

# Evidence Review



## Topic: Perioperative Use of NSAIDs in Total Hip and Total Knee Arthroplasty Patients

### Background

Postoperative pain is a complex phenomenon that stems from tissue trauma incurred during surgery. Health care providers are keen to minimize pain following orthopaedic surgery because the consequences of postoperative uncontrolled pain and medication-related side effects can include sub-optimal rehabilitation, delayed recovery, poor surgical outcomes, longer hospitalization, and greater health-care resource utilization.<sup>1,2</sup>

Opioid therapy has traditionally been viewed as the first line medication for postoperative analgesia following total hip (THA) and total knee arthroplasty (TKA).<sup>3</sup> At the same time, opioid use is associated with sedation, respiratory depression, nausea, vomiting, and other side-effects which are known to impair postoperative recovery following surgery.<sup>4</sup> A further concern for patients and physicians is the potential for opiate addiction, a fact which has contributed to the underutilization and suboptimal dosing of opiate narcotics in postoperative pain management.<sup>5</sup> Hence, since the 1980s there has been a move to limit reliance on opiate narcotics as the sole postoperative analgesic and a move towards the use of multimodal analgesia, defined as the simultaneous use of different analgesic regimens for the treatment of postoperative pain. The primary advantage with a multimodal approach is that it capitalizes on the synergist effects of different analgesic agents, which results in the use of smaller medication doses and minimizes the risk for complications.<sup>3</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs), such as acetaminophen and indomethacin, are routinely used as part of multimodal postoperative pain control.<sup>6</sup> In the 1990s, NSAIDs had an important role in the post-surgical management of pain, either administered alone or with opioids.<sup>7</sup> NSAIDs provide varying degrees of analgesia and anti-inflammatory effects, and unlike opioids, they do not cause respiratory depression or sedation.<sup>7</sup> Furthermore, the concurrent postoperative use of NSAIDs with opioids provides better respiratory function, improved sleep quality, and fast recovery of gastrointestinal function. These

properties highlight the opioid-sparing effects of NSAIDs. On the other hand, the limitation with using NSAIDs perioperatively has been the potential for blood thinning, gastrointestinal and renal side-effects.<sup>8</sup> For this reason, NSAIDs are typically discontinued 7 to 10 days prior to THA and TKA surgery as continued NSAID therapy is associated with a two-fold increase in blood loss following the arthroplasty surgery.<sup>9</sup>

A new subclass of NSAIDs, known as cyclooxygenase-2-selective (COX-2) inhibitors, emerged in the late 1990s as the improved NSAIDs which lack the side-effects of non-specific NSAIDs, such as increased postoperative bleeding.<sup>10</sup> Typified by Celebrex and Vioxx, COX-2 inhibitors have little or no effect on coagulation – a factor which has made COX-2 inhibitors more widely used in perioperative multimodal protocols.

Given the potential benefits and harms associated with NSAID usage in major orthopaedic surgery, the often cited concern is when to administer and suspend NSAIDs in patients receiving total joint replacements. The aim of this evidence review is to summarize the best available literature from Cochrane reviews, experimental clinical studies and official guidelines on perioperative NSAID usage, including dosing, frequency, and duration, for elective primary and revision THA and TKA procedures.

### Review Design

- This review is structured on a format similar to a Cochrane systematic review.
- The relevant Cochrane systematic review, if available, will be included and summarized in this evidence review.
- Next, the search strategy and inclusion/exclusion criteria of the Cochrane review will be used (or developed if a Cochrane review does not exist) to search for prospective comparative studies (RCT, Controlled Clinical Trial, Cohort Study) and systematic reviews published after the Cochrane review for selection to this evidence review.

- If prospective comparative studies are not available then retrospective comparative studies and case series reports will be included in this review.
- Finally, applicable clinical practice guidelines will also be included in this review.
- Selected literature and clinical practice guidelines must pass quality control (discussed below) for inclusion into this evidence review.

### Search Strategy:

The objective of this evidence review is to provide guidance on the appropriate perioperative usage of NSAIDs with regard to elective primary and revision THA and TKA procedures. To ensure the selection of high-quality primary studies for this evidence review, preference was given towards the inclusion of prospective comparative trials, although retrospective comparative studies could be included here as well. Non-comparative studies, such as case series, case studies, and expert opinions, are regarded as having the lowest level of evidence <sup>11</sup> and were not included in this review.

A search of the Cochrane Database of Systematic Reviews was performed with the following search strategy:

(NSAID OR “non-steroidal”).mp AND (arthroplasty OR replacement).mp

One potential Cochrane review was selected: Fransen and Neal. 2004. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty. Unfortunately, that Cochrane review did not report on NSAID usage parameters (e.g. dosing, frequency, duration, holding period) which is the focus of this evidence review. Thus, it was not included in this report.

A search of the PubMed and Embase medical databases was performed with the following search strategy:

(“non-steroidal anti-inflammatory” OR NSAID) AND (arthroplasty OR replacement) AND (hip OR knee) AND (Clinical trial[pt]) AND English[la]

### Clinical Study Inclusion and Exclusion Criteria:

Inclusion criteria for published studies were as follows:

- Comparative trials where intervention (NSAID) patient outcomes were compared to those of control (placebo or appropriate comparator) group patient outcomes; and
- Intervention treatment was given perioperatively; and
- Study patients received conventional primary or revision THA or TKA; and
- Study outcome measures included patient-level outcomes such as functional recovery, LOS, recovery from pain, and postoperative adverse events; and
- Studies published in English.

Exclusion criteria included:

- Joint replacements other than the hip and knee; and
- Studies based on prostheses that are not conventional devices (e.g., hip resurfacing systems).

Special Notes:

It was reported in March, 2009 that Dr. Scott S. Reuben, a US anesthesiologist and a former spokesperson for Pfizer, falsified data in 21 studies he had authored on rofecoxib and celecoxib in a manner that augmented the analgesic effects of the drugs. These retracted studies will be excluded from consideration for this evidence review.

Rofecoxib (Vioxx), manufactured by Merck, was recalled from the Canadian market in September, 2004 due to cardiovascular-related fatalities. Therefore, studies where the intervention is perioperative rofecoxib will be excluded from this evidence review.

Valdecoxib (Bextra), manufactured by Pfizer, was suspended for sale in Canada in April, 2005 due to safety concerns related to cardiovascular problems and skin reactions. Hence, studies based on valdecoxib will not be considered for inclusion into this review.

### Clinical studies selected for inclusion:

- Huang et al. (2008). Perioperative celecoxib administration for pain management after total knee arthroplasty – A randomized, controlled study. *BMC Musculoskelet Disord.* <sup>12</sup>
- Meunier, A. et al. (2007). Effects of celecoxib on blood loss, pain, and recovery of function after total knee replacement: A randomized placebo-controlled trial. *Acta Orthopaedica.* <sup>13</sup>

### Clinical studies excluded:

- Reuben, S.S. et al. 2008. A prospective randomized trial on the role of perioperative celecoxib administration for total knee arthroplasty: improving clinical outcomes. *Anesth Analg.* 106 (4):1258-64. [study retracted due to falsified data]
- Reuben, S.S. et al. 2002. Evaluation of the safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. *J Arthroplasty.* [study retracted due to falsified data]
- Li, W. et al. 2009. Experimental study of COX-2 selective and traditional non-steroidal anti-inflammatory drugs in total hip replacement. *J Internat Med Res.* [perioperative intervention was rofecoxib]
- Viscusi, et al. 2008. A multiple-day regimen of parecoxib sodium 20 mg twice daily provides pain relief after total hip arthroplasty. *Anesth Analg.* [perioperative intervention was parecoxib, a precursor to valdecoxib]
- Dorr, L.D. et al. 2008. Multimodal analgesia without parenteral

narcotics for total knee arthroplasty. *J Arthroplasty*. [intervention treatment was ropivacaine, not an NSAID]

- Emery, P. et al. 2008. Analgesic effectiveness of celecoxib and diclofenac in patients with osteoarthritis of the hip requiring joint replacement surgery: a 12-week, multicenter, randomized, double-blind, parallel-group, double-dummy, noninferiority study. *Clin Ther*. [intervention treatment was given preoperatively only]
- Suadan, M. et al. 2007. Celecoxib versus ibuprofen in the prevention of heterotopic ossification following total hip replacement: a prospective randomised trial. *J Bone Joint Surg Br*. [comparison of celecoxib to ibuprofen only done postoperatively following THA]
- Buvanendran, A. et al. 2003. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. *JAMA*. [perioperative intervention was rofecoxib]

#### Clinical studies excluded but of interest:

- Karvonen S. et al. 2008. Efficacy of oral paracetamol and ketoprofen for pain management after major orthopedic surgery. *Methods Find Exp Clin Pharmacol*. 30(9):703-6. [unable to retrieve study for assessment]<sup>14</sup>
- Fijn, R. et al. 2003. Prevention of heterotopic ossification after total hip replacement with NSAIDs. *Pharm World Sci*. [this study is a review, not comparative trial]<sup>15</sup>
- Tang, R. et al. 2009. Multimodal analgesia for hip arthroplasty. *Orthop Clin N Am*. [this study is a review, not comparative trial]<sup>16</sup>
- Fischer, H.B. and Simanski, C.J. 2005. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. *Anaesthesia*. [this study is a review, not comparative trial]<sup>17</sup>

#### Quality control

The quality of the two selected prospective randomized controlled trials<sup>12,13</sup> was assessed by an independent reviewer. Study quality was measured using a validated scale<sup>18</sup> developed by the Cochrane Collaboration Back Review Group. With this assessment tool, quality assessment of a prospective comparative trial is based firmly on the study design, data collection and analysis processes. The studies included here were judged to have moderate to high-quality. Lastly, the AGREE Instrument<sup>19</sup> was used to appraise the selected clinical practice guideline. This instrument gauges the quality of a guideline based on six domains: scope and purpose; stakeholder involvement; rigour of development; clarity and presentation; applicability; and editorial

independence. Based on this tool, the selected SIGN practice guideline was included in this evidence review.

#### Results

Two prospective, randomized controlled trials were identified and met the inclusion/exclusion criteria for this evidence review.

Huang et al. (2008) reported a Taiwan-based prospective, randomized controlled trial that featured 80 TKA patients. Patients recruited into that study had primary osteoarthritis and were aged 60 years or more, and the exclusion criteria were rheumatoid arthritis, end-stage renal disease, previous cerebral vascular accident history, peptic ulcers, recent myocardial infarction (within 1 year), and allergy to sulf, NSAIDs, or morphine. The intervention group patients (n=40; mean age=70 years) received 400 mg oral celecoxib 1 hour before surgery, and 200 mg every 12 hours, along with patient-controlled analgesia (PCA) morphine, over the first 5 postoperative days. The control group patients (n=40; mean age=70 years) received only PCA morphine over the same postoperative period. Both groups were comparable for age, preoperative ROM, operation length and surgical blood loss. This study found that patients who received perioperative celecoxib had better postoperative resting pain scores at 48 and 72 hours, better joint range of motion at 7 days post-surgery, lower opioid requirements, and marginally less nausea/vomiting (although this was not significant). At the same time, celecoxib patients did not differ from control patients in blood loss (intra- and postoperative). These authors conclude that perioperative celecoxib, beginning with 400mg, combined with opioids, is an effective and safe regimen for pain control in TKA patients. It ought to be noted that limitations of this study include the lack of an actual placebo in the control group and the limited 7-day postoperative study period.

A Swedish study reported by Meunier et al. (2008) was also a randomized, controlled trial that examined the perioperative efficacy of celecoxib, although here the COX-2 inhibitor was given at a 200 mg dose preoperatively, followed by 200 mg twice a day for 3 weeks. The intervention group patients (n=24; mean age=68 years) matched evenly with the control placebo group (n=20; mean age=69 years) in terms of age, height, weight, and surgery time comparisons. At 4 weeks after surgery, there were no differences in blood loss between the groups, although celecoxib patients had an average 30% lower pain score. This difference was not observed at the 1 year follow-up. Based on their results, the authors concluded that perioperative celecoxib (200 mg) does not increase blood loss but does reduce post-surgical pain following TKA. Consequently, the authors conclude that celecoxib does not have to be discontinued before surgery. Although a limitation of this clinical trial is its relatively short

follow-up period (1 year), its advantages include the use of a placebo in the control group and use of intent-to-treat analysis for statistical comparisons.

Although there are many published articles regarding the perioperative use of NSAIDs with respect to total joint arthroplasty, only two randomized controlled trials passed the strict inclusion/exclusion criteria of this evidence review. The chief reason for this is because the numerous randomized controlled trials available on this topic have focused on rofecoxib, a COX-2 specific inhibitor that has been withdrawn from the Canadian market. Of the studies included here, it is evident that the specific NSAID celecoxib results in better outcomes following TKA, such as less pain, quicker recovery of function, less blood loss, and a reduced need for opioids, as compared to placebo. The perioperative dosage of celecoxib reported here was either 200 or 400 mg preoperatively, followed by 200 mg twice daily for either 5 days or 3 weeks. Other studies have compared the postoperative outcomes of 200 mg vs. 400 mg celecoxib and have noted that oral premedication with celecoxib 400 mg was more effective than 200 mg in reducing severe postoperative pain and the need for rescue analgesics in the postoperative period.<sup>20</sup> Furthermore, the trials included in this evidence review utilized TKA patients. Although similar positive results may be expected with the perioperative use of celecoxib in THA patients, no randomized, controlled trial with hip arthroplasty patients were found for inclusion into this review. Lastly, the included trials here did not compare celecoxib head-on with non-specific NSAIDs as part of perioperative multimodal routines.

It must be noted that celecoxib is contraindicated in patients who have aspirin-sensitive asthma or allergic reactions to aspirin or certain sulfa drugs called sulfonamides, or who are in their third trimester of pregnancy. Also, some studies have explored the possible interaction of celecoxib on periprosthetic bone mineral density following THA and have found no detrimental effects of this NSAID at 3 and 6 months postoperatively compared to placebo.<sup>21</sup>

In summary, there is good evidence from limited randomized, controlled trials that celecoxib, as part of perioperative multimodal pain management, has a positive result on short-term postoperative outcomes following TKA and likely THA surgery. Advantages of its use in the multimodal analgesia regimen include opioid-sparing effects (e.g., less hypotension, less respiratory depression, less nausea/vomiting, less addiction potential), reduced intraoperative bleeding, and less GI irritation risks. A review of the literature here suggests that preoperative celecoxib (200-400 mg) may be followed with 200 mg twice daily for at least 5 days postoperatively.

Lastly, a check for current clinical practice guidelines for

recommendations on the perioperative usage of NSAIDs failed to identify guidelines specific to arthroplasty patients. One guideline<sup>22</sup> produced by the American Academy of Orthopaedic Surgeons is specific to osteoarthritis of the knee (non-arthroplasty) and recommends the following:

“The authors suggest patients with symptomatic OA of the knee and increased gastrointestinal (GI) risk (Age  $\geq$  60 years, comorbid medical conditions, history of peptic ulcer disease, history of GI bleeding, concurrent corticosteroids, and/or concomitant use of anticoagulants) receive one of the following analgesics for pain:

- Acetaminophen [not to exceed 4 grams per day]
- Topical NSAIDs
- Nonselective oral NSAIDs plus gastro-protective agent
- Cyclooxygenase-2 inhibitors
- (Grade B, Level II)”

### Summary

The current Alberta Hip & Knee Arthroplasty care path recommends the following analgesic options to start on the day of primary or revision THA and TKA surgery and continue throughout the in-patient stay:

Analgesics (reassess after 72 hours): Select one drug. Reassess use/dosages of medications in patients with renal or hepatic dysfunction.

- Acetaminophen 650-1000 mg po/pr QID x2 days (max 4000mg from all routes, consider Tylenol # 3 and Percocet)
- Ibuprofen po (suggest 200 - 600mg TID – QID)- duration at surgeon’s discretion
- Indomethacin prn(suggest 50 -100mg BID – TID) (maximum 150-200 mg per day)- duration at surgeon’s discretion
- Celecoxib po 100 – 200mg BID X 5 days
- Ketorolac IVPB 10mg q6 – 8h X2 days

### Opioids

Long acting:

- Oxycodone Slow Release (Oxycontin) 5mg-20mg po BID; maximum of 5 doses in total. If allergic/intolerant, check with surgeon for patient specific treatment

Short acting: Select one drug:

- Oxycodone Immediate Release 5mg with Acetaminophen (Percocet) 1-2 tabs po q4h prn for break through pain or;
- Acetaminophen with Codeine 30 mg (Tylenol #3) 1-2 tabs po q4h prn
- If orals are ineffective then morphine 1-5mg IV q1h prn piggybacked with infusion pump
- If patient allergic/intolerant to morphine then hydromorphone 2-4mg orally (tab) q4-6h as needed or 1-2mg IV q4-6h as needed



## Clinical Committee Comment

On October 15, 2009 the Hip and Knee Clinical Committee discussed the Hip and Knee Care Path's current pain management recommendations. Committee members agreed to the following amendments:

- Acetaminophen to be moved to appear under short acting and "select one drug" appearing next to short acting to be removed.
- "Communication regarding pain management between pain management service and orthopaedic surgeon to occur as needed" to be added next to pain management.

## Care Path Recommendation

For the 2009 Hip and Knee Care Path release, the pain management section will be amended to read:

**Pain Management** – Communication regarding pain management orders between pain management service and orthopaedic surgeon to occur as needed.

### Opioids

#### • Long acting:

Oxycodone Slow Release (Oxycontin) 5mg-20mg po BID; maximum of 5 doses in total. If allergic/intolerant, check with surgeon for patient specific treatment

#### • Short acting:

Oxycodone Immediate Release 5mg with Acetaminophen (Percocet) 1-2 tabs po q4h prn for break through pain or; Acetaminophen with Codeine 30 mg (Tylenol #3) 1-2 tabs po q4h prn  
Acetaminophen 650-1000 mg po/pr QID x2 days (max 4000mg from all routes, consider Tylenol # 3 and Percocet)<sup>8</sup>  
If orals are ineffective then morphine 1-5mg IV q1h prn  
If patient allergic/intolerant to morphine then hydromorphone 2-4mg orally (tab) q4-6h as needed or 1-2mg IV q4-6h as needed

#### • Analgesics/Anti-inflammatories (reassess after 72 hours):

**Select one drug.** Reassess use/dosages of medications in patients with renal or hepatic dysfunction.  
Ibuprofen po (suggest 200 - 600mg TID – QID)- duration at surgeon's discretion  
Indomethacin prn(suggest 50 -100mg BID – TID) (maximum 150-200 mg per day)- duration at surgeon's discretion  
Celecoxib po 100 – 200mg BID X 5 days  
Ketorolac IV 10mg q6 – 8h X2 days

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