Corticosteroids 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 corticosteroids in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of primary TJA patients and reduce practice variation by promoting a multidisciplinary, evidence-based approach to the use of corticosteroids following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of corticosteroids 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] Direct meta-analyses were performed when the data allowed, but network meta-analyses were not performed. Network meta-analyses are limited in their ability to control for significant variation particularly in the multimodal analgesic protocols utilized and the timepoints outcomes were reported. 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 perioperative corticosteroids affect postoperative pain, opioid consumption, nausea/vomiting, and/or complications?

Response/Recommendation 1A:

Perioperative intravenous dexamethasone reduces postoperative pain, opioid consumption, and nausea/vomiting after primary TJA.

Strength of Recommendation 1A: Strong

Response/Recommendation 1B:

There is insufficient evidence on whether intravenous dexamethasone increases the risk of complications after primary TJA, including periprosthetic joint infection and wound healing.

Strength of Recommendation 1B: Consensus

Rationale:

We reviewed sixteen studies that evaluated the impact of perioperative dexamethasone on outcomes after TJA.[2–17] Fourteen of the sixteen studies were assessed as high quality and two studies were assessed as moderate quality of evidence. Due to heterogeneity in the dosage, number of doses, frequency, and duration of treatment, a limited number of meta-analyses were performed.

All sixteen studies evaluated the effects of perioperative dexamethasone on postoperative pain. Eleven of the sixteen studies found that perioperative dexamethasone reduces postoperative pain.[5–14,16] Of the nine studies that looked at pain with activity, seven studies reported

dexamethasone significantly reduced pain compared to placebo.[6–8,10,11,13,16] At 24 hours postoperatively, six studies found dexamethasone reduced postoperative pain compared to placebo[5,7,9,11–13] while an additional six studies found no difference at the same timepoint.[2–4,8,10,14]

Fifteen studies evaluated opioid consumption within 72 hours after TJA.[2–14] Eleven studies found that administration of perioperative intravenous dexamethasone reduces postoperative opioid consumption[2,5–9,11–15] while the remaining four studies found no difference compared to placebo.[3,4,10,16] Five studies included in a direct meta-analysis with no heterogeneity ($I^2 = 0$) found that patients who received intravenous dexamethasone required significantly less opioids for breakthrough pain (0.44 relative risk [RR]; 95% confidence interval [CI] 0.28 to 0.68).[7,8,11,12,16]

Thirteen studies evaluated the incidence of postoperative nausea and vomiting among TJA patients who received intravenous dexamethasone.[2,4–12,14–16] Twelve of the thirteen studies found intravenous dexamethasone reduced postoperative nausea and vomiting.[2,4–12,14,16] Nine of these studies included in a direct meta-analysis with moderate heterogeneity ($I^2 = 48.3\%$) found that patients who received intravenous dexamethasone had significantly less nausea and vomiting postoperatively compared to placebo (0.43 RR; 95% CI 0.30 to 0.63).[4,6–8,10–12,15,16]

There was limited literature on complications after TJA with intravenous dexamethasone treatment. Only six studies evaluated complications with intravenous dexamethasone and found no difference compared to placebo in rates of superficial and deep infection, gastrointestinal hemorrhage, deep vein thrombosis (DVT), and intramuscular thrombosis.[6,8,11,12,15,16] Given the limitations of the current literature, it is the opinion of the workgroup that there is

insufficient evidence on whether intravenous dexamethasone influences the risk of complications after primary TJA, in particular periprosthetic joint infection and wound healing.

Guideline Question 2:

For patients undergoing primary TJA, does the dose of perioperative corticosteroid affect postoperative pain, opioid consumption, nausea/vomiting, and/or complications?

Response/Recommendation:

There is limited evidence to determine if there is a difference between high dose and low dose intravenous dexamethasone with regards to postoperative pain, opioid consumption, nausea/vomiting, or complications after primary TJA.

Strength of Recommendation: Limited

Rationale:

One high quality study and one moderate quality study evaluated the impact of dosing of perioperative intravenous dexamethasone on opioid consumption and pain after TJA.[3,14] Turner et al. compared 8 mg intravenous dexamethasone (e.g. high dose) versus 4 mg intravenous dexamethasone (e.g. low dose) following a psoas block prior to primary total hip arthroplasty (THA).[3] The authors found no difference in postoperative pain or opioid consumption between the two different dexamethasone doses.[3] Kim et al. compared postoperative intravenous dexamethasone at 0.2 mg/kg versus 0.1 mg/kg for 24 hours after primary total knee arthroplasty (TKA) and found no difference in postoperative opioid

consumption or postoperative pain at 2 days postoperatively.[14] Only Kim et al. evaluated postoperative nausea after TKA and found no difference between high and low dose intravenous dexamethasone.[14] While one high and one moderate quality study are sufficient to make a moderate recommendation, the workgroup downgraded the recommendation to limited as they believe that the data in these two studies alone are insufficient to make a definitive recommendation regarding the dose of corticosteroids that should be administered prior to primary TJA.

Guideline Question 3:

For patients undergoing primary TJA, do additional doses of perioperative corticosteroid affect postoperative pain, opioid consumption, and/or nausea/vomiting?

Response/Recommendation:

Multiple doses of perioperative intravenous dexamethasone lead to reduced pain, opioid consumption and nausea/vomiting compared to a single dose of perioperative intravenous dexamethasone.

Strength of Recommendation: Strong

Rationale:

We reviewed three high quality studies that compared multiple doses of intravenous dexamethasone to a single dose of dexamethasone.[6,9,12] Due to heterogeneity in the dosage, number of doses, frequency, and duration of treatment, no meta-analyses were performed.

Xu et al. compared 3 doses (20 mg intraoperatively, and 10 mg on postoperative day 1 and 2) to a single dose (20 mg dose intraoperatively).[6] Wu et al. compared two doses (10 mg intraoperatively and 10 mg 6 hours postoperatively) to a single dose of 10 mg intraoperatively.[12] Backes et al. also compared two doses of dexamethasone (10 mg prior to induction and 10 mg on postoperative day 1) with a single 10 mg dose before induction.[9] All three studies reported decreased opioid consumption and pain in the early postoperative period compared to a single dose.[6,9,12] Two of the three studies reported decreased nausea at 24 hours postoperatively with multiple doses while Xu et al. found no difference between multiple and single doses.

Since a multiple-dose regimen of dexamethasone provides improved reduction in pain, opioid consumption, and nausea compared to a single dose, the workgroup evaluated the number of additional doses needed for improved effect. One high quality study by Lei et al. compared two doses of intravenous dexamethasone (10 mg at induction and at 4 hours postoperatively) to three doses (10 mg at induction, 4 hours postoperatively and 24 hours postoperatively).[8] The authors found that patients who received three doses had decreased pain, opioid consumption, and nausea at 48 hours postoperatively compared to patients who received two doses.[8] Given there is only one study that compares multiple doses, the workgroup does not feel that there is enough evidence to make a definitive recommendation regarding the number of doses (e.g. two, three or more) that should be given postoperatively. However, the evidence does support that multiple doses of intravenous dexamethasone can help further reduce postoperative pain, opioid consumption, and nausea after primary TJA compared to a single dose.

Guideline Question 4:

For patients undergoing primary TJA, are there contraindications to perioperative corticosteroid use?

Response/Recommendation:

Perioperative corticosteroids may lead to increased postoperative blood glucose levels and should be used with caution in patients with diabetes mellitus.

Strength of Recommendation: Consensus

Rationale:

There are no studies in the literature that directly address contraindications to perioperative corticosteroid use in primary TJA. There is a concern that corticosteroids should be used with caution in patients with diabetes mellitus as this may lead to an increase in postoperative blood glucose levels. The long-term medical consequences of uncontrolled diabetes are well understood, but the short-term effects of transient increases in blood glucose remain unknown in both diabetic and non-diabetic patients. With regards to complications specific to TJA, Kheir et al. found that postoperative blood glucose levels on postoperative day 1 predict the risk of periprosthetic joint infection with a linear increase in the risk of PJI for blood glucose levels beyond 115 mg/dL.[18] The authors report that the optimal blood glucose threshold to reduce the risk of PJI is 137 mg/dL.

Of the 16 studies included in this clinical practice guideline evaluating dexamethasone, four studies excluded all patients with diabetes mellitus regardless of the type of diabetes or their hemoglobin A1c (HbA1c).[2–4,17] Three studies excluded patients with poorly controlled

diabetes, defined as a HbA1c > 7.5%.[9,10,14] One additional study excluded all type I diabetics as well as patients with a HbA1c > 7%.[13] Given patients with diabetes mellitus were excluded from a majority of the included studies in this clinical practice guideline, there is not enough evidence to make an evidence-based recommendation on the use of corticosteroids in patients with diabetes mellitus. However, it is the opinion of the workgroup that corticosteroids should be used with caution in patients with both type I and type II diabetes mellitus due to the aforementioned risks of both medical and TJA specific complications including PJI and wound complications. The authors recommend providers consider postoperative blood glucose monitoring in patients with diabetes mellitus that receive intravenous dexamethasone. The timing, dose, number of doses, and frequency of doses should be individualized to each patient based on their type of diabetes and their HbA1c.

Areas for Future Research:

The best available evidence on corticosteroids in primary TJA includes high quality data, however, there remain many limitations in the formulation of this clinical practice guideline. A majority of studies published on the use of corticosteroids in TJA evaluate intravenous dexamethasone. While there are other intravenous corticosteroids that have been studied in TJA including methylprednisolone and hydrocortisone this literature is limited by a small number of studies and inconsistent reporting of outcome measures between studies.[19–25] Unfortunately, this limits the ability to draw any conclusion on their efficacy. It is unclear if there are any differences in efficacy or side effect profiles between intravenous dexamethasone and other intravenous corticosteroids. Further research should compare the various corticosteroids in TJA.

The contraindications to corticosteroids in TJA remain unknown. Many studies evaluating dexamethasone in TJA exclude patients with diabetes mellitus for concern of affecting their blood glucose levels. However, no studies to date have directly studied any potential implication of administering dexamethasone to TJA patients with diabetes mellitus. As a result, the workgroup recommends corticosteroids be used cautiously in this population. Future research is warranted to investigate if it is safe to use corticosteroids in patients with diabetes mellitus and if so at what dose and how many doses. These patients will require longer follow-up than the perioperative period to see if corticosteroids administered to patients with diabetes mellitus may further increase their already elevated risk for PJI.

It is clear that intravenous dexamethasone administered in the perioperative period reduces postoperative pain, opioid consumption and nausea after primary TJA especially when multiple doses are given. However, there is significant heterogeneity in the number of doses, dosage, and frequency of corticosteroids administered in the current literature. For example, in this clinical practice guideline the dose of intravenous dexamethasone administered perioperatively ranged from 4 mg to 20 mg, which may have very different efficacies and risk of complications. Further research is needed to determine the optimal dose of corticosteroids, the number of doses, timing and duration of corticosteroid treatment to optimize their clinical effects while minimizing risks associated with their use. In addition, with the shift to outpatient TJA, further research should investigate whether there is any clinical utility to providing patients who leave the same day of surgery with a single dose or multiple doses of oral steroids after discharge.

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 opioids 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. In accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, all authors and contributors attest none of the current disclosures are relevant to the Clinical Practice Guidelines and no prior relevant financial conflict was within a year of initiating work on the guideline.

FDA Clearance Statement:

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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Regional Nerve Blocks in Primary Total Hip 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 regional nerve blocks in primary total hip arthroplasty (THA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary, evidence-based approach to the use of regional nerve blocks following primary THA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of regional nerve blocks in primary THA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analysis 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, and future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1

For patients undergoing primary total hip arthroplasty, do perioperative regional nerve blocks affect postoperative pain, opioid consumption, and/or complications?

Block vs. Control Recommendation

Response/Recommendation 1A:

Single-shot fascia iliaca block could reduce postoperative pain and opioid consumption without an increase in adverse events after primary total hip arthroplasty.

Strength of Recommendation 1A: Moderate

Response/Recommendation 1B:

Single-shot lumbar plexus nerve block could reduce postoperative pain and opioid consumption after primary total hip arthroplasty; however, providers should consider the technical demands of the procedure and safety concerns regarding the need for close patient monitoring with a lumbar plexus nerve block.

Strength of Recommendation 1B: Moderate

Response/Recommendation 1C:

Single-shot quadratus lumborum block may reduce postoperative pain and opioid consumption after primary total hip arthroplasty; however, providers should consider the technical demands of the procedure and safety concerns regarding the need for close patient monitoring with a quadratus lumborum block.

Strength of Recommendation 1C: Limited

Block vs. Block Recommendation

Response/Recommendation 1D:

There is no difference between a single-shot fascia iliaca or lumbar plexus nerve block in postoperative pain or opioid consumption after primary total hip arthroplasty; however, providers should consider the different risks associated with each regional nerve block.

Strength of Recommendation 1D: Moderate

Rationale:

We reviewed eight high quality randomized clinical trials that represented the best available evidence to assess the effectiveness of fascia iliaca compartment, lumbar plexus nerve, and quadratus lumborum regional nerve blocks to reduce pain and/or opioid consumption following primary THA.[2-9] Although additional regional nerve blocks have been studied with randomized clinical trials following primary THA, the workgroup excluded these alternative regional nerve blocks because of limited evidence and lack of clinical relevance. For instance, the use of a femoral or sciatic nerve block is not as anatomically relevant compared to more widely used regional nerve blocks following primary THA. Additionally, the only comparison between types of regional nerve blocks was the single high quality randomized clinical trial comparing the fascia iliaca compartment and lumbar plexus nerve blocks to reduce pain and/or opioid consumption postoperatively following primary THA.[10] The same limitations encountered in the prior clinical practice guidelines prevented the use of meta-analysis due to the inconsistency in the reporting of outcomes and timepoints for reporting the outcomes.[11-

14] Therefore, qualitative review of the available literature was used to develop the recommendations.

Among the regional nerve blocks evaluated for the clinical practice guidelines, five high quality studies investigated single-shot fascia iliaca compartment block, two high quality studies investigated single-shot lumbar plexus nerve block, and one high quality study investigated single-shot quadratus lumborum block.[2-9] Qualitative analysis of each regional nerve block consistently demonstrated an overwhelmingly significant response of a reduction in postoperative pain and opioid consumption for all three types of regional nerve blocks.[2-9] Although no significant difference was observed in adverse events between the regional nerve blocks and controls, the reporting was focused on adverse events related to opioid use (e.g., nausea/vomiting, pruritus, somnolence, and respiratory depression).[2-9] The lumbar plexus nerve and quadratus lumborum blocks are technically demanding procedures and are considered “deep blocks,” which have the same anticoagulation restrictions as neuraxial anesthesia.[15] In addition, lumbar plexus nerve and quadratus lumborum blocks require post-procedure monitoring because there is the possibility of bilateral spread due to placement in the epidural or intrathecal spaces.[15] In contrast, the fascia iliaca compartment block is a less technically demanding procedure without the same safety concerns, and is not considered a “deep block.”[15]

The workgroup downgraded the strength of the recommendations for fascia iliaca compartment, lumbar plexus nerve, and quadratus lumborum blocks based on the increased cost associated with the blocks, particularly in light of our advancements with effective multimodal analgesia of oral medications and peri-articular local anesthetic

infiltration for THA. In addition, the lack of appropriate reporting of adverse events for lumbar plexus nerve and quadratus lumborum blocks were an additional concern cited for downgrading the strength of the recommendation for lumbar plexus nerve and quadratus lumborum blocks. Although the workgroup would advocate for reporting of adverse events specific to the nerve blocks, the relatively small sample sizes may not be large enough to accurately represent the frequency of these adverse events.

Among the clinically relevant regional nerve blocks for primary THA, only a single high quality randomized clinical trial offered a comparison between nerve blocks.[10] When comparing the fascia iliaca compartment and lumbar plexus nerve blocks, it demonstrated no significant difference in postoperative pain and opioid consumption.[10] Therefore, when a regional nerve block is used after primary THA, the workgroup would favor a fascia iliaca compartment block, as the increased risks and technical demands of a lumbar plexus nerve block do not come with any additional benefit.

Guideline Question 2

For patients undergoing primary total hip arthroplasty, is there a difference between perioperative regional nerve blocks, peri-articular local anesthetic infiltration, or combination of these methods in postoperative pain, opioid consumption, and/or complications?

Response/Recommendation 2A:

There is no difference between a single-shot fascia iliaca block or peri-articular local anesthetic infiltration in postoperative opioid consumption after primary total hip arthroplasty.

Strength of Recommendation 2A: Moderate

Response/Recommendation 2B:

There is no difference between a single-shot lumbar plexus nerve block or peri-articular local anesthetic infiltration in postoperative pain or opioid consumption after primary total hip arthroplasty.

Strength of Recommendation 2B: Moderate

Rationale:

Among the clinically relevant regional nerve blocks for primary THA, a single high quality randomized clinical trial compared a fascia iliaca compartment block and peri-articular local anesthetic infiltration, and a single high quality randomized clinical trial compared a lumbar plexus nerve block and peri-articular local anesthetic

infiltration.[16, 17] Both randomized clinical trials demonstrated peri-articular local anesthetic infiltration is equivalent to either a fascia iliaca compartment or lumbar plexus nerve block regarding postoperative pain and opioid consumption.[16, 17] Peri-articular local anesthetic infiltration should be considered first before resorting to a regional nerve block in primary THA because the additional cost and risk associated with a regional nerve block do not offer any additional benefit compared to peri-articular local anesthetic infiltration. Therefore, we recommend the use of peri-articular local anesthetic infiltration over the routine use of regional nerve blocks following primary THA. However, if a patient‘s circumstance does warrant a regional nerve block, we recommend use of a fascia iliaca compartment block.

Areas for Future Research:

Although the best available evidence included numerous high quality randomized clinical trials, we are still presented with limitations in the literature when formulating the clinical practice guidelines. We were unable to make stronger recommendations regarding the comparison between individual regional nerve blocks as well as between regional nerve blocks and peri-articular local anesthetic infiltration due to a lack of more high-quality studies. We suggest future research on regional nerve blocks for primary THA focus on providing supplemental literature comparing between the relevant regional nerve blocks as well as between the regional nerve blocks and peri-articular local anesthetic infiltration. Additionally, we suggest the reporting of adverse events for future studies on regional nerve blocks be expanded to include events specific to the anesthetic procedures in order to provide a better evaluation of the risks associated with each procedure.

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, followed by the Council on Research and Quality, and lastly, the AAOS Board of Directors. Additionally, the publication of the systematic review and meta-analysis on regional nerve blocks in primary hip total arthroplasty 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. In accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, all authors and contributors attest none of the current disclosures are relevant to the Clinical Practice Guidelines, and no prior relevant financial conflict was within a year of initiating work on the guideline.

FDA Clearance Statement:

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Regional Nerve Blocks in Primary Total Knee 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 regional nerve blocks in primary total knee arthroplasty (TKA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidence-based approach to the use of regional nerve blocks following primary TKA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of regional nerve blocks in primary TKA. 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 total knee arthroplasty, is there a difference between regional nerve blocks in postoperative pain, opioid consumption, and/or complications?

Block vs. Control Recommendations

Response/Recommendation 1A:

Regional nerve blocks, including single-shot or continuously administered femoral nerve block or adductor canal block, effectively reduce postoperative pain and opioid consumption without an increase in adverse events, but femoral nerve blocks are associated with decreased quadriceps strength after primary total knee arthroplasty.

Strength of Recommendation 1A: Strong

Response/Recommendation 1B:

The infiltration between Popliteal Artery and Capsule of Knee (iPACK) may reduce postoperative pain, but iPACK does not effectively reduce postoperative opioid consumption after primary total knee arthroplasty.

Strength of Recommendation 1B: Limited

Block vs. Block Recommendations

Response/Recommendation 1C:

There is no difference between a single-shot or continuous femoral nerve block in postoperative pain, opioid consumption, or adverse events after primary total knee

arthroplasty; however, providers should consider the side effects of quadriceps weakness associated with femoral nerve blocks when selecting a regional nerve block.

Strength of Recommendation 1C: Strong

Response/Recommendation 1D:

There is no difference between a single-shot femoral nerve block or adductor canal block in postoperative pain, opioid consumption, or adverse events, but a single-shot femoral nerve block is associated with decreased quadriceps strength after primary total knee arthroplasty as compared to a single-shot adductor canal block.

Strength of Recommendation 1D: Strong

Response/Recommendation 1E:

There is no difference between a continuous femoral nerve block or adductor canal block in postoperative pain, opioid consumption, or adverse events, but a continuous femoral nerve block is associated with decreased quadriceps strength after primary total knee arthroplasty as compared to a continuous adductor canal block.

Strength of Recommendation 1E: Strong

Response/Recommendation 1F:

Continuous adductor canal block could reduce postoperative pain and opioid consumption without an increase in adverse events compared to a single-shot adductor canal block following primary total knee arthroplasty.

Strength of Recommendation 1F: Moderate

Rationale:

We reviewed twenty-nine randomized clinical trials, which represented the best available evidence, including twenty high quality and nine moderate quality studies to evaluate the effectiveness of a single-shot or continuous femoral nerve block or adductor canal block or infiltration between Popliteal Artery and Capsule of Knee (iPACK) to reduce pain and/or opioid consumption following primary TKA.[2-30] Among the included studies comparing a regional nerve block to control, thirteen studies investigated a single-shot femoral nerve block, eight studies investigated a continuous femoral nerve block, six studies investigated a single-shot adductor canal block, four studies investigated a continuous adductor canal block, and one study investigated iPACK.[2-30] Although additional regional nerve blocks have been studied with randomized clinical trials following primary TKA, the workgroup excluded these alternative regional nerve blocks because of limited evidence or lack of clinical relevance. For instance, a combined femoral and sciatic nerve block effectively provides total analgesia of the lower extremity, but it causes significant motor weakness not conducive to early postoperative mobilization. Similar to prior clinical practice guidelines on postoperative analgesia, only a limited number of meta-analyses were capable of being performed to support the recommendations.[31-34] Inconsistencies in the reporting of outcomes and timepoint for reporting of outcomes frequently resulted in substantial heterogeneity in the meta-analyses.

Despite the numerous high and moderate quality studies on single-shot or continuous femoral nerve blocks, the meta-analyses related to pain and opioid

consumption were omitted from consideration in the recommendations due to the presence of substantial heterogeneity. However, qualitative analyses of studies on single-shot or continuous femoral nerve block consistently demonstrate a significant reduction in postoperative pain and opioid consumption for both types of blocks compared to controls.[4, 9-11, 13, 14, 16-19, 22-30] In direct meta-analysis and with no heterogeneity single-shot adductor canal block demonstrate reduced opioid consumption compared to controls (-0.46 standard mean difference [SMD]; 95% confidence interval [CI] -0.78 to -0.13; $I^2 = 0\%$).[3, 21] Similarly, continuous adductor canal block demonstrated with no heterogeneity in direct meta-analysis to reduce opioid consumption compared to controls (-0.54 SMD; 95% CI -0.81 to -0.27; $I^2 = 0\%$).[6, 15, 20] Because meta-analysis was not available to evaluate postoperative pain, qualitative assessment demonstrated evidence of a reduction in postoperative pain for a single-shot or continuous adductor canal block compared to controls.[3, 5-8, 12, 15, 20, 21] Among the fifteen studies reporting on adverse events, the studies consistently demonstrate no increase in adverse events with a single-shot or continuous femoral nerve block or adductor canal block compared to controls.[3, 9, 12-16, 19-23, 26-28]

One study evaluated the iPACK block. In this high quality randomized clinical trial of 69 patients, iPACK reduced postoperative pain but not opioid consumption following primary TKA.[2] The workgroup chose to downgrade the strength of the recommendation from moderate to limited strength based on the inconsistency in the results of the reported outcomes on postoperative visual analogue scale pain with and without activity.

Although strong evidence demonstrated that single-shot and continuous femoral nerve and adductor canal blocks are safe and effective methods to reduce postoperative pain and opioid consumption following primary TKA, we reviewed twenty-three high and moderate quality randomized clinical trials comparing the efficacy and safety between regional nerve blocks.[4, 5, 16, 35-54] Among the included studies, the following comparisons were made between regional nerve blocks: 1. single-shot femoral nerve block versus continuous femoral nerve block, 2. single-shot femoral nerve block versus single-shot adductor canal block, 3. continuous femoral nerve block versus continuous adductor canal block, and 4. continuous adductor canal block versus single-shot adductor canal block. The qualitative analysis demonstrated no difference in postoperative pain, opioid consumption, or adverse events between single-shot and continuous femoral nerve blocks following primary TKA.[4, 16, 36, 48] Single-shot femoral nerve and adductor canal blocks demonstrated (with no heterogeneity in direct meta-analysis) no difference in postoperative pain at 24 hours (-0.10 SMD; 95% CI -0.40 to 0.19; $I^2 = 0\%$), pain at 48 hours (0.08 SMD; 95% CI -0.21 to 0.38; $I^2 = 0\%$) or opioid consumption (-0.06 SMD; 95% CI -0.35 to 0.24; $I^2 = 0\%$) following primary TKA.[39, 41, 43, 44, 51, 54] However, the five studies reporting on motor function consistently demonstrated decreased quadriceps strength persisting as long as 24 hours with a single-shot femoral nerve block.[39, 41, 43, 51, 54] Similarly, continuous femoral nerve and adductor canal blocks demonstrated (with no heterogeneity in direct meta-analysis) no difference in rescue opioid consumption on the first postoperative day (1.5 SMD; 95% CI -0.51 to 4.44; $I^2 = 0\%$) while qualitative analysis demonstrated no difference in pain following primary TKA, but continuous femoral nerve block was associated with the

presence of decreased quadriceps strength persisting up to 24 hours.[37, 40, 47, 49, 53] Continuous adductor canal block demonstrated (with limited heterogeneity in direct meta-analysis) reduced postoperative pain at 8 hours (-1.26 SMD; 95% CI -1.56 to -0.96; $I^2 = 0\%$) and at 36 hours (-0.59 SMD; 95% CI -0.89 to -0.29; $I^2 = 0\%$) and reduced 48 hour opioid consumption (-0.32 SMD; 95% CI -0.64 to -0.001; $I^2 = 23\%$) following primary TKA compared to single-shot adductor canal block.[5, 35, 38, 42, 45, 46, 50, 52] Despite the evidence demonstrating improved efficacy for continuous compared to single-shot adductor canal block, the workgroup downgraded the recommendation from strong to moderate due to concerns regarding the associated cost, increased resource utilization, and risk of retained catheters with a continuous adductor canal block.

Based on the best available evidence, the workgroup believes a femoral nerve block has a limited role in primary TKA due to the association of quadriceps weakness and demonstrated efficacy of an adductor canal block. We recommend the use of a single-shot adductor canal block when regional anesthesia is used in primary TKA; however, the workgroup would recommend consideration of a continuous adductor canal block in patients at risk for poor postoperative pain control.

Guideline Question 2

For patients undergoing primary total knee arthroplasty, is there a difference between perioperative regional nerve blocks, peri-articular local anesthetic infiltration, or combination of these methods in reducing postoperative pain, opioid consumption, and/or complications?

Response/Recommendation 2A:

There is no difference between a single-shot adductor canal block or peri-articular local anesthetic infiltration in postoperative pain, opioid consumption, or adverse events after primary total knee arthroplasty.

Strength of Recommendation 2A: Moderate

Response/Recommendation 2B:

Combined single-shot adductor canal block and peri-articular local anesthetic infiltration could reduce postoperative pain with no difference in postoperative opioid consumption or adverse events compared to peri-articular local anesthetic infiltration alone after primary total knee arthroplasty.

Strength of Recommendation 2B: Moderate

Response/Recommendation 2C:

Combined single-shot adductor canal block and peri-articular local anesthetic infiltration could reduce postoperative pain and opioid consumption compared to a single-shot adductor canal block alone after primary total knee arthroplasty.

Strength of Recommendation 2C: Moderate

Rationale:

We reviewed eleven randomized clinical trials, which represented the best available evidence, including ten high quality and one moderate quality study to evaluate the effectiveness of regional nerve blocks and peri-articular local anesthetic infiltration to reduce pain and/or opioid consumption following primary TKA.[3, 7, 8, 12, 55-61] Because the workgroup recommends the use of an adductor canal block over alternative regional nerve blocks, these recommendations only focused on a single-shot adductor canal block. Among the included studies, the following comparisons were made in the recommendations: 1. single-shot adductor canal block versus peri-articular local anesthetic infiltration, 2. combined single-shot adductor canal block and peri-articular local anesthetic infiltration versus peri-articular local anesthetic infiltration alone, 3. combined single-shot adductor canal block and peri-articular local anesthetic infiltration versus single-shot adductor canal block alone. Although direct meta-analysis was utilized to evaluate the individual comparisons, network meta-analysis would have provided more clarity to the potential differences or similarities between combined single-shot adductor canal block and peri-articular local anesthetic or either procedure in isolation. However, network meta-analysis must rely on the assumption of transitivity to compare between treatments not directly compared in a study.[62] Because of the variability in multimodal analgesic protocols, network meta-analysis cannot control for differences in multimodal analgesic protocols as well as direct meta-analysis. Therefore, no network meta-analysis was performed in the formulation of the recommendations.

Compared to periarticular local anesthetic infiltration, single-shot adductor canal block demonstrated (with limited heterogeneity in direct meta-analysis) no significant difference in postoperative pain with activity at 72 hours (-0.21 SMD; 95% CI -0.55 to 0.13; $I^2 = 7\%$) or opioid consumption at 12 hours (-0.03 SMD; 95% CI -0.36 to 0.30; $I^2 = 0\%$) or 72 hours (0.24 SMD; 95% CI -0.04 to 0.53; $I^2 = 0\%$) following primary TKA.[7, 56, 58, 60] Although the quantitative analysis that included four studies shows no significant difference between a single-shot adductor canal block or peri-articular local anesthetic infiltration, the qualitative analysis of all eight studies demonstrates conflicting results with the quantitative analysis.[7, 55-61] Of the eight studies reporting on postoperative pain, five studies favored single-shot adductor canal block, two studies favored peri-articular local anesthetic infiltration, and one study had no difference in pain following primary TKA.[7, 55-61] Of the seven studies reporting on opioid consumption, three studies favored single-shot adductor canal block, one study favored peri-articular local anesthetic infiltration, and three studies had no difference in opioid consumption following primary TKA.[7, 55, 56, 58-61] The workgroup chose to downgrade the strength of the recommendation from strong to moderate strength based on the inconsistency between the quantitative and qualitative analysis. Because a strong recommendation represents future research is not likely to change the recommendation, the workgroup believes additional research has the potential to clarify the discordance in the analyses.

Combined single-shot adductor canal block and peri-articular local anesthetic infiltration demonstrated (with no heterogeneity in direct meta-analysis) reduced postoperative pain at 24 hours (-0.38 SMD; 95% CI -0.65 to -0.10; $I^2 = 0\%$) but no

difference in opioid consumption at 24 hours (-0.07 SMD; 95% CI -0.34 to 0.20; I^2 = 0%), 48 hours (0.05 SMD; 95% CI -0.22 to 0.32; I^2 = 0%), or 72 hours (-0.06 SMD; 95% CI -0.34 to 0.21; I^2 = 0%) following primary TKA compared to peri-articular local anesthetic infiltration alone.[3, 7] However, the qualitative analysis among the four studies show the potential for reduced pain and opioid consumption for combined single-shot adductor canal block and peri-articular local anesthetic infiltration.[3, 7, 8, 12] Similar to the prior recommendation, the workgroup chose to downgrade the strength of the recommendation from strong to moderate based on the inconsistency between the quantitative and qualitative analysis. When comparing combined single-shot adductor canal block and peri-articular local anesthetic infiltration to single-shot adductor canal block alone, qualitative analysis demonstrated reduced pain and opioid consumption following primary TKA for the combination treatment.[7, 61]

The workgroup recommends routine use of either a single-shot adductor canal block or peri-articular local anesthetic infiltration for patients undergoing primary TKA. Although the current available evidence does not suggest the combination of a single-shot adductor canal block and peri-articular local anesthetic infiltration is necessary in primary TKA, it could provide additional reduction in postoperative pain and opioid consumption compared to either alone.

Areas for Future Research:

Despite the numerous high and moderate quality randomized clinical trials, we are still presented with the need for additional research to improve future clinical practice guidelines. We suggest future research on regional nerve blocks focus on evaluation of the combination of a single-shot adductor canal block and peri-articular local anesthetic infiltration or either treatment in isolation, as the current literature does not provide clarity whether the additional risks and costs associated with combined procedures is warranted to reduce pain and/or opioid consumption. Because continuous adductor canal blocks potentially provide reduced pain and opioid consumption compared to a single-shot adductor canal block, we suggest additional research to determine the ideal patient population whereby the additional cost and risks are warranted for the procedure. Lastly, future research may help determine the optimal timing of performing a single-shot adductor canal block and the potential for the addition of other contents to the block injection to improve the efficacy or duration of action.

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 followed by the Council on Research and Quality, and lastly the AAOS Board of Directors. Additionally, the publication of the systematic review and meta-analysis on regional nerve blocks in primary total knee arthroplasty that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

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Ketamine 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) collaborated to develop evidence-based guidelines on the use of ketamine in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of primary TJA patients and reduce practice variation by promoting a multidisciplinary evidenced-based approach to the use of ketamine in primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of ketamine 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] Direct meta-analyses were performed when the data allowed, but network meta-analyses were not performed. Network meta-analyses are limited in their ability to control for significant variation particularly in the multimodal analgesic protocols utilized and the timepoints outcomes were reported. The current clinical practice guidelines were based on the best available evidence, so future updates may become necessary as additional literature becomes available with new research.

Guideline Question 1:

For patients undergoing primary TJA, does perioperative ketamine affect postoperative pain, opioid consumption, and/or complications after surgery?

Response/Recommendation 1A:

Ketamine administered intraoperatively decreases postoperative opioid consumption.

Strength of Recommendation: Strong

Response/Recommendation 1B:

Ketamine administered intraoperatively may decrease postoperative pain and reduce postoperative nausea and vomiting.

Strength of Recommendation: Moderate

Response/Recommendation 1C:

Ketamine administered intraoperatively is not associated with an increase in adverse events.

Strength of Recommendation: Strong

Rationale:

Six high quality studies evaluated the influence of intraoperative ketamine on opioid consumption after primary TJA.[2–7] Three of these studies also included a postoperative ketamine intravenous infusion for 24 hours.[2,3,6] Five of the six studies found reduced postoperative opioid consumption after primary TJA when intraoperative ketamine was administered.[2–6] The one study that did not demonstrate this finding from Tan et al. compared

intraoperative ketamine administered at 6mcg/kg/ minute to placebo and found no difference in opioid consumption at 24 hours postoperatively. Due to heterogeneity in the dosing of ketamine administered intraoperatively, we were unable to conduct a meta-analysis.

Seven high quality studies evaluated the influence of intraoperative ketamine on pain after primary TJA.[2–8] Four of these studies also included a postoperative ketamine infusion for 24 hours.[2,3,6,8] Four studies, two intraoperative only and two intraoperative plus postoperative ketamine, found decreased pain in the first 48 hours after primary TJA.[3,4,7,8] The three other studies found no difference in postoperative pain between ketamine and placebo at all timepoints.[2,5,6] Although all studies that evaluated postoperative pain are high quality, the workgroup downgraded this recommendation to moderate because of the mixed evidence on the influence of intraoperative ketamine on postoperative pain.

Four high quality studies evaluated the effects of intraoperative ketamine on postoperative nausea and vomiting.[4–6,8] A meta-analysis of these four studies with limited heterogeneity ($I^2 = 4.9\%$) found that ketamine significantly reduces postoperative nausea and vomiting. (0.68 relative risk [RR]; 95% confidence interval [CI] 0.50 to 0.92). The workgroup downgraded this recommendation to moderate as this is not the primary purpose of intraoperative ketamine. While the anti-emetic effect is a beneficial secondary effect of ketamine, ketamine is primarily used as an anesthetic for sedation and as an analgesic for pain control.

Four high quality studies evaluated the adverse effects of intraoperative ketamine for primary TJA.[4–6,8] All four studies found no increase in adverse events with the use of intraoperative ketamine, including delirium and urinary retention. A meta-analysis of three studies with no heterogeneity ($I^2 = 0$) found no increased risk of postoperative delirium with

intraoperative ketamine administration (0.70 RR; 95% CI 0.29 to 1.69).[4–6] Another meta-analysis of three studies with no heterogeneity ($I^2 = 0$) found no increased risk of postoperative urinary retention with intraoperative ketamine administration (1.02 RR; 95% CI 0.53 to 1.94).[5,6,8] Although the meta-analyses demonstrate no increased risk of postoperative delirium or postoperative urinary retention, the rarity of the event makes it more difficult to study in randomized clinical trials. Database studies might be better suited to evaluate rare adverse events such as delirium. Two database studies have evaluated the association between intraoperative ketamine and delirium, with conflicting results between the studies.[9,10]. In one study using claims data from the Premier database evaluating nearly 1.7 million total hip/knee arthroplasties between 2006-2016, no increase in delirium was observed with the use of ketamine [10]. However, in a single institution retrospective review of 41,766 hip/knee arthroplasties between 2005-2014, the use of intraoperative ketamine (OR 1.27 CI 1.01 – 5.26 – 1.59) or a postoperative ketamine infusion did increase the risk of postoperative delirium (OR 10.59 CI 5.26-19.91) [9]. The authors were unable to determine a threshold dose of intraoperative ketamine beyond which the risk of delirium increases.

Areas for Future Research:

The best available evidence on ketamine in primary TJA includes high quality data, however, there remain limitations in the formulation of this clinical practice guideline. A majority of studies published on the use of ketamine in TJA evaluate intravenous ketamine administered intraoperatively. However, several of these studies included a postoperative ketamine infusion for up to 48 hours postoperatively. With the evolution of modern multimodal analgesia and anesthetic protocols, along with decreasing length of stay, postoperative infusions

of anesthetics such as ketamine are not commonly utilized. In addition, there is significant variation in the dosing of ketamine utilized in the studies included in this clinical practice guideline. Further studies are warranted to determine the optimal clinical dose of ketamine that maximizes the anesthetic and analgesic effects while minimizing postoperative side effects. In addition, with the shift to outpatient TJA, further research should investigate the role of ketamine for same day surgery.

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 opioids 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. In accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, all authors and contributors attest none of the current disclosures are relevant to the Clinical Practice Guidelines, and no prior relevant financial conflict was within a year of initiating work on the guideline.

FDA Clearance Statement:

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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Periarticular Injection 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 periarticular injection in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of primary TJA patients and reduce practice variation by promoting a multidisciplinary, evidence-based approach to the use of periarticular injection in primary TJA.

The combined clinical practice guidelines mean to address common and important questions related to the efficacy and safety of periarticular injection 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] Direct meta-analyses were performed when the data allowed, but network meta-analyses were not performed. Network meta-analyses are limited in their ability to control for significant variation, particularly in the multimodal analgesic protocols utilized, and the timepoints outcomes were reported. 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 total joint arthroplasty, does intraoperative periarticular injection affect postoperative pain and/or opioid consumption?

Response/Recommendation:

Intraoperative periarticular injection reduces postoperative pain and opioid consumption after primary total hip and knee arthroplasty.

Strength of Recommendation: Strong

Rationale:

We reviewed thirty-four studies that evaluated the effectiveness of intraoperative periarticular injection on reducing postoperative pain and/or opioid consumption after primary TJA.[2–35] Thirty studies were high quality, and four were moderate quality.[2–35] Due to heterogeneity in the outcomes reported, and the timepoints at which the outcomes were reported, a limited number of direct meta-analyses were performed.

All studies, except for one, evaluated the effectiveness of periarticular injection on postoperative pain after primary TJA.[2–16,18–35] Periarticular injection consistently reduced postoperative pain after primary TJA compared to control. Among the thirty-three studies, twenty studies found that periarticular injection reduced postoperative pain after primary TJA compared to control.[2–4,6–13,16,17,19,20,23,26,31,33,35] Five studies included in a direct meta-analysis with limited heterogeneity ($I^2 = 30.4\%$) found that patients who received

periarticular injection reported reduced pain with activity at 24 hours postoperatively (-0.53 standardized mean difference [SMD]; 95% confidence interval [CI] -0.80 to -0.25).[3,5,8,19,35]

Twenty-five studies evaluated the effectiveness of periarticular injection on postoperative opioid consumption after primary TJA. [2–5,7,9,11,12,14–24,26,28,30–32,35] Only a qualitative analysis was performed due to the different timepoints at which opioid consumption was reported postoperatively. Similar to postoperative pain, periarticular injection consistently reduced postoperative opioid consumption after primary TJA. Seventeen studies reported reduced opioid consumption with periarticular injection administered during primary TJA.[2–5,9,11,14,16–19,24,26,30–32,35] The remaining eight studies found no difference in postoperative opioid consumption between periarticular injection and control.[7,12,15,20–23,28]

Guideline Question 2:

For patients undergoing primary total joint arthroplasty, do differences in the content of intraoperative periarticular injections affect postoperative pain, opioid consumption, and/or complications?

Response/Recommendation 2A:

Long-acting local anesthetics (e.g. ropivacaine, bupivacaine, liposomal bupivacaine) in periarticular injection are effective at reducing postoperative pain and opioid consumption without an increase in adverse events after primary total hip and knee arthroplasty.

Strength of Recommendation 2A: Strong

Response/Recommendation 2B:

There is no difference between periarticular injections with liposomal bupivacaine or other long-acting local anesthetics (e.g. ropivacaine, bupivacaine) in postoperative pain, opioid consumption, or adverse events after primary total hip and knee arthroplasty.

Strength of Recommendation 2B: Strong

Response/Recommendation 2C:

Ketorolac in periarticular injection is effective at reducing postoperative pain and may reduce opioid consumption without an increase in adverse events after primary total knee arthroplasty.

Strength of Recommendation 2C: Moderate

Response/Recommendation 2D:

In the absence of reliable evidence, it is the opinion of the workgroup that ketorolac may be used in periarticular injection to reduce postoperative pain and may reduce postoperative opioid consumption without an increase in adverse events after primary total hip arthroplasty.

Strength of Recommendation 2D: Consensus

Response/Recommendation 2E:

Corticosteroid in periarticular injection is effective at reducing postoperative pain and may reduce opioid consumption without an increase in adverse events after primary total knee arthroplasty.

Strength of Recommendation 2E: Moderate

Response/Recommendation 2F:

In the absence of reliable evidence, it is the opinion of the workgroup that a corticosteroid may be used in periarticular injection to reduce postoperative pain and could reduce postoperative opioid consumption without an increase in adverse events after primary total hip arthroplasty.

Strength of Recommendation 2F: Consensus

Response/Recommendation 2G: Morphine in periarticular injection has no additive effect in reducing postoperative pain and opioid consumption and may increase postoperative nausea and vomiting after primary total hip and knee arthroplasty.

Strength of Recommendation 2G: Strong

Response/Recommendation 2H: There is insufficient evidence on whether epinephrine in periarticular injection influences postoperative pain, opioid consumption, and adverse events after primary total knee arthroplasty.

Strength of Recommendation 2H: Limited

Response/Recommendation 2I: In the absence of reliable evidence, it is the opinion of the workgroup that there is insufficient evidence on whether epinephrine in periarticular injection influences postoperative pain, opioid consumption, and adverse events after primary total hip arthroplasty.

Strength of Recommendation 2I: Consensus

Response/Recommendation 2J: There is insufficient evidence on whether clonidine in periarticular injection influences postoperative pain, opioid consumption, and adverse events after primary total knee arthroplasty.

Strength of Recommendation 2J: Limited

Response/Recommendation 2K: In the absence of reliable evidence, it is the opinion of the workgroup that there is insufficient evidence on whether clonidine in periarticular injection influences postoperative pain, opioid consumption, and adverse events after primary total hip arthroplasty.

Strength of Recommendation 2K: Consensus

Rationale:

We reviewed forty-seven studies that evaluated the contents of periarticular injections in primary TJA and the effects on postoperative pain, opioid consumption, and adverse events. [17,19–29,31–34, 36, 52–64] Direct meta-analyses were performed when the data allowed; however, only a few were completed due to heterogeneity in the outcomes and timepoints at which outcomes were reported.

Sixteen studies, including twelve high quality and four moderate quality studies, compared a local anesthetic periarticular injection alone versus control.[19–29,31–34,36] All sixteen studies evaluated postoperative pain and six studies found improved postoperative pain compared to control.[19,20,23,26,31,33] The remaining ten studies found no difference between local anesthetic and control in postoperative pain.[21,22,24,25,27–29,32,34,36] Eleven studies compared postoperative opioid consumption between a periarticular injection with local

anesthetic and control. [19–24,26,28,31,32,36] Six studies found reduced postoperative opioid consumption when a periarticular injection was used with local anesthetic alone compared to control.[19,24,26,31,32,36]

Eighteen high-quality studies compared a periarticular injection containing local anesthetic with additional medications as an injection cocktail versus control. [2–18,35] All eighteen studies evaluated postoperative pain and fourteen studies demonstrated reduced postoperative pain with a periarticular cocktail injection. Only fourteen studies compared postoperative opioid consumption between a periarticular injection cocktail and control, and twelve studies reported reduced opioid consumption with a periarticular injection cocktail. Although periarticular injection with only local anesthetic is an effective method of postoperative pain management, the use of a periarticular injection combined with additional agents appears to have a greater effect on reducing postoperative opioid consumption following primary TJA. The observed difference in the effectiveness of only local anesthetic and a combination of medications in the periarticular injection may represent a synergistic effect of the combined medications. As a result, the workgroup strongly recommends the use of periarticular injection cocktails with local anesthetic to reduce postoperative pain and opioid consumption. The effectiveness of common components of a periarticular injection cocktail were evaluated to provide guidance on best components to consider using in a periarticular injection. There were no differences between local anesthetic and control in adverse events reported in all studies except for nausea and vomiting. Of the three studies that reported postoperative nausea and vomiting, one study reported increased nausea and vomiting with local anesthetic compared to control.[33]

Twelve high quality studies compared liposomal bupivacaine to other long-acting local anesthetics, including bupivacaine and ropivacaine.[37–48] Eleven of these studies compared postoperative pain between liposomal bupivacaine and other long-acting local anesthetics and seven studies found no difference between them.[37,39,41–43,45,46] Three other studies found reduced postoperative pain with liposomal bupivacaine, while one other study found no difference in pain at three timepoints, but reduced maximal pain with liposomal bupivacaine.[40,44,47,48] Three studies included in a direct meta-analysis with limited heterogeneity ($I^2 = 4.3\%$) found no difference in postoperative pain at 24 hours between patients who received periarticular injection with liposomal bupivacaine versus other local anesthetics (-0.33 weighted mean difference [WMD]; 95% CI -0.79 to 0.13).[39,44,45] All twelve studies compared postoperative opioid consumption after primary TJA between periarticular injection with liposomal bupivacaine and other long-acting local anesthetics.[37–49] Seven studies found no difference in postoperative opioid consumption between patients who received periarticular injection with liposomal bupivacaine and other long-acting local anesthetics.[39,41,42,44–46,50] Three studies reported decreased opioid consumption at all timepoints reported with liposomal bupivacaine compared with other long-acting local anesthetics.[38,47,48] Perets et al. reported decreased opioid consumption within the 12 hours postoperatively after primary total hip arthroplasty (THA) with liposomal bupivacaine compared with bupivacaine, but there was no difference in opioid consumption at any other timepoints up to 72 hours and no difference in cumulative opioid consumption measured in morphine equivalents.[37] In their study of 165 primary total knee arthroplasty (TKA) patients, Amundson et al. reported no difference in cumulative opioid consumption between liposomal bupivacaine and ropivacaine, but found that more of the patients that received liposomal bupivacaine required opioids for breakthrough

pain.[43] Three studies included in a direct meta-analysis with no heterogeneity ($I^2 = 0.0\%$) found no difference in postoperative cumulative opioid consumption between patients who received periarticular injection with liposomal bupivacaine versus other local anesthetics (-0.18 SMD; 95% CI -0.43 to 0.07).[37,44,45] Seven studies reported adverse events and reported no difference in all adverse events except for over-sedation and muscle spasms.[38,40,42,43,45,46,48] Dysart et al. reported increased muscle spasms, and Hyland et al. reported over-sedation with liposomal bupivacaine compared with other long-acting local anesthetics.[45,48] An additional study by Mont et al. was evaluated, but excluded from this clinical practice guideline by the workgroup as it directly did not address our PICO question.[49] In their study, Mont et al. compared liposomal bupivacaine with 20mLs of 0.5% ropivacaine versus 20mLs of 0.5% ropivacaine alone. The workgroup study excluded this study because it did not directly answer whether there was a difference between other long-acting local anesthetics and liposomal bupivacaine. Second, it was the only study that evaluated a combination of liposomal bupivacaine with another long-acting local anesthetic and the workgroup determined including this different treatment would add too much heterogeneity when interpreting the results as any observed difference between the treatment groups could have been the result of a dose effect of local anesthetic instead of the result of the liposomal bupivacaine.

Three high-quality studies evaluated ketorolac in periarticular injection used intraoperatively during primary TKA and its influence on postoperative pain, opioid consumption, and adverse events.[17,51,52] Due to the limited number of studies on ketorolac in periarticular injection and the heterogeneity in the data and timepoints reported, no meta-analyses were able to be performed. The two studies that reported postoperative pain found

reduced postoperative pain when periarticular injection contained ketorolac and local anesthetic compared to control with local anesthetic alone.[51,52] All three studies reported postoperative opioid consumption. Two studies reported no difference with the addition of ketorolac to periarticular injection and one study found reduced cumulative postoperative opioid consumption.[17,51,52] The workgroup downgraded the recommendation of ketorolac from strong to moderate for several reasons. First, the data on both postoperative pain and opioid consumption was mixed. Only two studies reported postoperative pain and one of those two reported no difference with activity and reduced postoperative pain with ketorolac at another timepoint. As discussed previously, the results on opioid consumption were also mixed. In addition, a strong recommendation implies that future research is unlikely to change the recommendation. The workgroup believes that further research will clarify the mixed results observed in the data and thus downgraded the recommendation to moderate.

The two studies that reported adverse events found no difference when ketorolac was added to periarticular injection compared to long-acting local anesthetic alone.[17,51] The workgroup made a consensus recommendation regarding the role of ketorolac in periarticular injection for THA because there are no studies in the literature evaluating ketorolac in periarticular injection for THA. As a result, the workgroup extrapolated the results from TKA to make a similar consensus statement for THA regarding ketorolac in periarticular injection.

Eight high quality studies evaluated corticosteroid in periarticular injection used intraoperatively during TKA and its influence on postoperative pain, opioid consumption and adverse events.[17,53–59] Due to the limited number of studies on corticosteroid in periarticular injection and the heterogeneity in the data and timepoints reported, no meta-analyses were able to be performed. A majority of the studies found that the addition of corticosteroid to

periarticular injection reduced postoperative pain after TKA. Of the seven studies that compared postoperative pain after TKA between patients who received periarticular injection with and without corticosteroid, four studies reported reduced postoperative pain when corticosteroid was added to the periarticular injection.[54,55,57,58] The other three studies reported no difference in postoperative pain between patients who received periarticular injection with and without corticosteroid.[53,56,59] Four of the five studies that reported postoperative opioid consumption after primary TKA found no difference with the addition of corticosteroid to the periarticular injection compared to control.[17,53,58,59] Sean et al. in their study of 100 primary TKA patients found reduced cumulative postoperative opioid consumption when triamcinolone was added to the periarticular injection compared to ropivacaine alone.[57] There were no differences in any adverse events in the five studies that compared adverse events after primary TKA between patients who received periarticular injection with and without corticosteroid.[17,53–56] Despite the number of high quality studies, the workgroup downgraded the recommendation on corticosteroid in periarticular injection, similar to ketorolac, to a moderate recommendation for several reasons. First, the data on both postoperative pain and opioid consumption was mixed with some studies reporting reduced postoperative pain and opioid consumption with corticosteroid and others reporting no difference. In addition, a strong recommendation implies that future research is unlikely to change the recommendation. The workgroup believes that further research will clarify the mixed results observed in the data and thus downgraded the recommendation to moderate. The workgroup made a consensus recommendation regarding corticosteroid in periarticular injection for THA because there are no studies in the literature evaluating corticosteroid in periarticular injection for THA. As a result, the workgroup

extrapolated the results from TKA to make a similar consensus statement for THA regarding corticosteroid in periarticular injection.

Five high quality studies evaluated the addition of morphine to periarticular injection and the effects on postoperative pain, opioid consumption and adverse events after primary TJA.[17,60–63] Meta-analyses were performed, but were excluded due to the significant heterogeneity between the studies in the outcomes and timepoints reported. The addition of morphine consistently did not have an impact on postoperative pain after primary TJA compared to periarticular injection without morphine. Of the four studies that reported postoperative pain, three studies found no difference in postoperative pain with the addition of morphine to periarticular injection compared to periarticular injection without morphine.[60–62] Only two studies reported postoperative cumulative opioid consumption.[17,63] Kim et al. reported decreased opioid consumption with the addition of morphine to periarticular injection while Mauerhan et al. found no benefit to the addition of morphine in postoperative opioid consumption.[17,63] Four studies reported adverse events and there were no differences in adverse events with the addition of morphine to periarticular injection except for postoperative nausea and/or vomiting[17,60–62] Two of the four studies reported increased rates of postoperative nausea and/or vomiting with the addition of morphine to periarticular injection.[60,62]

There was limited evidence on clonidine and epinephrine in periarticular injection. One study evaluated clonidine in periarticular injection and one study evaluated epinephrine in periarticular injection.[52,64] Both high-quality studies only included primary TKA patients. As a result, the workgroup made a limited recommendation for TKA and a consensus recommendation for THA that there is insufficient evidence to make a recommendation on

whether clonidine or epinephrine in periarticular injection influences postoperative pain, opioid consumption, and adverse events after primary TJA.

Areas for Future Research:

This clinical practice guideline was formulated with the best available evidence which includes high quality data, however there are several limitations. It is clear periarticular injection is effective at reducing pain and opioid consumption in primary TJA without an increase in adverse events. In terms of the contents of periarticular injection, long-acting local anesthetics, corticosteroids and ketorolac are beneficial. However, it is unclear at what dose/concentration these medications should be used in combination. The benefit of epinephrine and clonidine, which are often added to modern periarticular injection cocktails, remain unknown and require future study. In addition, the workgroup was unable to make a recommendation regarding the amount of periarticular injection that should be injected, where it should be injected, and at what point during the primary TJA. Future research should be focused on further understanding the dose of contents, volume, location and timing of periarticular injection used during 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 opioids 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. In accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, all authors and contributors attest none of the current disclosures are relevant to the Clinical Practice Guidelines and no prior relevant financial conflict was within a year of initiating work on the guideline.

FDA Clearance Statement:

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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