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AMERICAN ASSOCIATION OF HIP AND KNEE SURGEONS

Clinical Practice Guideline

Acetaminophen in Total Joint Arthroplasty

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AAHKS
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Acetaminophen 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

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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 acetaminophen 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 acetaminophen following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of acetaminophen 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, does perioperative intravenous (IV) or oral acetaminophen affect postoperative pain and/or opioid consumption?

Response/Recommendation:

Administration of IV or oral acetaminophen reduces pain and opioid consumption during the perioperative period of a primary TJA.

Strength of Recommendation: Moderate

Rationale:

We reviewed seventeen randomized clinical trials that represented the best available evidence including fifteen high quality and two moderate quality studies to assess the ability of IV or oral acetaminophen to reduce pain and/or opioid consumption during the perioperative period following TJA.[2-18] Among the included studies, eleven studies investigated IV acetaminophen compared to placebo, five studies investigated IV acetaminophen compared to oral acetaminophen, and three studies compared oral acetaminophen to placebo.[2-18] Despite the numerous high and moderate quality randomized clinical trials, only a limited amount of meta-analyses were able to be performed due to inconsistency in the reporting of outcomes and timepoints for reporting the outcomes.

Intravenous acetaminophen has been shown with limited heterogeneity in direct meta-analyses to demonstrate favorable reductions in postoperative pain and opioid consumption

compared to placebo. Among the studies reporting on postoperative pain, direct meta-analysis of IV acetaminophen demonstrated lower 6-hour sum of pain intensity differences (outcome is a four-point scale that summarizes the treatment benefit over a specific time period) and postoperative pain scores (i.e. visual analogue scale and numeric pain rating scale) between 24- and 48-hours compared to placebo following surgery. Additionally, direct meta-analysis of opioid consumption measured 24-hours following TJA had improved outcomes for IV acetaminophen compared to placebo.

Due to the lack of consistent outcomes, no meta-analysis could be performed comparing IV and oral acetaminophen. However, among the five high quality randomized clinical trials investigating the comparison of IV and oral acetaminophen, no difference was observed between the routes of administration to reduce postoperative pain and/or opioid consumption.[4, 9, 10, 14, 17] Similarly, no meta-analysis could be performed comparing oral acetaminophen and placebo. Only three high quality randomized studies were available to assess the ability of oral acetaminophen to reduce postoperative pain and/or opioid consumption compared to placebo.[6, 9, 16] Qualitative review of the available literature would suggest oral acetaminophen reduces postoperative pain and opioid consumption, but the results do not consistently favor oral acetaminophen over placebo at statistically significant levels.

Although IV acetaminophen has been shown to be superior to placebo and equivalent to oral acetaminophen with regards to reduction in postoperative pain and/or opioid consumption, the lack of overwhelming evidence supporting the superiority of oral acetaminophen compared to placebo has resulted in a downgrade of the recommendation

from strong to moderate for oral acetaminophen. Furthermore, the strength of the recommendation for IV acetaminophen was downgraded from strong to moderate due to concerns regarding the significantly higher cost of IV acetaminophen compared to oral acetaminophen. However, the US Food and Drug Administration has granted approval for marketing of a generic IV acetaminophen starting in December 2020, which is has the potential to dramatically reduce the cost and change the downgrade of the recommendation of IV acetaminophen.

Guideline Question 2:

For patients undergoing primary TJA, does acetaminophen after discharge affect postoperative pain and/or opioid consumption?

Response/Recommendation:

In the absence of reliable evidence, it is the opinion of the workgroup that oral acetaminophen may be used after discharge as part of a multimodal pain regimen, as it is a low-cost and low-risk treatment for pain after discharge from a primary TJA.

Strength of Recommendation: Consensus

Rationale:

Oral acetaminophen has widely been accepted as a safe, effective, and low-cost analgesic medication. Despite the numerous high and moderate quality randomized clinical trials investigating perioperative acetaminophen in the setting of a primary TJA, we lack specific evidence to guide a recommendation on the use of oral acetaminophen after discharge. As a result, we must rely on the available evidence regarding acetaminophen in the nonsurgical treatment of osteoarthritis and its use during the perioperative period of primary TJA to guide our recommendation. In the setting of nonsurgical treatment of osteoarthritis of the knee, direct meta-analysis of oral acetaminophen showed a significant improvement in pain and function compared to an oral placebo.[19] Lastly, the results from the current clinical practice

guidelines has shown the effectiveness of oral acetaminophen to reduce postoperative pain and opioid consumption during the inpatient period following primary TJA.

Although acetaminophen has not been proven to be effective in isolation for postoperative pain management following primary TJA, it has been demonstrated as an effective adjunct as part of a multimodal pain management protocol.[20] When used in conjunction with other non-opioid analgesic medications, patients experienced a decreased risk of medical complications.[20] Therefore, we can support the use of oral acetaminophen after discharge as part of a multimodal pain regimen.

Guideline Question 3:

For patients undergoing primary TJA, does perioperative acetaminophen compared to placebo have an increased risk of postoperative complications?

Response/Recommendation:

Administration of IV or oral acetaminophen does not increase the risk of complications following primary TJA.

Strength of Recommendation: Strong

Rationale:

Among the reviewed high and moderate quality randomized clinical trials, eleven studies reported on complications related to the administration of acetaminophen.[2-6, 12, 13, 15-18] Qualitative examination demonstrated no consistent difference between IV acetaminophen, oral acetaminophen, and placebo. Direct meta-analysis was only capable of being performed for IV acetaminophen, which showed no significant difference with regards to any complication (0.98 relative risk; 95% confidence interval of 0.83 to 1.16) or vomiting (1.16 relative risk; 95% confidence interval of 0.30 to 4.45). Therefore, IV and oral acetaminophen are considered to be safe analgesic medications to administer during the perioperative episode of a primary TJA.

Areas for Future Research:

Although we had numerous high and moderate quality randomized clinical trials to formulate the clinical practice guidelines on the use of acetaminophen, we were presented with limitations in the available literature. We suggest future research of acetaminophen focus on the oral route of administration during the perioperative period and after discharge from a primary TJA. We have robust literature consistently demonstrating IV acetaminophen is favored compared to placebo and no different compared to oral acetaminophen; however, the inconsistent outcomes of literature on oral acetaminophen compared to placebo limited our ability to provide a strong recommendation. As a result, additional high quality randomized clinical trials of oral acetaminophen compared to placebo would likely provide more consistent evidence for or against oral acetaminophen to strengthen the recommendation. Because acetaminophen has typically been prescribed as a fixed combination pill with an opioid, the literature investigating the isolated effect of oral acetaminophen with hip and knee patients in an outpatient setting has been focused on the nonsurgical management of osteoarthritis. Therefore, future research on the utilization of oral acetaminophen after discharge from a primary TJA would allow for an evidenced based recommendation in a future clinical practice guideline.

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 Acetaminophen in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

FDA Clearance Statement:

Acetaminophen is a drug described in this Clinical Practice Guideline that has been approved by the Food and Drug Administration (FDA). The oral formulation has been approved for over the counter use. The intravenous formulation has been approved for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid medications, and fever reduction in adults and pediatric patients 2 years or older. Intravenous acetaminophen has an FDA block-box warning for risk of medication errors and hepatotoxicity. 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.

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.

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