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AMERICAN ASSOCIATION OF HIP AND KNEE SURGEONS

Clinical Practice Guideline

Nonsteroidal Anti-Inflammatory Drugs in Total Joint Arthroplasty

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OFFICE: 847-698-1200 • FAX: 847-698-0704 • WEB: www.AAHKS.org
9400 W. Higgins Rd., Suite 230 • Rosemont, IL USA 60018-4976

Nonsteroidal Anti-Inflammatory Drugs in Total Joint Arthroplasty: The Clinical Practice Guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society

Yale A. Fillingham MD[1], Charles P. Hannon MD, MBA[2], Karl C. Roberts MD[3], AAHKS Anesthesia & Analgesia Clinical Practice Guideline Workgroup[4], William G. Hamilton MD[5*], Craig J. Della Valle MD[2*]

[1]Department of Orthopaedic Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

[2]Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

[3]Department of Orthopaedic Surgery, Michigan State University, Grand Rapids, MI, USA

[4]Workgroup Comprised of the following individuals: Justin T. Deen MD (Department of Orthopaedics and Rehabilitation, University of Florida College of Medicine, Gainesville, FL, USA), Greg A. Erens MD (Department of Orthopaedic Surgery, Emory University, Atlanta, GA, USA), Jess H. Lonner MD (Rothman Institute at Thomas Jefferson University, Philadelphia, PA, USA), Aidin E. Pour MD (Department of orthopaedic surgery, University of Michigan, Ann Arbor, MI, USA), Robert S. Sterling MD (Department of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA)

[5]Anderson Orthopedic Research Institute, Alexandria, VA, USA

[*]Denotes co-senior authors

Introduction

The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society, The Knee Society and The American Society of Regional Anesthesia and Pain Medicine (ASRA) have worked together to develop evidence-based guidelines on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidenced-base approach on the use of NSAIDs following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of NSAIDs in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analyses to support the clinical practice guidelines.[1] For each question, we have provided a recommendation, assessed the strength of the recommendation, and elaborated on the rationale of the recommendation, which should be interpreted in accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*.[1] The current clinical practice guidelines were based on the available evidence, so future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1:

For patients undergoing primary TJA, do oral NSAIDs administered either immediately preoperatively and/or in the early postoperative period, affect postoperative pain and/or opioid consumption?

Response/Recommendation 1A:

An oral NSAID administered either preoperatively and/or in the early postoperative period reduces pain and opioid consumption following primary TJA.

Strength of Recommendation 1A: Strong

Response/Recommendation 1B:

Administration of an oral selective clyclooxygenase-2 (COX-2) NSAID immediately preoperatively, compared to early postoperative administration, provides improved postoperative pain control and reduced opioid consumption following primary TJA.

Strength of Recommendation 1B: Moderate

Rationale:

We reviewed seventeen randomized clinical trials that represented the best available evidence including nine high quality and eight moderate quality studies to assess the effectiveness of selective COX-2 (includes selective [i.e. Celecoxib] and preferential [i.e. Meloxicam] COX-2 inhibitory agents) and non-selective (COX-1 and -2 inhibitory agents) oral NSAIDs to reduce pain and/or opioid consumption postoperatively following TJA.[2-18] Among

the included studies comparing either a selective and/or non-selective NSAID to placebo, ten studies investigated a selective NSAID and five studies investigated a non-selective NSAID.[2-5, 7-15, 17] Similar to other topics within the clinical practice guidelines, only a limited amount of meta-analyses was able to be performed due to inconsistency in the reporting of outcomes and timepoints for reporting the outcomes.

Oral NSAIDs demonstrated with limited heterogeneity in direct meta-analysis to reduce opioid consumption and sum of pain intensity differences (outcome is a four-point scale that summarizes the treatment benefit over a specific time period) compared to placebo. When direct meta-analysis was performed individually for primary total hip and knee arthroplasty, opioid consumption was lower when patients were administered preoperative and/or postoperative oral NSAIDs. Combined analysis of primary hip and knee arthroplasties demonstrated similar results favoring reduced opioid consumption and improved sum of pain intensity differences for oral NSAIDs compared to placebo.

Due to a lack of consistent outcomes, no direct or network meta-analysis could be performed comparing selective or non-selective NSAIDs. However, qualitative analysis of selective and non-selective oral NSAIDs consistently demonstrate an overwhelmingly significant response of a reduction in postoperative pain and opioid consumption for both types of NSAIDs. Three studies have directly compared selective and non-selective oral NSAIDs, which showed no significant difference in the outcomes of postoperative opioid consumption or pain scale.[13, 16, 18] Similarly, no direct or network meta-analysis could be performed to investigate preoperative verses postoperative dosing of oral NSAIDs. Among the studies comparing a selective NSAID to placebo, three studies included preoperative dosing, three

studies included postoperative dosing, and four studies included both preoperative and postoperative doses.[2, 3, 5, 7-9, 11-14] The studies comparing a non-selective NSAID to placebo included four studies utilizing postoperative dosing and one study utilizing both preoperative and postoperative doses.[4, 10, 13, 15, 17] However, one high quality study comparing preoperative and postoperative administration of a single dose of a selective NSAID showed a reduction in opioid consumption with the preoperative administration of the oral selective NSAID.[12]

Guideline Question 2:

For patients undergoing primary TJA, do oral NSAIDs administered after discharge affect postoperative pain and/or opioid consumption?

Response/Recommendation 2A:

Administration of an oral selective COX-2 NSAID after discharge reduces pain and opioid consumption during the six-week period following a primary total knee arthroplasty (TKA).

Strength of Recommendation 2A: Moderate

Response/Recommendation 2B:

In the absence of reliable evidence, it is the opinion of the workgroup that oral selective COX-2 NSAIDs may be used after discharge as part of a multimodal pain regimen to reduce postoperative pain and opioid consumption in patients undergoing primary total hip arthroplasty (THA).

Strength of Recommendation 2B: Consensus

Rationale:

Despite the numerous high and moderate quality randomized clinical trials investigating administration of oral NSAIDs during the perioperative period, such as preoperatively or during the postoperative admission, we lack the same level of evidence to evaluate the use of oral NSAIDs after discharge. Because of concerns regarding the safety of non-selective oral NSAID administration for an extended duration and lack of specific evidence for non-selective oral

NSAIDs after discharge, the workgroup has elected to only make a recommendation regarding the use of selective oral NSAIDs after discharge from a primary TJA.

Similar to the administration of oral selective COX-2 (includes selective [i.e. Celecoxib] and preferential [i.e. Meloxicam] COX-2 inhibitory agents) NSAIDs during the perioperative period, such as preoperatively or during the postoperative admission, utilization of an extended duration of oral selective COX-2 NSAIDs reduces the postoperative pain and opioid consumption. A single high quality study investigating the administration of an oral selective COX-2 NSAID compared to placebo for six-weeks provides overwhelming evidence favoring oral selective COX-2 NSAID use following a primary TKA.[19] Because we lack similar evidence after a primary THA, the workgroup provides a consensus recommendation favoring the administration of an oral selective COX-2 NSAID after discharge from primary THA. Furthermore, the inclusion of an oral NSAID as a component of a postoperative multimodal pain management protocol following primary TJA has demonstrated a reduction in pain, opioid consumption, and the risk of opioid-related adverse effects, such as respiratory depression, nausea/vomiting, sedation, or urinary retention.[20] Therefore, we can support the use of oral selective COX-2 NSAIDs after discharge from a primary TJA as part of a multimodal pain regimen.

Guideline Question 3:

For patients undergoing primary TJA, does intravenous (IV) ketorolac administered preoperatively, intraoperatively, or early postoperatively affect postoperative pain and/or opioid consumption?

Response/Recommendation 3A:

Administration of IV ketorolac preoperatively, intraoperatively, or within 24 hours postoperatively reduces pain and opioid consumption postoperatively (within the first 48 hours) following primary TJA.

Strength of Recommendation 3A: Strong

Response/Recommendation 3B:

Low-dose (15 mg) and high-dose (30 mg) administration of IV ketorolac immediately postoperatively are equivalent at reducing pain and opioid consumption postoperatively (within the first six hours) following primary TJA.

Strength of Recommendation 3B: Moderate

Rationale:

We reviewed seven randomized clinical trials that represented the best available evidence including four high quality and three moderate quality studies to assess the ability of IV ketorolac to reduce postoperative pain and/or opioid consumption following TJA.[21-27] Qualitative analysis consistently demonstrated statistically favorable outcomes for IV ketorolac

compared to placebo regarding the reduction in postoperative pain and opioid consumption with no significant increase of medical complications such as adverse events, nausea/vomiting, blood loss, pruritus, urinary retention, or respiratory depression. Despite the high and moderate quality randomized clinical trials, only direct meta-analysis of opioid consumption could be performed due to inconsistency in the reporting of pain outcomes and timepoints for reporting the outcomes. The direct meta-analysis of opioid consumption significantly favored IV ketorolac compared to placebo with limited heterogeneity.

Among the included studies, the total dosage of IV ketorolac administered to patients ranged between 15 mg and 150 mg given within the first 24 hours after surgery.[21-27] However, only one high quality study compared low- and high-doses of IV ketorolac, which demonstrated no difference between a single postoperative dose of 15 mg or 30 mg of IV ketorolac.[27] Although no difference was observed between the low- and high-dose treatments, 15 mg and 30 mg IV ketorolac doses are still considered relatively low-doses compared to the other published doses of IV ketorolac. Therefore, the lack of an observed difference could simply be the result of not having a large enough difference between the dose amounts to observe a dose response. Despite the potential for reduced postoperative pain and opioid consumption with higher IV ketorolac doses, the workgroup suggests the use of minimally effective doses to diminish the risk of medical complications such as acute kidney failure.

Guideline Question 4:

For patients undergoing primary TJA, do NSAIDs given preoperatively, intraoperatively, or postoperatively compared to placebo have an increased risk of postoperative medical complications?

Response/Recommendation:

Oral or IV NSAIDs administered preoperatively, intraoperatively, or postoperatively do not appear to increase the risk of medical complications following primary TJA; however, providers should consider patient comorbidities, the type of NSAID administered, dose, and duration of administration.

Strength of Recommendation: Limited

Rationale:

Among the reviewed high and moderate quality randomized clinical trials comparing perioperative oral NSAIDs and placebo, twelve studies reported on medical complications related to the administration of NSAIDs.[2-5, 7-9, 11-15] Qualitative examination demonstrated no consistent difference between oral selective COX-2 (includes selective [i.e. Celecoxib] and preferential [i.e. Meloxicam] COX-2 inhibitory agents) NSAIDs, oral non-selective (COX-1 and -2 inhibitory agents) NSAIDs, and placebo with the exception of a lower incidence of postoperative fever with patients receiving an oral NSAID. Direct meta-analysis was capable of being performed comparing various complications between perioperative NSAIDs and placebo, which

showed no significant difference with regards to any adverse event (0.93 relative risk; 95% confidence interval of 0.85 to 1.02), vomiting (0.82 relative risk; 95% confidence interval of 0.52 to 1.31), nausea (0.84 relative risk; 95% confidence interval of 0.68 to 1.04), blood loss (-0.23 standard mean difference; 95% confidence interval of -0.54 to 0.08), pruritus (1.73 relative risk; 95% confidence interval of 0.96 to 3.13), urinary retention (1.24 relative risk; 95% confidence interval of 0.34 to 4.59), and sedation (0.46 relative risk; 95% confidence interval of 0.16 to 1.26). Similar to oral NSAIDs, direct meta-analysis of medical complications between IV ketorolac and placebo were not significant with regards to any adverse events (0.94 relative risk; 95% confidence interval of 0.59 to 1.50), nausea (0.89 relative risk; 95% confidence interval of 0.70 to 1.12), vomiting (0.73 relative risk; 95% confidence interval of 0.47 to 1.14), blood loss (-0.14 standard mean difference; 95% confidence interval of -0.46 to 0.17), pruritus (0.50 relative risk; 95% confidence interval of 0.22 to 1.12), urinary retention (0.75 relative risk; 95% confidence interval of 0.43 to 1.32), or respiratory depression (-0.05 standard mean difference; 95% confidence interval of -0.28 to 0.18).

Despite the evidence favoring oral and IV NSAIDs in the qualitative and quantitative analysis of numerous high and moderate quality studies to reduce postoperative pain and opioid consumption, the gastrointestinal and renal safety profile of oral and IV NSAIDs have not been thoroughly studied in patients following primary TJA. Although nausea and vomiting were frequently reported among the studies, more severe complications including upper gastrointestinal bleeding and acute renal failure were not reported. It is possible the lack of reporting an upper gastrointestinal bleed is due to the rarity of the complication. As a result, clinicians should consider the safety of perioperative NSAIDs as it relates to severe

gastrointestinal and renal failure complications. Therefore, the work group downgraded the recommendation strength by only assigning a limited strength to the recommendation.

Areas for Future Research:

While the best available evidence included numerous high and moderate quality randomized clinical trials, we were still presented with limitations of the literature in the formulation of the clinical practice guidelines on the use of NSAIDs following primary TJA. We suggest future research on perioperative administration of NSAIDs focus on determining the optimal timing of the dosage and type of NSAID (selective or non-selective) to reduce the postoperative pain and/or reduction in opioid consumption. Because the current literature only has a single study investigating the use of a selective NSAID after discharge of a primary TKA, additional research is still necessary. We suggest future research focus on the use of selective NSAIDs after discharge of primary hip and knee arthroplasties. If future research has been able to demonstrate the safe utilization of extended non-selective NSAIDs following primary TJA, then we would suggest the inclusion of non-selective NSAIDs in future research following discharge from primary TJA. Although we have robust literature to favor the effectiveness of IV ketorolac, we lack evidence to support the appropriate dosage that weighs the need to achieve adequate pain control while avoiding the risks of higher doses. The workgroup believes the largest impediment to wider adoption of NSAIDs relates to concerns surrounding the gastrointestinal and renal safety of the broad use of medications such as preoperative and postoperative oral NSAIDs with IV ketorolac, IV corticosteroids, and DVT prophylaxis of aspirin. As a result, we suggest continued monitoring for adverse events as NSAIDs become more widely adopted following primary TJA.

Peer Review Process:

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the publication of the systematic review and meta-analysis on NSAIDs in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

Disclosure Requirement:

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopaedic Disclosure Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines.

FDA Clearance Statement:

Non-selective NSAIDs are a class of drugs described in this Clinical Practice Guideline that has been approved by the Food and Drug Administration (FDA) for various prescription uses including relief of symptoms associated with osteoarthritis, inflammatory arthritis, primary dysmenorrhea, bursitis, tendonitis, and acute gout flares based on the individual drug. Additionally, oral formulations have been approved for over the counter use. Meloxicam is a preferential COX-2 inhibitory agent that has been FDA approved for relief of symptoms associated with osteoarthritis and rheumatoid arthritis. Celecoxib is the only highly selective

COX-2 inhibitory agent available on the US market, which has FDA approval for the management of acute pain as well as relief of symptoms associated with osteoarthritis, inflammatory arthritis, and primary dysmenorrhea. All NSAIDs carry the FDA's block-box warning for an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke) and serious gastrointestinal events (including bleeding, ulceration, and perforation of the stomach or intestines). According to the FDA, it is the prescribing physician's responsibility to ascertain the FDA clearance status for all medications prior to use in a clinical setting.

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