Evidence Review Conducted for the Agency for Healthcare Research and Quality Safety Program for Improving Surgical Care and Recovery: Focus on Anesthesiology for Total Knee Arthroplasty

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Enhanced recovery after surgery (ERAS) has rapidly gained popularity in a variety of surgical subspecialities. A large body of literature suggests that ERAS leads to superior outcomes, improved patient satisfaction, reduced length of hospital stay, and cost benefits, without affecting rates of readmission after surgery. These patterns have been described for patients undergoing elective total knee arthroplasty (TKA); however, adoption of ERAS to orthopedic surgery has lagged behind other surgical disciplines. The Agency for Healthcare Research and Quality, in partnership with the American College of Surgeons and the Johns Hopkins Medicine Armstrong Institute (AI) for Patient Safety and Quality, has developed the Safety Program for Improving Surgical Care and Recovery. The program comprises a national effort to incorporate best practice in perioperative care and improve patient safety, for over 750 hospitals and multiple procedures over the next 5 years, including orthopedic surgery. We have conducted a full evidence review of anesthetic interventions to derive anesthesiology-related components of an evidence-based ERAS pathway for TKA. A PubMed search was performed for each protocol component, focusing on the highest levels of evidence in the literature. Search findings are summarized in narrative format. Anesthesiology components of care were identified and evaluated across the pre-, intra-, and postoperative phases. A summary of the best available evidence, together with recommendations for inclusion in ERAS protocols for TKA, is provided. There is extensive evidence in the literature, and from society guidelines to support the Agency for Healthcare Research and Quality Safety Program for Improving Surgical Care and Recovery goals for TKA. (Anesth Analg XXX;XXX:00–00)

Enhanced recovery after surgery (ERAS) programs provide an organizational framework to deliver integrated, evidence-based care.[1] ERAS success relies on minimizing variation in care, and maximizing interdisciplinary, evidence-based practice.

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The Agency for Healthcare Research and Quality (AHRQ), together with the American College of Surgeons and the Johns Hopkins Medicine Armstrong Institute (AI) for Patient Safety and Quality at Johns Hopkins, created the Safety Program for Improving Surgical Care and Recovery (ISCR).[1] The goal of this national effort is to disseminate best practices in perioperative care to >750 hospitals over the next 5 years. The program integrates evidence-based interventions directed toward improving outcomes, enhancing patient experience, and promoting perioperative safety. Evidence-based interventions will be organized into clinical pathways.

Most efforts to adapt ERAS to orthopedic surgery have focused on patients undergoing total hip/knee arthroplasty. ERAS for total knee arthroplasty (TKA) is associated with increased patient satisfaction, improved outcomes, reduced length of hospital stay, lower mortality, and cost savings.[2–5] A meta-analysis (MA) of ERAS for total joint arthroplasty confirmed that ERAS is associated with reduced length of stay and complications without any effect on 30-day readmission.[5]

We have evaluated the evidence to support anesthetic-based components for TKA. The surgical components will be reviewed and reported separately. The goals of this evidence review are to evaluate the best evidence relating to anesthetic components of TKA and develop the evidence-based TKA protocol for hospitals participating in the AHRQ Safety Program for ISCR.

METHODS

A review protocol was developed with input from stakeholders (anesthesiologists and surgeons listed as the authors in this article) (Figure). Two researchers (E.M.S., C.L.W.) reviewed current TKA pathways from several major US health systems, extracted data on items included in major TKA pathways, and presented each item to the group (anesthesiologists and surgeons listed as the authors in this article) for consideration. Items were included for consideration if majority consensus from the group was reached. The group sought expert feedback to identify individual components in each perioperative phase of care (Table 1).

This evidence review should not be considered as a systematic review (SR) but an attempt to incorporate the latest evidence. The protocol was developed based on guidelines from several professional associations/societies (Table 2). In addition, literature reviews for each individual protocol component were performed in PubMed for English-language articles published before June 2017. Each search initially targeted TKA; if no TKA literature was identified, the search was broadened to surgical procedures in general. Given the volume of literature in this field, a hierarchical method of inclusion was used based on study design. If we identified a well-designed SR/MA, the study was included. We also included randomized controlled trials (RCTs) or observational studies published after the SR/MA. Results are described narratively.

RESULTS

Preoperative

Carbohydrate Loading and Duration of Fasting Before Surgery

Rationale. The preoperative administration of oral carbohydrates (CHO) may be associated with an attenuation in the perioperative catabolic state, reduction in postoperative insulin resistance, and decrease in protein breakdown.

Evidence. There are no data specifically exploring preoperative CHO after TKA. The SRs examining preoperative CHO loading in non-TKA surgical procedures suggest that preoperative CHO may be associated with an attenuation in postoperative insulin resistance, a small reduction in length of hospital stay, faster return of bowel function, and less loss of muscle mass.[11,12] There are no reported adverse effects of CHO loading.

One SR in non-TKA patients noted no evidence to suggest that a shortened fluid fast resulted in an increased risk of aspiration.[13] The American Society of Anesthesiologists allows clear liquids up to 2 hours and a light meal 6 hours before induction of anesthesia in healthy patients who are undergoing elective procedures.[7] An SR of 19 fasting guidelines before surgery noted consistent evidence for the minimization of perioperative fasting.[14]

Summary. There is sufficient evidence for benefit, and lack of harm, to recommend CHO treatment before TKA. The optimal composition, volume, and timing of administration remain unclear. There is no consensus on the optimal preoperative CHO-loading regimen for patients with diabetes mellitus; in these patients, ongoing glucose monitoring and management are recommended. Patients presenting for elective TKA should be encouraged to have free intake of clear fluids up to 2 hours and solid food up to 6 hours before induction of anesthesia.

Multimodal Preanesthetic Medications

Rationale. A standardized group of preanesthetic medications may be administered as part of a multimodal approach to analgesia and postoperative nausea and vomiting (PONV) prophylaxis. Although many of the antiemetic agents are typically administered during the intraoperative period to optimize their pharmacologic effect, some agents if used (eg, scopolamine) would be administered in the preanesthesia/surgical incision period.

Acetaminophen

Evidence. There are no RCTs examining acetaminophen (per os, intravenous [IV]) administration preoperatively in patients undergoing TKA. Two observational studies in TKA patients failed to find benefit for the administration of IV acetaminophen in decreasing perioperative opioid use.[15,16]

Data for non-TKA surgical procedures indicate an analgesic benefit and decrease in PONV with the use of acetaminophen.[17–20] The MAs/SRs assessing the role of preoperative acetaminophen on outcomes after elective surgery including orthopedic procedures indicate a reduction in 24-hour opioid consumption, superior pain control, and lower incidence of PONV. Rectal administration of acetaminophen is discouraged due to the unreliable absorption and excessively high doses needed to achieve sustained therapeutic plasma concentrations. Acetaminophen should be decreased/held in patients with hepatic disease.

Celecoxib/Cyclo-Oxygenase (COX)-2 Inhibitors

Evidence. The administration of nonsteroidal anti-inflammatory agents (NSAIDs) should be scheduled and integrated into most ERAS pathways. There are no large-scale studies specifically in TKA patients examining the analgesic efficacy of preoperative NSAIDs on perioperative pain.

There are 2 MAs in non-TKA patients suggesting a benefit of preoperative per os celecoxib on reducing postoperative pain, opioid use, and PONV.[21,22] COX-2 inhibitors may be preferred to traditional NSAIDs before surgery because they have minimal effect on platelet function, even at supratherapeutic doses. An MA of COX-2 inhibitors indicated that these agents did not significantly increase the risk of perioperative bleeding and had no significant effect on platelet function.[23] A typical dose of preoperative celecoxib is 200–400 mg.[24]

Gabapentanoids

Evidence. Several MAs in TKA patients show that perioperative per os gabapentanoids (gabapentin and pregabalin) may be associated with a decrease in opioid consumption.[25,26] However, there are inconsistent benefits of gabapentanoids on analgesia and opioid-related side effects in patients undergoing TKA, and 1 MA showed no decrease in pain with ambulation or improvement of knee flexion with gabapentanoids.[25] Of the numerous RCTs/observational trials examining gabapentanoids in patients undergoing TKA,

Goal of our evidence review is to find the highest level evidence for each component of the clinical pathway.

General Overview

STEPS:

1. **PROTOCOL COMPONENTS**. Identify the critical components of the Optimal Surgical Recovery (OSR) protocol(s). These components will form the general foundation for the searches. Topics include – colorectal (CR) surgery, emergency general surgery, orthopedic (hip/knee), gynecology (hysterectomy), and bariatric.

2. **SEARCH**. For each component, perform a literature search that is procedure-specific. Search should be limited to English only. Keep track of the search terms. Initial searches can be for the specific component or for ERAS– this may vary by procedure so adjust as you see appropriate. We will also run our search terms by a librarian – as time permits. Also, you may need to search for broad surgical procedures. Examples of terms for ERAS: "fast track", "enhanced recovery", "clinical pathway", "critical pathway", "multimodal perioperative" and "perioperative protocol". (Don't limit searches by study design).

3. **INCLUSION/EXCLUSION terms and Screening**. Develop these terms for each protocol component – inclusion: specific procedure, perioperative period, component topic, reports outcomes, not case report, > ten sample size. Not necessary to track the reasons for exclusion at the title and abstract level.

   - For the full text article screen, track reasons for includes and excludes. Includes: 1. SR/MA, 2. RCTs, 3. Prospective/case controlled observational studies, 4. Retrospective observational studies. Excludes: 1. Not on the specific procedure, 2. Lack of postop outcome, 3. Not primary data, 4. Non SR, etc.

     Hierarchy of the selecting includes:

     i. First identify well-done recent SR/Mas (within the past 5 years, if possible. If you have multiple SR/MAs then pick the most recent or the better quality ones. Well-done studies are:
        - Was a specific question(s) defined that the SR/MA set out to answer? Yes
        - Provided inclusion/exclusion terms and the search terms? Yes
        - Did the studies they included make clinical sense to do so? Yes (this is often a fail)
        - They did not pool RCT and observation data together unless state a strong justification. Yes
        - Was a quality assessment of the studies performed? (doesn't really matter which tool). Yes

     ii. Of note, if there is a well-done SR/MAs cross reference with search results looking for additional studies – ones performed after the SR/MA or ones that simply weren't included. Include RCTs and observational studies performed after the SR/MA.

     iii. If you use primarily observational studies (find none or just a few RCTs) then limit to the highest study design. For example, limit by sample size (n>100)/matched cohort/ multi-institutional, etc. Need to keep track of any specific decisions that change the inclusion/exclusions at this point.

4. **DATA ABSTRACTION**
   - Evidence tables for RCTs. This can be done later, but It will be helpful to develop these and include: **Article author name and year of publication, study design, multi- or single institution, sample size (f/u rate if relevant), surgical procedure(s), details of the component of interest, outcomes measured and findings (f/u time period for some outcomes)**.

   - Evidence tables for observational studies. Include: **author name and year of publication, study design, multi or single institution, sample size (f/u rate if relevant), surgical procedure(s), details of the component of interest, outcomes measured and findings (f/u time period for some outcomes)**.

5. **REFERENCE MINING.** Check the references of the better studies for articles we may have missed. Then those identified from this step need to be screened.

Figure. Overview of evidence review protocol.

only a few showed a decrease in postoperative pain.[27,28] When added to a comprehensive multimodal analgesic regimen, gabapentin provided no additional analgesic effect on postoperative pain in TKA patients.[29]

Summary. A multimodal strategy including acetaminophen and NSAIDs is recommended in the management of TKA. Per os gabapentanoids may decrease opioid consumption, but the analgesic efficacy is uncertain and risks and benefits

Table 1. Improving Surgical Care and Recovery: Total Knee Arthroplasty Protocol Components—Anesthesia

Immediate preoperative
Reduced fasting
Carbohydrate loading
Multimodal preanesthesia medication
Intraoperative
Standard intraoperative anesthesia pathway
Fluids/goal-directed fluid therapy
Normothermia
Tranexamic acid
Glycemic control
Postoperative
Standard postoperative multimodal analgesic regimen

Table 2. Summary of AHRQ Safety Program for Improving Surgical Care and Recovery: Total Knee Arthroplasty Protocol Components, Associated Outcomes, and Support From the Literature and/or Guidelines—Anesthesia

Intervention	Outcome(s)	Evidence	Guidelines[a]
Immediate preoperative			
Carbohydrate loading	↓ Insulin resistance, ↓ protein catabolism, ↓ LOS, faster return of bowel function	[b]	6
Reduced fasting	No adverse outcomes	[b]	7
Multimodal preanesthesia medication	↓ Pain, ↓ PONV, ↓ opioid use	[b]	6
Intraoperative			
Standard intraoperative anesthesia pathway	↓ Pain, ↓ PONV, ↓ opioid use	[b]	6
Fluids/goal-directed fluid therapy	↓ Morbidity, ↓ LOS	[b]	8
Tranexamic acid	↓ Blood loss	[b]	9
Glycemic control	↓ SSI	[b]	10
Postoperative			
Standard postoperative multimodal analgesic regimen	↓ Pain, ↓ PONV, ↓ opioid use	[b]	6

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; LOS, length of stay; PONV, postoperative nausea and vomiting; SSI, surgical site infection.

[a]Designates a component for which all guidelines supported a given practice.

[b]Designates a component for which all evidence supported a given practice.

of gabapentanoids may be carefully considered on an individual basis. There is currently insufficient evidence to guide the optimal dose, selection, combinations, and timing of the individual agents.

PONV Prophylaxis

Evidence. Control of PONV is important to facilitate patient oral intake and recovery. While the majority of medications to prevent PONV is administered intraoperatively, some (eg, scopolamine) will need to be initiated in the preoperative period. A relatively recent evidence-based guideline for the management of PONV has been published.[30]

Intraoperative

Standardized Evidence-Based Intraoperative Anesthetic Pathway

Rationale. A standardized, evidence-based intraoperative anesthetic pathway is essential for every surgical ERAS protocol because standardization is a strategy to improve patient outcomes.[31] The intraoperative anesthetic should be tailored to optimize anesthetic depth while facilitating a rapid awakening after completion of the surgical procedure. Within these parameters, there are many anesthetic regimens that can be used.

Regional Anesthesia (Neuraxial and Peripheral Nerve Blocks)

Rationale. The use of regional anesthetic/analgesic techniques features prominently in many ERAS pathways. Local anesthetic-based techniques facilitate patient recovery by providing superior analgesia and decreasing opioid consumption. For TKA, the use of neuraxial (epidural and spinal) anesthesia or peripheral nerve blocks (PNB) may be used for intraoperative anesthesia/analgesia.

Neuraxial (Epidural or Spinal) Anesthesia

Evidence. We identified several SRs and large-scale observational studies/RCT examining the use of neuraxial anesthesia and TKA.[32–35] Neuraxial anesthesia provides comparable analgesia to PNB for TKA.[32] The data suggest that neuraxial anesthesia (versus general anesthesia [GA]) in those patients undergoing TKA is associated with improved outcomes including a decrease of in-hospital mortality, pneumonia, and systemic infections.[33–35]

Summary. Neuraxial anesthesia is associated with improved outcomes in TKA patients. For patients without any contraindications, and assuming local expertise and resources are available, the use of neuraxial anesthesia is preferred over GA for TKA. The concurrent use of anticoagulants with neuraxial blocks/catheters should be approached with caution.[36]

Peripheral Nerve Blocks

Evidence. We identified multiple MAs/SRs/large-scale observational studies examining the use of PNBs in patients undergoing TKA.[37–44] The observational studies indicate that the use of PNBs for TKA is associated with improved outcomes including a decrease in wound complications, pulmonary complications, and opioid consumption.[43,44] When compared to no block, PNBs (femoral/adductor canal and sciatic nerve block) provide more effective analgesia and reduce opioid consumption.[37,40–43] The analgesia provided by PNBs for TKA may be comparable to that produced by an epidural technique but with an improved side-effect profile (less hypotension).[32]

The MAs comparing femoral nerve block to adductor canal block for TKA suggest that the adductor canal block may be associated with preservation of quadriceps strength and faster knee function recovery, without any difference in analgesia, opioid consumption, or complications.[39,45]

The SR/MAs[38,46] comparing PNBs to local infiltration analgesia (LIA) for TKA support the combination of femoral/sciatic nerve blocks for providing comparable analgesia to LIA at rest, and possibly superior analgesia with movement; however, there are significant methodological issues present in most of these studies.[47]

Summary. For patients without any contraindications, and assuming local expertise and resources are available, the use of or PNBs and/or LIA are preferred over opioid monotherapy for perioperative analgesia for TKA.

Intrathecal Morphine

Evidence. A single dose of intrathecal (IT) opioid may be administered before surgery for postoperative analgesia. We found several RCTs/MA investigating the use of IT morphine in patients undergoing TKA.

There is 1 MA comparing IT morphine to femoral nerve block for TKA.[48] Results supported equivalent analgesia between the 2 techniques, but fewer side effects (decreased pruritus) are associated with femoral nerve block. IT morphine provides equivalent or superior analgesia to femoral nerve block for post-TKA analgesia.[49] We found 2 RCTs comparing IT morphine to periarticular infiltration of local anesthetics.[50,51] IT morphine provided equivalent analgesia in 1 RCT.[50] Conversely, LIA provided superior postoperative analgesia and earlier mobilization than IT morphine in the other.[51]

We found 2 RCTs comparing dose-response effects of IT morphine on post-TKA pain.[52,53] IT morphine (0.3–0.5 mg) produced superior analgesia compared to placebo or 0.2 mg.[52] Two MAs investigating the use of IT morphine in orthopedic and nonorthopedic patients support the use of IT morphine (0.05–0.2 mg) to decrease pain scores and systemic opioid requirements.[54,55]

The use of IT opioids is associated with several side effects including respiratory depression/PONV.[54,55] Doses of IT morphine above 0.3 mg are generally associated with more episodes of respiratory depression.[56] Guidelines for the prevention, detection, monitoring, and management of respiratory depression associated with neuraxial opioid administration have been published.[57]

Summary. PNBs and locoregional analgesic techniques are recommended over IT opioid analgesia. Administration of a single dose of IT opioid may be considered for post-TKA analgesia, but the lowest efficacious dose (generally ≤0.3 mg) should be administered. IT opioids should be used cautiously in patients at risk for respiratory depression (eg, obesity, obstructive sleep apnea).

Ventilation and Oxygenation

Rationale. Optimization of perioperative oxygenation may reduce surgical site infections (SSIs). Use of an intraoperative protective lung ventilation strategy may reduce pulmonary complications.

Evidence. There are no studies specifically examining the effect of intraoperative protective ventilation strategy and pulmonary outcomes in TKA patients. There are also no studies exploring the effect of oxygenation or oxygen status on SSI in TKA patients. There are several MAs examining the effect of oxygenation on SSI; most of the included studies do not include orthopedic surgery patients.[58–60]

The MAs that include orthopedic surgery cohorts have provided mixed data on whether perioperative supplemental (typically F_{IO_2} >0.8) oxygen therapy decreases SSIs. Subgroup analyses suggest that some surgical patients (colorectal but "not" joint arthroplasty) may benefit from perioperative supplemental oxygen therapy in decreasing SSIs.[60] The potential benefits of hyperoxia need to be balanced against the potential harms of hyperoxia including possible elevated risk of mortality.[61]

There are several MAs examining an intraoperative protective ventilation strategy and pulmonary outcomes in nonorthopedic patients.[62,63] Overall, the data indicate that lower tidal volume ventilation (6–8 vs 10–12 mL/kg) is associated with fewer pulmonary complications.

Summary. If GA is to be used, then an intraoperative protective ventilation strategy including lower tidal volumes (6–8 mL/kg predicted body weight) is recommended. Routine perioperative hyperoxia for patients undergoing TKA is not recommended.

Perioperative Nausea and Vomiting

Rationale. Control of PONV is an important anesthesiology component of any ERAS pathway. ERAS pathways often incorporate multimodal, preventive PONV strategies.

Evidence. We identified several studies examining PONV in TKA patients.[64–66] One observational trial associated decreased PONV with laryngeal mask airway compared to endotracheal intubation for airway management in TKA performed under GA.[64] The remaining studies examined the efficacy of various combinations of serotonin antagonists and dexamethasone in decreasing PONV after TKA.[65,66]

A recent and comprehensive evidence-based guideline and SR for the management of PONV in all types of surgical patients have been published.[30,67]

Intraoperatively, the use of a propofol-based total IV anesthetic is recommended to reduce the risk for PONV.[30] One observational study associated neuraxial anesthesia with less PONV in a joint arthroplasty cohort.[68]

Summary. The use of a multimodal antiemetic regimen for the prevention and treatment of PONV is recommended in patients undergoing TKA. Anesthetic techniques and agents (regional anesthesia/propofol) may be associated with a lower incidence of PONV and are recommended. Several antiemetic agents can be given preoperatively (transdermal scopolamine), while others (serotonin (5-HT3) receptor antagonists, dexamethasone) are given intraoperatively and/or postoperatively.

Tranexamic Acid

Rationale. Tranexamic acid (TXA) is an antifibrinolytic drug that inhibits fibrinolysis by blocking the conversion of plasminogen to plasmin (which breaks down fibrin in already-formed clots).

Evidence. There are multiple RCTs/MAs/SRs examining the use of TXA in TKA surgical patients.[69–74] The data

suggest that TXA significantly reduces the intraoperative/postoperative blood loss/transfusion requirements for TKA. IV, topical, and intraarticular routes of administration are all effective in reducing perioperative blood loss and all appear to be equally effective. MAs/SRs of TXA for TKA do not suggest any increased risk of deep venous thrombosis, myocardial infarction (MI), cerebrovascular accident, or pulmonary embolism.[73,74] Many studies have excluded these high-risk groups (MI, cerebrovascular accident, and pulmonary embolism), and the efficacy and safety in these high-risk patients are uncertain.

Summary. Perioperative administration of TXA for TKA is recommended for all patients, without contraindication, to minimize intraoperative/postoperative blood loss and transfusion. The optimal dose, timing, and route of administration are uncertain, particularly in high-risk patients.

Glycemic Control

Rationale. Perioperative control of glucose may contribute to a reduction in SSIs.

Evidence. The 1 observational study in TKA patients[75] noted that elevated glucose during the postoperative period in diabetic and nondiabetic patients undergoing TKA increases postoperative medical/infectious complications. The Center for Disease Control recently released a guideline (not specific to any 1 surgical procedure) for the prevention of SSI, which recommended perioperative glycemic control with blood glucose target levels <200 mg/dL in patients with and without diabetes.[10]

Summary. During surgery, glycemic control should be implemented using blood glucose target levels <200 mg/dL in patients with and without diabetes.

N-Methyl-D-Aspartate Receptor Antagonists: Ketamine

Rationale. The perioperative administration of an IV ketamine bolus and/or infusions may provide analgesia via a nonopioid receptor mechanism and decrease perioperative opioid consumption.

Evidence. There are several RCTs/observational trials examining IV ketamine in TKA.[76–78] Addition of low-dose (subanesthetic) IV ketamine may reduce pain intensity, decrease opioid consumption, and improve mobilization after TKA performed under GA.[76–78] One MA suggests that IV ketamine, compared to placebo, may also protect against the development of persistent postsurgical pain and represent a useful anesthetic/analgesic agent in opioid-tolerant patients.[79] There is no consensus regarding the precise dose or timing of ketamine administration. An intraoperative bolus of 0.25–1 mg/kg followed by an infusion of 0.1–0.25 mg/kg/h has been described in the RCTs included in the MAs.[76,77]

Summary. IV ketamine may be a useful nonopioid intraoperative anesthetic agent for TKA, particularly when performed under GA, or in opioid-tolerant patients. The decision to use ketamine should be made on an individual basis.

IV Lidocaine

Rationale. The perioperative administration of an IV lidocaine bolus and/or infusions may provide analgesia via a nonopioid receptor mechanism and decrease perioperative opioid consumption.

Evidence. There are no studies specifically examining the use of IV lidocaine in patients undergoing TKA. However, there are several MAs examining perioperative IV lidocaine infusions in a variety of nonorthopedic surgical procedures.[80–82] The data associate perioperative IV lidocaine infusions with decreased postoperative pain, reduced opioid consumption, and earlier return of gastrointestinal function. None of the MAs that included joint arthroplasty found evidence to support an analgesic benefit, opioid-sparing capacity, or effect on length of stay of IV lidocaine. Toxic plasma levels of lidocaine were reported in several of the included studies.

Summary. IV lidocaine may be a useful nonopioid intraoperative analgesic adjunct, but the optimal dose and duration of administration are uncertain. The benefits for the routine use of IV lidocaine for TKA are not demonstrated, and the decision to use IV lidocaine should be made on an individual basis. Caution should be exercised whenever multiple sources of local anesthetics are used, and doses should be reduced accordingly to minimize risk of systemic toxicity.

Fluid Minimization/Goal-Directed Fluid Therapy

Rationale. Optimizing perioperative fluid management is a key component of ERAS pathways. Excessive perioperative fluid administration is associated with cardiac, pulmonary and renal dysfunction, inhibition of gastrointestinal function, and delayed recovery.

Evidence. There are no studies specifically examining the goal-directed fluid therapy (GDFT) in patients undergoing TKA, but a cohort study that included TKA patients noted that high intraoperative fluid volumes were associated with an increase in length of hospital stay and total costs.[83] Several MAs in mostly nonorthopedic patients showed that compared to a liberal fluid therapy regimen, a GDFT regimen was associated with a reduction in wound infection, cardiac complications, intensive care unit admission, hospital length of stay, time to tolerate oral intake, abdominal complications, and postoperative hypotension although no differences in mortality were noted.[84–86] The benefits of GDFT were most apparent in high-risk patients undergoing major surgery and patients not treated within an ERAS pathway. The superiority of GDFT therapy versus a restrictive fluid strategy remains uncertain.

The goal of intraoperative fluid therapy is to maintain euvolemia and achieve a "near-zero" fluid balance.[87] Hydroxyethyl starches are not recommended due to their association with increased mortality.[88]

Summary. There is a lack of procedure-specific evidence to guide fluid administration for TKA. The amount, composition, and monitoring of IV fluids should take into account that elective TKA is likely to be of minimal to moderate risk, with predictable preoperative deficits, perioperative blood loss, and fluid shifts. Although the overall benefits of GDFT

have been demonstrated for a wide range of surgical procedures, the specific value of GDFT for TKA patients is not yet demonstrated.

Postoperative

Standardized, Evidence-Based Postoperative Multimodal Analgesic Regimen

Rationale. Control of postoperative pain in patients undergoing TKA is an important component of any TKA ERAS pathway. Optimal pain control facilitates patient mobility and recovery. Typically, a multimodal analgesic approach with multiple nonopioid analgesics agents and techniques is used to minimize the use and side effects of opioids.

Nonsteroidal Anti-Inflammatory Drugs

Rationale. As part of a nonopioid multimodal approach to control perioperative pain, per os/IV nonsteroidal anti-inflammatory drugs (NSAIDs) may be used with other nonopioid analgesic to produce additive/synergistic analgesia while minimizing opioid use and opioid-related side effects.

Evidence. We identified several RCTs, 1 observational trial, and 1 MA examining the use of per os/IV NSAIDs (including COX-2 inhibitors) for the treatment of pain after TKA.[89–92] The use of NSAIDs is associated with decreased postoperative pain, opioid consumption, and PONV.

We identified several additional MA/SRs of perioperative use of NSAIDs (including COX-2 inhibitors) in orthopedic/nonorthopedic surgical patients.[22,24,93,94] These MAs also suggest that addition of NSAIDs resulted in a reduction in pain scores and opioid-sparing effect. We found 2 MAs suggesting that NSAIDs, when added to an opioid-IV patient-controlled analgesia (PCA) regimen, provide effective postoperative analgesia and minimize opioid utilization and PONV.[95,96]

NSAIDs should be administered on a scheduled basis for most ERAS pathways. It should be noted that the combined duration of the use of parenteral and oral ketorolac should not exceed 5 days.[97] NSAIDs are associated with several side effects including platelet dysfunction, gastrointestinal irritation/bleeding, and renal dysfunction. A brief perioperative use of NSAIDs does not appear to be associated with increased risk for MI after total hip/knee replacement.[98]

Summary. The use of per os/IV NSAIDs should be administered on a scheduled basis. The dose of NSAIDs should be decreased/withheld in patients with certain comorbidities and in elderly patients.

Acetaminophen

Rationale. Per os/IV acetaminophen may be used with other nonopioid analgesic to produce additive/synergistic analgesia while minimizing opioid use and opioid-related side effects.

Evidence. We did not identify any studies specifically examining acetaminophen administration postoperatively in patients undergoing TKA. However, there are several MAs[17,19,20] examining the use of per os/IV acetaminophen for the treatment of postoperative pain in orthopedic and nonorthopedic patients. The data suggest that postoperative acetaminophen is associated with superior analgesia and decreased opioid consumption/PONV.

We identified 1 SR suggesting that wherever possible, acetaminophen should be concurrently administered NSAIDs because administration of both (on a scheduled basis) is associated with superior analgesia compared to either agent alone.[18]

Summary. The use of per os/IV acetaminophen should be administered on a scheduled basis. When possible, acetaminophen should be concurrently administered with NSAIDs. The dose of acetaminophen should be decreased/held in patients with liver disease.

Gabapentanoids

Rationale. Gabapentin and pregabalin are anticonvulsants that have been used for the prevention and treatment of both acute and chronic pain.

Evidence. We found several MAs exploring the role of the per os gabapentanoids in post-TKA analgesia.[25,26] All MAs demonstrated a decrease in opioid consumption; however, effects on opioid-related side effects were inconsistent. In addition, only a few of the multiple RCTs/observational trials examining gabapentanoids in patients undergoing TKA showed a decrease in postoperative pain[27,28] with the remainder of studies demonstrating no effect on postoperative pain when gabapentanoids were added to a multimodal analgesic regimen.[29]

Summary. The use of per os gabapentanoids may decrease opioid consumption, but the analgesic efficacy of per os gabapentanoids in TKA is uncertain. Gabapentanoids may be carefully considered on an individual basis as part of a multimodal analgesic strategy for TKA.

Local Anesthetic Infusions (Subcutaneous)

Rationale. Local anesthetics may be administered via continuous wound infusions to provide nonopioid analgesia at the incision site.

Evidence. There are 2 MAs[99,100] and 1 observational trial[101] investigating the use of continuous wound infusions of local anesthetics for patients undergoing TKA. The 2 MAs found a statistical decrease in pain scores early in the postoperative period (24 hours), but there were no differences in length of hospital stay, incidence of deep venous thrombosis, or PONV. The local anesthetic infusion pump may be associated with higher incidence of infection.[99,100] The observational study associated continuous wound infusion of local anesthetics with inferior analgesia compared to PNBs and femoral nerve catheter.[101]

We identified several SRs of the use of continuous wound infusions for postoperative analgesia in orthopedic and nonorthopedic surgical patients.[102,103] The analgesic efficacy of continuous wound infusions with local anesthetics for postoperative analgesia could not be demonstrated. Methodological issues prohibit conclusive recommendation of this technique.

Summary. The analgesic efficacy of continuous wound infusions with local anesthetics for postoperative analgesia is uncertain and cannot be recommended on a routine basis for TKA.

Intraarticular (Single) Injection

Rationale. Administration of a local anesthetic-based solution may provide effective postoperative analgesia while minimizing systemic side effects from opioid analgesic medications.

Evidence. There are several RCTs/observational studies and 1 MA examining the use of intraarticular (single injection) analgesia for pain control after TKA.[104–107] A single intraarticular injection of a local anesthetic-based regimen was associated with lower pain scores. Individual studies indicate that intraarticular injection may potentially provide analgesia comparable to epidural analgesia,[104] periarticular/extraarticular analgesia,[106] or femoral nerve block.[107]

Summary. Intraarticular injection of a local analgesic-based solution may be a useful nonopioid postoperative analgesic agent, particularly when regional analgesic techniques are unavailable.

LIA and Periarticular Injection Analgesia

Rationale. Tissue infiltration with local anesthetics may be analgesic, cause minimal side effects, and facilitate early mobilization.

Evidence. We identified several MAs/RCTs/observational studies[46,108–110] examining the use of LIA/periarticular injection (PAI) in patients undergoing TKA. Overall, the data suggest that compared to placebo, LIA/PAI is associated with lower post-TKA pain scores and opioid consumption. LIA/PAI may provide equivalent analgesia to femoral nerve block after TKA.

Summary. Tissue infiltration of local anesthetics by the surgeon may be a useful nonopioid postoperative analgesic agent, particularly where other regional analgesic options are unavailable. The optimal composition, dose, site, and method of injection of LIA and PAI are unknown at this time.

Continuous PNBs (Femoral-Adductor Canal/Sciatic)

Rationale. Perioperative PNBs minimize pain, facilitate rehabilitation, and are associated with less opioid use and side effects after TKA.

Evidence. We identified several MAs[40,42,111] examining the use of continuous peripheral nerve catheters for perioperative anesthesia/analgesia in patients undergoing TKA. Compared to placebo or no nerve block, continuous peripheral nerve catheters provided more effective analgesia and reduced morphine consumption.

Summary. Peripheral nerve catheters (when available) are recommended over opioid monotherapy for TKA analgesia. The optimal drug, dosing regimen, and duration of continuous nerve catheters in patients undergoing TKA are unknown at this time.

Tramadol

Rationale. Tramadol is synthetic analgesic that exhibits both opioid and nonopioid activities. Tramadol is a weak μ-opioid receptor agonist and inhibitor of serotonin/norepinephrine reuptake.

Evidence. We did not identify any SR/MAs specifically examining per os tramadol in patients undergoing TKA. We found 3 MAs of tramadol for the treatment of postoperative pain, which included orthopedic and nonorthopedic surgical patients.[112–114] The evidence suggests that tramadol has a mild–moderate analgesic benefit that is improved when combined with acetaminophen. There is 1 RCT comparing combination tramadol/acetaminophen with NSAID after TKA supporting superiority of tramadol/acetaminophen for post-TKA analgesia and rehabilitation potential.[115] Human studies suggest that tramadol causes less respiratory depression than other opioids.[116] Tramadol should be held or used with caution in patients with renal disease, seizure disorder, or taking selective serotonin receptor inhibitors.

Summary. Per os tramadol may be a useful analgesic agent after TKA, although the overall analgesic efficacy of per os tramadol for TKA is unclear.

Dextromethorphan

Rationale. Dextromethorphan has *N*-methyl-D-aspartate receptor antagonist activity and may provide analgesia via nonopioid mechanisms.

Evidence. We identified 1 RCT examining per os dextromethorphan in patients undergoing TKA.[117] Intramuscular dextromethorphan given either before/after surgery augmented the postoperative analgesic effect of morphine and reduced post-TKA pain.

We identified 1 additional SR and 1 MA on the use of per os dextromethorphan for postoperative pain in orthopedic and nonorthopedic surgical patients.[118,119] The MA[118] included 21 RCTs and associated perioperative dextromethorphan with reduced postoperative opioid consumption (up to 48 hours) and pain scores (up to 24 hours) after surgery. Although results were inconsistent, an earlier SR[119] reported that dextromethorphan is a potential safe adjunct agent to opioid analgesia for postoperative pain management. Dextromethorphan may be associated with nausea, vomiting, dizziness, and sedation; it is unclear whether these side effects occur more frequently than that seen with opioids.[118]

Summary. Per os dextromethorphan may be a useful nonopioid analgesic agent for post-TKA pain. The optimal dose and duration of administration are uncertain. The decision to use per os dextromethorphan should be made on an individual basis.

Summary (Postoperative). A multimodal analgesic regimen is recommended to achieve optimal pain control/minimize opioid-related side effects after TKA. Opioid analgesics should be used judiciously, at the lowest dose, for the shortest duration possible, except in patients with baseline/chronic opioid dependence.

DISCUSSION

This evidence review evaluates the current evidence for all anesthetic interventions that may improve outcomes

after TKA. This evidence base can be translated into local practice to potentially improve outcomes, enhance patient satisfaction, and minimize patient harm. We identified components of care for the AHRQ Safety Program for ISCR TKA protocol (please see Supplemental Digital Content, Table 1, http://links.lww.com/AA/C454), which are supported by the literature, existing guidelines, and/or expert consensus.

ERAS pathways have been associated with superior outcomes, cost savings, and shorter length of hospital stay after joint arthroplasty.[2–5] Within the published literature, there is considerable heterogeneity in ERAS components and techniques used for TKA.

The evidence review suggests that the preoperative phase of care should include CHO administration 2 hours before induction of anesthesia, and limited duration of preoperative fasting. The optimal composition of the carbohydrate load is still uncertain.[120] A preoperative medication bundle (acetaminophen, COX-2 inhibitor) is recommended. PONV prophylaxis should be provided.

Intraoperatively, TXA should be given. Available literature supports a judicious use of fluids based on the goal of euvolemia. Where local resources permit, a regional anesthetic technique is recommended. Where a regional anesthetic is not available, total IV anesthesia–based GA/inhalational-based GA without nitrous oxide is recommended.[121,122] PONV prophylaxis should be provided based on patient risk factors. Where local expertise is available, PNBs or catheters (femoral nerve or adductor canal) are recommended. In practice settings lacking regional anesthesia/analgesia services, surgeon-administered LIA/PAI should substitute for PNB. The postoperative anesthetic management of TKA patients focuses on effective, multimodal analgesia. Regional analgesic techniques can be continued/extended into the postoperative phase via use of peripheral nerve catheters. Ongoing prevention and management of PONV should be provided.

The ideal intraoperative anesthetic protocol to support ERAS principles has yet to be definitively established for TKA.[123] The recommendations from our protocol are similar to that from the American Academy of Orthopaedic Surgeons TKA guideline[9] which demonstrated moderate to strong evidence for use of PNBs, neuraxial anesthesia, LIA, and TXA. Our protocol is also very similar to a recently published practice pathway for TKA by the American and European Societies of Regional Anesthesia and Pain Medicine.[124] While the anesthesia and analgesic components are similar between the 2, our protocol is part of a comprehensive (anesthesiology and surgery) pathway and includes other aspects (eg, glycemic control, TXA) not covered by the recently published practice pathway.[124]

Successful implementation of ERAS pathways rests on multiple factors, including local resources, expertise, and policy and administrative support. Although a main tenet of ERAS is the application of best evidence to practice, a degree of adaptation and selection of components based on local practice are both logical and desirable. The evidence-based recommendations provided here can be used as a framework for developing consensus and a standardized ERAS pathway for TKA. ■

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