2. Comparison of Opioid Consumption**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 60)</th>
<th>Ibuprofen (n = 60)</th>
<th>Celecoxib (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr</td>
<td>16 +/- 0.2</td>
<td>16 +/- 0.2</td>
<td>15 +/- 0.3</td>
</tr>
<tr>
<td>48 hr</td>
<td>17 +/- 0.2</td>
<td>17 +/- 0.2</td>
<td>16 +/- 0.2</td>
</tr>
<tr>
<td>72 hr</td>
<td>17 +/- 0.2</td>
<td>17 +/- 0.2</td>
<td>16 +/- 0.2</td>
</tr>
</tbody>
</table>

* P < 0.05 vs control group

**Note.** Patients were given Vicodin (5 mg hydrocodone + acetaminophen 500 mg) for breakthrough pain.

**Conclusion**
Ibuprofen 400 mg TID and celecoxib 400 mg BID were found to be equivalent in their ability to reduce pain, opioid consumption and the incidence of constipation, and improve patient satisfaction and quality of life. Given the lower cost of ibuprofen when compared to celecoxib, these data suggest that it may be a more cost effective alternative to celecoxib when administered as part of a multimodal post-surgical pain management regimen after ambulatory surgery.

**Comment**
The results of this study are not surprising. Multimodal therapy, which combines the use of local anesthetics injected into the wound along with opioids, acetaminophen, and NSAIDS or COX-2 inhibitors, is better than opioids alone. In this study, the investigators found lower pain scores and opioid consumption, and higher patient satisfaction and quality of recovery scores. However, these differences were not as dramatic when compared to the difference seen in the incidence of constipation.

<table>
<thead>
<tr>
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</table>

* QoR scores were significantly higher in the two treatment groups when compared to the control group (P < 0.01).
Patients in the placebo group had an absolute 15% higher incidence of constipation when compared to the two treatment groups. This was most likely due to the decreased opioid consumption in the two treatment groups. I suspect the lower incidence of constipation contributed to the higher patient satisfaction and quality of recovery scores.

The decreased pain and opioid consumption outcomes in the two treatment groups were modest at best and are probably a reflection of the types of surgeries (i.e., hernia repair, lipoma excision) and judicious use of local anesthetics. It is important to point out that volatile anesthetics where not used in these cases, and this may have influenced the results. I think this study demonstrates that these types of procedures can be performed under local anesthesia and TIVA with propofol and fentanyl.

The authors based their power analysis on the number of days until resuming normal activities. However, the investigators failed to provide a clear definition of what this outcome meant. I view this as a limitation. Additionally, by choosing this outcome for sample size calculation they were more likely to find statistically significant, though not clinically significant differences. For example, they found patient satisfaction was significantly higher in the treatment groups, however the groups only differed by one point.

Nonetheless, I think these findings support the use of multimodal therapy with NSAIDS or COX-2 inhibitors. The investigators recommended ibuprofen because it costs much less than celecoxib; however in terms of ease of use, celecoxib may be better because patients only have to take it twice a day rather than three times a day with ibuprofen. Celecoxib has a lower risk of bleeding. Anesthesia providers should consider the findings of this study and these issues when making recommendations to surgeons and patients on postoperative analgesic regimens. I think the key is around the clock administration of non-opioid analgesics for at least the first 72 hours after ambulatory surgery.

**Dennis Spence, PhD, CRNA**

**Quality of Recovery Tool:** The QoR\(^1\) tool contains 9 questions scored as 0 = not at all, 1 = some of the time, or 2 = most of the time. The total score ranges from 0 to 18. The questions ask about: (1) general feeling of well being, (2) support from others, (3) understanding instructions, (4) able to look after toilet and personal hygiene needs unaided, (5) ability to urinate and free of constipation, (6) able to breathe easily, (7) free of headache, backache and muscle pains, (8) free of nausea and vomiting, and (9) free from severe pain or constant moderate pain.


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