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SPECIAL ARTICLE

Anesthesia and Analgesia Practice Pathway Options for Total Knee Arthroplasty

An Evidence-Based Review by the American and European Societies of Regional Anesthesia and Pain Medicine

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Abstract: In 2014, the American Society of Regional Anesthesia and Pain Medicine in collaboration with the European Society of Regional Anaesthesia and Pain Therapy convened a group of experts to compare pathways for anesthetic and analgesic management for patients undergoing total knee arthroplasty in North America and Europe and to develop a practice pathway. This review is intended to be an analysis of the current literature to assist individuals and institutions in designing a pathway for total knee arthroplasty that is based on existing evidence and expert recommendation and may be customized according to individual settings.

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Total knee arthroplasty (TKA) is one of the most commonly performed orthopedic procedures, with an estimated more than 700,000 total knee replacements (TKRs) performed annually in the United States. The annual expected growth rate of TKA is 7.9% in the United States and 5.3% to 14.7% in the main European countries.[1] Patients undergoing TKA report improved health-related quality of life and functional status.[2–4] Unfortunately, it is known to cause moderate to severe pain in most patients and is therefore regarded as one of the most painful orthopedic procedures.[5] In addition, patients who are identified as at risk of chronic pain may benefit from aggressive perioperative pain management in an attempt to prevent central sensitization.[6] The extensive increase in the number of patients undergoing TKA requires specific customized management of care. Clinical pathways are tools created to organize care of well-defined groups of patients while maintaining a high quality of efficient care during a well-defined, limited episode of care.[2] An effective TKA pathway would link the current evidence to individual practices with the goal of having a positive impact on perioperative outcomes (Fig. 1). In 2014, the American Society of Regional Anesthesia and Pain Medicine (ASRA) in collaboration with the European Society of Regional Anaesthesia and Pain Therapy (ESRA) convened a group of experts to compare pathways for anesthetic and analgesic management for patients undergoing TKA between North America and Europe and develop a practice pathway. It became immediately clear that standardized pathways are not ubiquitous in Europe or North America. Rather, each practice was using a combination of different techniques dictated by the orthopedic surgeons, anesthesiologists, or simply the needs of the site. The panel quickly determined that it was going to be impossible to define or compare a specific pathway on either continent. Therefore, this review is intended to be an analysis of the current literature to assist individuals and institutions in designing a pathway for TKA that is based on existing evidence and expert recommendation and may be customized according to individual settings.

METHODS

The ASRA and ESRA panelists were chosen based on their demonstrated expertise in various issues related to anesthetic (neuraxial vs general) and analgesic (eg, multimodal analgesia, peripheral nerve blocks [PNBs]) management for patients undergoing TKA. Panelists received no compensation for their contributions; nor did any declare a conflict of interest pertinent to the topic. Panelists were charged with performing an extensive review of the literature; summarizing and presenting their findings at the 2014 American Society of Regional Anesthesiology and Acute Pain Medicine Conference, Chicago, Illinois; and producing an article based on their scholarly work. A comprehensive review of the subtopics (anesthesia type and outcomes, PNBs, infiltrative techniques, and multimodal oral analgesia) was performed, including publications involving comparative techniques, efficacy, and complications. In each section, the authors created their work with a combination of literature review and experience-based opinion. This document is not intended to define the standard of care and is not a formal systematic review. Rather, it is intended to provide a scoping review of specific components of a regional anesthesia pathway for TKA.[7]

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RESULTS

Anesthesia Type and Outcomes

The discussion regarding the choice of anesthesia and the potential impact on outcomes has been ongoing for many decades, and much controversy still remains.[8] A number of studies including clinical trials, meta-analyses, and population-based investigations have compared anesthetic (general vs neuraxial vs peripheral) and analgesic (neuraxial, PNBs, infiltration, and multimodal medication) options (Table 1). Despite significant additions to our knowledge in recent years, many questions remain, and important caveats need to be considered when interpreting the data.[15]

For example, with perioperative practices substantially differing between institutions, results of both randomized trials conducted in single-center settings and population-based investigations may have limited applicability to highly specialized practices, which may have developed protocols with good outcomes. Whereas the former may be burdened by lack of external validity, the latter sources of information, representing population-based averages, may lack applicability to a specific institution. It must also be noted that anesthetic and analgesic techniques represent only a small piece of the many interventions that influence major perioperative outcomes.

Until recently, evidence regarding the impact of the type of anesthesia on perioperative outcomes relied on a number of relatively small, often single-institutional investigations widely considered underpowered to detect differences in perioperative morbidity and mortality. More recently, however, a meta-analysis involving 28 studies and 1538 patients performed by Macfarlane et al[16] focusing on randomized controlled trials (RCTs) involving TKR patients concluded that "there was insufficient evidence from RCTs alone to conclude that anesthetic technique influenced mortality, cardiovascular morbidity other than postoperative hypotension, or the incidence of deep venous thrombosis and pulmonary embolism when using thromboprophylaxis." Furthermore, the authors did not find a difference in blood transfusions or length of operating time but improved pain management profiles and possibly decreased length of stay (LOS) attributable to neuraxial anesthesia/analgesia. The inability to identify significant differences in major complications, however, was likely related to the relatively low sample size in the included studies.

With the advent of large database research, many of the previous limitations regarding sample size and external validity could be overcome, but at the expense of the inability to determine causality and take into account important clinical cofounders. In this context, an analysis of population-based administrative data from hundreds of hospitals in the United States including information on more than a quarter of a million TKA patients suggested that the risk of perioperative complications was significantly reduced when neuraxial anesthesia was used compared with general anesthesia.[17] Benefits of neuraxial anesthesia included an 83% lower mortality risk as well as similar reductions in the odds of pulmonary complications. Other benefits were found for lung infections and for gastrointestinal and renal complication risk. Interestingly, patients receiving a combination of neuraxial and general anesthesia had risk of various complications between those for neuraxial and general anesthesia alone. Advantages in LOS and cost were also observed. In addition, the study showed that approximately only one fourth of patients actually received a neuraxial anesthetic, pointing toward a potentially large positive impact on the health care system if the use of neuraxial anesthesia was to be expanded. With the inability to establish causal relationships, however, the potential attributable impact remains speculative.

Using various databases, other authors were able to draw similar conclusions. Without specifically differentiating between hip and knee arthroplasties, Chang et al[18] observed higher surgical site infection (SSI) risk among joint arthroplasty patients receiving general compared with neuraxial anesthesia in a cohort of 3081 Taiwanese patients. Similarly, Liu et al[12] linked the use of neuraxial versus general anesthesia to reduced pneumonia and systemic infection risk using the American College of Surgeons National Surgical Quality Improvement Program database. Working with data from the same source,[12] Pugely et al[13] found that short-term complication risk was higher in those receiving general versus neuraxial anesthesia for TKR. A recent retrospective case-control study undertaken to confirm or refute these findings found no difference in the incidence of SSI in patients undergoing total joint arthroplasty under general versus neuraxial anesthesia.[7] In this study, Kopp et al[7] also examined the effects of PNBs on SSI and found no significant effect. However, increasing body mass index and current smoking were found to significantly increase the incidence of SSI in patients undergoing lower-extremity total joint arthroplasty. A recent meta-analysis that included 13 studies concluded that the use of neuraxial anesthesia was associated with a significant reduction in the incidence of postoperative SSI compared with general anesthesia in TKA and total hip arthroplasty (THA).[19] Additional studies have linked neuraxial anesthesia to be independently associated with reduced need for critical care services (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.51–0.6) as well as inpatient falls (OR, 0.70; 95% CI, 0.56–0.87).[10,20] It has to be mentioned, however, that, although population-based analyses seem to produce results favoring the use of neuraxial anesthesia, not all studies show better outcomes for all complications. Furthermore, clinical trial results from highly specialized institutions may show good outcomes in terms of recovery profiles with general anesthesia.[11]

A recent retrospective, propensity score–matched cohort study also suggests a strong association between spinal anesthesia and a lower 30-day mortality, as well as a shorter hospital LOS after elective TKA or THA.[21] The propensity score matching allowed the authors to minimize the baseline differences between groups, therefore limiting the treatment selection bias that is often present in retrospective studies.

- ☑ **Decrease pain**
- ☑ **Decrease hospital length of stay**
- ☑ **Decrease cost**
- ☑ **Decrease morbidity & mortality**
- ☑ **Decrease the use of resources**
- ☑ **Improve long-term functional outcomes**
- ☑ **Decrease in-hospital falls**
- ☑ **Decrease surgical site infection**
- ☑ **Decrease rate of blood transfusion**
- ☑ **Decrease the incidence of chronic pain**
- ☑ **Improve patient satisfaction**

FIGURE 1. Goals of a TKA pathway.

TABLE 1. General Versus Regional Anesthesia in TKA

Year	Author	Title/Findings	Type	No. Patients	Journal
2016	Perlas et al[21]	Anesthesia Technique and Mortality After Total Hip or Knee Arthroplasty: A Retrospective, Propensity Score–Matched Cohort Study	Cohort	10,868	*Anesthesiology*
		Lower 30-d mortality, shorter LOS with spinal anesthesia			
2015	Fleischut et al[22]	Variability in Anesthetic Care for Total Knee Arthroplasty: An Analysis From the Anesthesia Quality Institute	Observational	108,625	*Am J Med Qual*
		Differences in anesthetic care by patient and provider characteristics are prevalent			
2014	Liu et al[23]	Peripheral Nerve Blocks Versus General Anesthesia for Total Knee Replacement in Elderly Patients on the Postoperative Quality of Recovery	RCT	213	*Clin Interv Aging*
		Regional anesthesia with sedation facilitates faster postoperative recovery compared with general anesthesia			
2014	Memtsoudis et al[10]	Inpatient Falls After Total Knee Arthroplasty: The Role of Anesthesia Type and Peripheral Nerve Blocks	Observational	191,570	*Anesthesiology*
		Peripheral nerve block use is not associated with inpatient falls			
2013	Harsten et al[11]	Recovery After Total Intravenous General Anesthesia or Spinal Anesthesia for Total Knee Arthroplasty: A Randomized Trial	RCT	120	*Br J Anaesth*
		General anesthesia showed more favorable recovery effects than spinal anesthesia			
2013	Liu et al[12]	Neuraxial Anesthesia Decreases Postoperative Systemic Infection Risk Compared With General Anesthesia in Knee Arthroplasty	Observational	16,555	*Anesth Analg*
		Neuraxial anesthesia was associated with lower odds for complications compared with general anesthesia			
2013	Pugely et al[13]	Differences in Short-term Complications Between Spinal and General Anesthesia for Primary Total Knee Arthroplasty	Observational	14,052	*J Bone Joint Surg Am*
		General anesthesia was associated with higher risk of complications compared with spinal anesthesia			
2012	Stundner et al[14]	Comparative Perioperative Outcomes Associated With Neuraxial Versus General Anesthesia for Simultaneous Bilateral Total Knee Arthroplasty	Observational	15,687	*Reg Anesth Pain Med*
		Neuraxial anesthesia was associated with lower rates of blood transfusions and, by trend, decreased morbidity			
2007	Napier et al[24]	Postoperative Benefits of Intrathecal Injection for Patients Undergoing Total Knee Arthroplasty	2-Group comparison	85	*Orthop Nurs*
		The overall effect of pain control was greater with intrathecal injections vs general anesthesia			
2006	Chu et al[25]	Postoperative Outcome in Chinese Patients Having Primary Total Knee Arthroplasty Under General Anaesthesia/Intravenous Patient-Controlled Analgesia Compared to Spinal-Epidural Anaesthesia/Analgesia	RCT	60	*Hong Kong Med J*
		Regional anesthesia was associated with superior pain relief compared with general anesthesia			
2004	Kudoh et al[26]	A Comparison of Anesthetic Quality in Propofol-Spinal Anesthesia and Propofol-Fentanyl Anesthesia for Total Knee Arthroplasty in Elderly Patients	RCT	150	*J Clin Anesth*

Continued next page

TABLE 1. *(Continued)*

Year	Author	Title/Findings	Type	No. Patients	Journal
		Propofol-spinal anesthesia provided better and faster recovery than propofol-fentanyl anesthesia			
1996	Williams-Russo et al[27]	Randomized Trial of Epidural Versus General Anesthesia: Outcomes After Primary Total Knee Replacement	RCT	262	*Clin Orthop Relat Res*
		Epidural anesthesia is associated with faster postoperative rehabilitation			
1995	Williams-Russo et al[28]	Cognitive Effects After Epidural vs General Anesthesia in Older Adults. A Randomized Trial	RCT	262	*JAMA*
		Type of anesthesia does not affect the magnitude or pattern of postoperative cognitive dysfunction			
1992	Sharrock et al[29]	Fibrinolytic Activity Following Total Knee Arthroplasty Under Epidural or General Anesthesia	RCT	21	*Reg Anesth Pain Med*
		No effect of anesthetic technique was found on clot formation and fibrinolytic activity			
1991	Jørgensen et al[30]	Antithrombotic Efficacy of Continuous Extradural Analgesia After Knee Replacement	RCT	48	*Br J Anaesth*
		Use of continuous extradural analgesia was associated with a lower incidence of deep vein thrombosis			
1991	Mitchell et al[31]	Prevention of Thromboembolic Disease Following Total Knee Arthroplasty. Epidural Versus General Anesthesia	RCT	72	*Clin Orthop Relat Res*
		The incidence of proximal vein thrombosis was significantly lower with epidural anesthesia compared with general anesthesia			
1991	Sharrock et al[32]	Effects of Epidural Anesthesia on the Incidence of Deep-Vein Thrombosis After Total Knee Arthroplasty	Observational	705	*J Bone Joint Surg Am*
		Use of epidural anesthesia reduced the risk of proximal thrombosis			
1990	Nielsen et al[33]	Lower Thrombosis Risk With Epidural Blockade in Knee Arthroplasty	RCT	36	*Acta Orthop Scand*
		The incidence of thrombosis was 2/13 in the epidural vs 10/16 in the general anesthesia group ($P < 0.05$)			
1990	Nielson et al[34]	Long-term Cognitive and Social Sequelae of General Versus Regional Anesthesia During Arthroplasty in the Elderly	RCT	64	*Anesthesiology*
		General anesthesia poses no more risk to long-term mental function than regional anesthesia			

Anesthesia Type and Outcomes in Subpopulations

Although less extensively studied, recent population-based analyses have identified benefits of neuraxial anesthesia over general anesthesia in subpopulations of patients undergoing TKA.[35–39] Patients with sleep apnea have been shown to benefit from having a neuraxial compared with a general anesthetic. Neuraxial anesthesia was associated with a reduction of major complications. Interestingly, the use of PNBs also decreased the need for critical care services after surgery.[39] For patients undergoing bilateral TKA, the use of neuraxial anesthesia was associated with an independent decrease in the need for blood transfusions (OR, 0.52; 95% CI, 0.45–0.6) but did not affect overall complication rates significantly.[14] Finally, a study examining whether there are beneficial effects of neuraxial anesthesia in patients across various age groups and/or levels of comorbidity burden suggested that this was indeed the case. Although the incidence of major complications was found to be significantly higher among older and sicker patients (26.1%) compared with the younger group without cardiopulmonary disease (4.5%), the use of neuraxial anesthesia was independently associated with better outcomes across all age and comorbidity cohorts.[37] It must be mentioned that some of the previously mentioned studies included both hip and knee arthroplasty patients in their cohorts, but in each case, the procedure type was taken into account during adjustment steps, thus rendering results relevant for TKA patients.

Peripheral Nerve Blocks

Although epidural infusion was historically a popular analgesic option, limitations involving anticoagulation (eg, epidural hematoma),[40,41] opioid adverse effects (eg, nausea and pruritus),[42] hemodynamic issues (eg, hypotension),[42] and catheter-related complications (eg, unilateral nonoperative side insertion)[43] have left PNBs as a standard, commonly used alternative. Peripheral nerve block techniques have been shown to reduce perioperative complications.[44] In addition, they have proven to decrease the time to discharge readiness, conserve hospital resources, and improve patient satisfaction.[45–47] Single-injection femoral nerve blocks (FNBs) have been widely used to provide potent analgesia, but in doing so, they simultaneously induce profound quadriceps weakness for the duration of the injected local anesthetic. Continuous FNBs have been shown to provide a longer duration of analgesia than single-injection FNB.[3]

The quests for fast-track surgery, younger patients undergoing TKA, and early patient mobilization have been drivers for change in the management of postoperative pain. Years ago, as regional anesthesia was gaining popularity, it was common to combine a posterior lumbar plexus block (psoas) with a sciatic block to provide complete unilateral analgesia for patients undergoing TKA.[48] Although the analgesia provided was ideal, changes in postoperative thromboprophylaxis and recommendations to treat these blocks similarly to epidurals had an impact on this practice.[41] To decrease the risk of bleeding, yet maintain a similar degree of analgesia, FNBs, often in combination with a sciatic block, became commonplace. More recently, the impact of quadriceps weakness in the postoperative period has led practitioners to seek alternatives to femoral block that result in less quadriceps weakness. The ability to selectively block the sensory articular branches, or a combination of these, to the knee joint using ultrasound guidance without or with minimal motor impairment is an appealing option.

For surgical procedures such as TKA and anterior cruciate ligament reconstruction, randomized controlled clinical trials have focused on selective ultrasound-guided saphenous and obturator nerve blocks and reported significant reductions in postoperative pain management and opioid consumption.[49–52] This is not surprising because the saphenous nerve can be easily visualized with ultrasound from the proximal thigh[53] at the level of the lesser trochanter and distally to the adductor canal.[54] It is notable that the adductor canal block (ACB) described by Lund et al[55] has been proven to have a significant pain-reducing effect in some studies evaluating TKA[56,57] but that other studies have failed to detect a similar effect.[58] Despite these conflicting results, many clinical centers have started to use ACBs after TKA, thereby replacing femoral catheters and lessening the postoperative quadriceps weakness.

Studies involving volunteers and surgical patients have conclusively established a decrease in quadriceps weakness after a single-injection ACB compared with the femoral nerve.[54] In 2 trials involving healthy volunteers, ACB decreased quadriceps strength less than 8% from baseline, compared with greater than 49% for femoral blocks, leading to improved mobilization.[59,60] Similarly, dramatic results are reported for surgical patients after TKA, without compromising analgesia to a statistically significant degree.[56,61,62] However, because of the protocol designs, it is possible that ACBs provided undetected inferior analgesia within the first 4 postoperative hours compared with femoral blocks,[56,61,62] and in fact, evidence for this supposition is provided in a study involving a single initial local anesthetic bolus and subsequent perineural local anesthetic infusion.[63]

Although the ACB as described by Lund et al[55] has exhibited very promising results, there have been some controversy and academic discussion as to what actually constitutes a block into the adductor canal, how the adductor canal can be clearly identified, and whether local anesthetic should be injected into the femoral triangle or adductor canal proper.[64,65] One must remember that the most common type of surgical approach for TKA involves a medial parapatellar arthrotomy and that the human knee joint is innervated by an anterior and a posterior group of sensory nerves. The most important anterior group of sensory nerves for this procedure can be targeted, based on solid anatomical evidence, with a selective low-volume block in the femoral triangle to anesthetize the saphenous nerve, the medial retinacular nerve (the terminal branch of the medial vastus muscle nerve), and the anterior branch of the medial femoral cutaneous nerve.[66]

Detailed cadaveric studies of the adductor canal consistently showed that the medial vastus nerve enters a separate fascial tunnel in the fascia covering the medial vastus muscle and superficial to the vastoadductor membrane.[66] When this fascial tunnel is opened, it can be seen that the entire tunnel is superficial to the vastoadductor membrane. Thus, an injection into the true adductor canal will not anesthetize the medial vastus nerve. Thus, a block in the femoral triangle seems to be more appropriate.

To determine the optimal point of injection of local anesthetic in the mid thigh for maximal sensory inhibition and minimal motor impairment, it is preferable to use internal landmarks visible by ultrasound.[67] With this technique, it is possible to ensure blockade of both the saphenous and the medial vastus nerve when injecting into the femoral triangle cephalad to the apex of the said triangle and not into the adductor canal missing to anesthetize the medial vastus nerve.

Perineural catheters have also been inserted into the adductor canal,[55,61] with randomized placebo-controlled investigations demonstrating the analgesic potential of continuous blocks after knee arthroplasty.[68,69] The results from studies comparing adductor and femoral catheters for knee arthroplasty provide a more complex picture compared with the single-injection data. The first randomized trial found that subjects with an adductor canal catheter retained 52% of their baseline quadriceps strength 24 hours after catheter insertion, compared with only 18% for subjects with a femoral catheter ($P = 0.004$).[57] In contrast to the single-injection studies, no benefits on mobilization were identified.[57] A second

randomized trial reported improved mobilization at 24 hours for subjects with adductor canal versus femoral catheters[70]; however, the study protocol design makes the data for continuous blocks questionable,[71] and its results require future confirmation. Two additional randomized trials documented both improved mobilization (eg, standing, sitting) and ambulation with continuous adductor canal versus femoral infusions, but inferior analgesia at rest[63] and during physical therapy.[72] As with any technique, there is the potential for complications, and the ACB is not unique. Severe and relatively long-lasting muscle weakness due to myotoxicity has been reported in 3 patients after continuous ACBs.[73] These cases were diagnosed based on clinical presentation, imaging, and neurophysiologic studies (not biopsy proven) and represent a divergence from the previously accepted belief that local anesthetic myotoxicity was not clinically relevant in humans. Further study on the incidence and mechanism is important.

Sciatic Nerve Block for TKA

The sciatic nerve block (SNB) is used as a supplement to the FNB for complete analgesia after TKA. Although most of the knee is innervated by branches of the femoral nerve, the posterior compartment of the knee is supplied by branches of the sciatic nerve. Despite the tenable anatomic explanation of the analgesic contribution, SNB has been associated with considerable controversy. The main concern is whether the analgesic value of an SNB outweighs concerns of concomitant motor and sensory loss of the lower leg.[74]

Previous observational and retrospective studies and small RCTs, searching for the analgesic value of an additional SNB, revealed conflicting results. In a systematic review, Abdallah and Brull[75] found insufficient evidence to qualitatively define the effect of adding SNB to FNB for analgesia, but the authors noted that the quality of the included studies was low to moderate. Recent RCTs with larger groups of patients showed a significant reduction in postoperative opioid consumption, less opioid-induced adverse effects, and significantly lower resting and dynamic pain scores. These effects persisted during the first 24 hours after a single-injection SNB and even longer when continuous SNB was used.[76–80] When compared with local infiltration analgesia (LIA) of the posterior capsule, SNB resulted in a significant opioid-sparing effect during and after the first 8 postoperative hours of TKA.[81]

Most recently, a systematic review and meta-analysis demonstrated evidence in favor of adding SNB to FNB for TKA.[82] Data from 386 patients retrieved from 8 RCTs proved that the addition of an SNB (single-injection or continuous) reduced the cumulative postoperative morphine equivalent consumption up to 24 hours after general and spinal anesthesia. This meta-analysis also demonstrated significant reduction in pain after a single-injection SNB during the first postoperative 8 hours.

However, despite these benefits, there are concerns related to the motor and sensory block of the lower leg, limiting a widespread use in clinical TKR pathways. Sciatic nerve block may disguise perioperative nerve injury of the lower leg and may cause a delay in early detection and treatment of surgically induced nerve injury. The reported incidence of surgical nerve injury after TKR, usually common peroneal nerve palsy, is 0.8% to 10%.[83] In a large prospective study of orthopedic patients, incidence of transient nerve injury after PNB was 8%, whereas permanent nerve injury was very rare (0.05%) and non–block related.[84] Also, in a prospective audit of more than 7000 PNBs, incidence of late neurologic complications was 0.5%, including block-related incidence of only 0.04%.[85] Neurologic complications after PNB are 10 to 100 times more likely to be related to nonblock causes.[86] Several patient- and surgery-related risk factors of peroneal nerve injury after TKR have been identified, such as valgus deformity, flexion contracture, previous neuropathy or radiculopathy, rheumatoid arthritis, tourniquet use, constrictive dressing, and postoperative hematoma.[83,87,88] A 20-year cohort study demonstrated an unchanged risk of nerve injury after TKR when any PNB technique was used.[89]

In the context of an accelerated TKR pathway, concerns have been expressed about inability to ambulate on the day of operation after an additional SNB.[90,91] Remarkably, no delay in discharge or functional outcome was found when SNB was combined with FNB.[76,82] Ambulation on the first postoperative day after SNB was significantly impaired in some patients compared with local infiltration techniques of the posterior capsule but did not differ from the second postoperative day until discharge.[82] Also, no difference was found in time to discharge among groups with single injection, continuous SNB, or no SNB.[76,82]

Infiltrative Techniques for TKA

Epidural and perineural catheter techniques are very effective in controlling postoperative pain after TKA; however, these techniques require technical expertise and are associated with block failures, as well as require postoperative catheter management by acute pain service. Despite increased use of ultrasound-guided nerve blocks and their well-documented superior analgesic efficacy, some anesthesiologists have been unable to introduce these techniques in routine clinical practice. In recent years, several infiltrative techniques have received increasing attention as "simple" and less invasive local anesthesia–based alternatives as stand-alone or as part of multimodal regimens to treat TKA postoperative pain. A significant proportion of surgical pain originates from the joint and surgical wound; therefore, it would be logical to use local anesthetics to provide site-specific analgesia while allowing ambulation without motor weakness. In addition, there are animal studies that demonstrate the benefit of LIA with multiple drug combinations in a rat model of knee surgery.[92] These techniques can be single-dose or catheter techniques and are usually surgeon administered.[93]

Liposome bupivacaine is a long-acting formulation of bupivacaine HCl approved in the United States for infiltration directly into a surgical wound. When infiltrated into the knee joint during a TKA, liposome bupivacaine resulted in less apparent quadriceps femoris weakness than a single-injection ropivacaine FNB (although it also provided inferior analgesia) and therefore theoretically may decrease the risk of falling.[94] Unfortunately, 4 RCTs found no evidence of improving post-TKA analgesia using liposome versus unencapsulated bupivacaine, suggesting, at least until additional data with positive results are reported, that no additional benefits are provided infiltrating the knee joint with liposome bupivacaine if bupivacaine HCl is an option.[95–98]

There is currently no liposome local anesthetic approved within the United States for use in PNBs. However, 1 phase 2 study suggests that single-injection FNBs with liposome bupivacaine can provide duration of action of more than 72 hours in healthy volunteers.[99] A phase 3, multicenter RCT demonstrated a treatment effect of at least 72 hours in subjects undergoing TKA, with statistically and clinically relevant analgesic benefits provided versus placebo up to 24 hours (minimal differences at time points after 24 hours).[100] Comparisons with a single-injection or continuous FNB are lacking but will be required to demonstrate the relevance of liposome bupivacaine FNBs if such a formulation is ultimately approved by the US Food and Drug Administration.

Wound Catheter Infusion Techniques

Wound catheter infusion techniques are well established in the management of postoperative pain for a variety of surgical

procedures for more than 15 years.[101] A 2006 systematic review of 44 RCTs including 16 RCTs of patients undergoing major orthopedic surgery concluded that the technique was associated with improved analgesia, reduced opioid use, increased patient satisfaction, and perhaps reduced hospital stay. No major adverse effects were reported, and the rates of wound infection were similar to those in the control group (0.7%).[102] A more recent meta-analysis of 14 RCTs (756 patients) focused on ropivacaine for wound catheter infusion; the authors noted consistent evidence of effective analgesia and opioid sparing across a wide range of surgical procedures including TKA.[103] Plasma concentration of local anesthetic was below toxic levels, despite 8 to 20 mg/h ropivacaine infusion for 48 hours.[103]

Wound catheter infusion techniques should preferably be called surgical-site catheter techniques because the catheters are not always strictly in the surgical wound. In clinical practice, catheters have been placed through the surgical wound into deeper layers and in cavities (subcutaneous, subfascial, subacromial, intra-articular, intraperitoneal, preperitoneal, intraosseous, etc).[104]

Local Infiltration Analgesia

Despite its name, the original LIA technique is not only infiltration of local anesthetic but also a multicomponent optimization package including several components of enhanced postoperative recovery protocols. A mixture of ropivacaine, ketorolac (where available), and epinephrine is infiltrated into all tissues subject to surgical trauma, and a catheter is often placed intra-articularly for 24 hours for top-ups of the mixture. The LIA technique has shown favorable results when compared with traditional methods of pain relief such as epidural analgesia, intrathecal morphine, and FNB.[93] A systematic review of 27 RCTs on LIA for TKA and THA showed that LIA for TKA was associated with reduced pain scores and opioid requirements up to 72 hours after surgery.[105]

Multimodal Oral and Intravenous Analgesia

Total knee arthroplasty surgical procedures produce tissue inflammation, triggering the production of prostaglandins (PGs),[106] particularly PGE_2, which have been implicated in acute postoperative pain. There are several additional mediators released including histamine and bradykinin.[107] Increased sensitivity to painful stimuli is mediated by repetitive release of excitatory amino acids (glutamate and aspartate). In addition, the expression of c-fos, nitric oxide synthase, and cyclooxygenase 2 (COX-2) genes leads to sensitization. Multimodal analgesic techniques use individual agents that interact with the various mediators or their targets to produce pain relief.[108,109] The goal is to reduce or eliminate the use of opioids because there are reports of increased morbidity and mortality from prescribed opioids.[110] A large number of nonopioids are available such as acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, ketamine, and glucocorticoids.[111] Literature on the topic has demonstrated the benefits of multimodal analgesia but does not address the potential problems

TABLE 2. Perioperative Analgesics

Drug	Analgesic Dose	Dosing Interval	Maximum Daily Dose	Comments
Acetaminophen (paracetamol)	500–1000 mg PO	q 4–6 h	3000 mg	As effective as aspirin; 1000 mg more effective than 650 mg in some patients
NSAIDs				
Celecoxib	400 mg initial, then 200 mg PO	q 12 h		Celecoxib is a COX-2 inhibitor
Ibuprofen	200–400 mg PO	q 4–6 h	3200 mg	200 mg equal to 650 mg of aspirin or acetaminophen
Naproxen	500 mg PO	q 12 h	1000 mg	250 mg equal to 650 mg of aspirin, but with longer duration
Ketorolac	15–30 mg IM/IV	q 4–6 h	60 mg (>65 y); 120 mg (<65 y)	Comparable with 10 mg morphine; reduce dose in patients <50 kg or with renal impairment; total duration of administration is 5 d
Ketamine	0.15–0.3 mg/kg IV			CNS effects are possible
Gabapentin	300–1200 mg PO	Preop		Adjust dose based on age and creatinine clearance; can be used in the postoperative period
Pregabalin	150–300 mg PO	Preop		Adjust dose based on age and creatinine clearance; can be used in the postoperative period
Opioids*				
Extended-release oxycodone	10–20 mg PO	q 12 h		Limit to a total of 2 doses to avoid accumulation and opioid-related adverse effects
Extended-release morphine	15–30 mg PO	q 8–12 h		Limit to a total of 2 doses to avoid accumulation and opioid-related adverse effects
Oxycodone	5–10 mg PO	q 4–6 h		Combination products* of oxycodone/acetaminophen (Percocet, Tylox) and oxycodone/aspirin (Percodan) are also available
Hydromorphone	2–4 mg PO	q 4–6 h		Also available as Dilaudid suppository (3 mg) with 6- to 8-h effect
Hydrocodone	5–10 mg PO	q 4–6 h		All preparations contain acetaminophen* or ibuprofen
Tramadol	50–100 mg PO	q 6 h	400 mg; less in cases of renal or hepatic disease	Combination product of tramadol/acetaminophen (Ultracet) is also available

*Recommend starting with immediate-release opioids.

CNS indicates central nervous system; IM, intramuscular; IV, intravenous; PO, per os (by mouth); preop, preoperative; q, quaque (every).

of combining multiple drugs.[112,113] Meta-analysis has shown beneficial analgesic effects when opioids are combined with nonopioid analgesics[114] (Table 2).

Nonsteroidal Anti-inflammatory Drugs: COX-2 Inhibitors and Acetaminophen

Nonsteroidal anti-inflammatory drugs are among the most widely used analgesic medications in the world because of their ability to reduce pain and inflammation. The mechanism of action of the NSAIDs is inhibition of PG production by either reversible or irreversible acetylation of the COX enzyme. Administration of COX-2 inhibitors in the perioperative period has consistently demonstrated decreased opioid consumption postoperatively and improved outcomes in joint replacement, such as range of motion.[115] It is ideal to continue the COX-2 inhibitor after major surgery for a period of at least 2 weeks, coinciding with the duration of the surgical inflammatory process.

Injectable NSAIDs

Ketorolac tromethamine is an NSAID with activity at both COX enzymes, thus blocking PG production. Ketorolac is available for enteral, ophthalmic, and parenteral delivery. Ketorolac has an onset of action of approximately 10 minutes, peak analgesic effect at 2 to 3 hours, and analgesic duration of 6 to 8 hours, making it attractive for postoperative analgesia. It has been used to treat mild to severe pain after major surgical procedures. Ketorolac has been used as an adjuvant in arthroplasties as a means to provide multimodal pain management by reducing the amount of opioid consumed.[116,117]

Caution is warranted in patients with renal insufficiency and elderly patients in whom the creatinine clearance is impaired. Another route of administering ketorolac is intranasal. Intranasal ketorolac has been shown to provide analgesia characterized by rapid onset and duration of 6 to 8 hours.[118] The rapid onset and improved analgesia seen with intranasal ketorolac may be due to higher penetration of the cerebrospinal fluid via the cribriform plate; higher cerebrospinal fluid levels of NSAIDs have been associated with enhanced analgesia.

Recently, an injectable form of ibuprofen was developed and approved by the Food and Drug Administration for use in patient care. Intravenous ibuprofen has not been well studied; however, its ability to inhibit the COX enzymes is likely to produce effects similar to ketorolac. The bleeding properties of injectable NSAIDs need to be considered in the perioperative period, especially in patients concomitantly receiving systemic anticoagulation.

Acetaminophen

Acetaminophen (paracetamol) produces its analgesic effect by inhibiting central PG synthesis with minimal inhibition of peripheral PG synthesis.[119] Often labeled as an NSAID, acetaminophen and NSAIDs have important differences such as acetaminophen's weak anti-inflammatory effects and its generally poor ability to inhibit COX in the presence of high concentrations of peroxides, as are found at sites of inflammation,[120,121] as well as it does not have an adverse effect on platelet function[122] or the gastric mucosa.[121] The comparative efficacy of different analgesics has also been shown to vary with the type and extent of surgical procedure.[123] A qualitative systematic review comparing acetaminophen and NSAIDs in postoperative pain management found NSAIDs to be superior after dental surgery, with similar results after knee surgery.[124] Intravenous acetaminophen has reliable bioavailability and onset of meaningful pain relief of 25 to 27 minutes in patients undergoing orthopedic surgery.[125] With a greater central role of action than the commonly used NSAIDs, acetaminophen may be combined with COX-2 inhibitors or NSAIDs as part of a multimodal regime. A systematic review investigating the combination of acetaminophen and NSAIDs concluded that the combination confers superior analgesia than either drug alone.[126]

Gabapentinoids

The anticonvulsant class of medications includes both gabapentin and pregabalin. These medications have been shown to be effective in treating a number of chronic pain states[120,127] and, more recently, acute postoperative pain. Gabapentin, 1-(aminomethyl) cyclohexane acetic acid, is a structural analog of the neurotransmitter γ-aminobutyric acid. Pregabalin is the active *S*-enantiomer of racemic 3-isobutyl γ-aminobutyric acid, modifying voltage-gated calcium channels in a similar manner to gabapentin. These medications may produce their antinociceptive effect by inhibiting calcium influx via these channels, subsequently inhibiting the release of excitatory neurotransmitters such as substance P and calcitonin gene–related peptide. These receptors may also play an important role in the development of chronic pain because presynaptic voltage-gated calcium channels are upregulated in the dorsal root ganglia after surgical trauma, leading to central sensitization.[121] In fact, pregabalin has been shown in animal models to reduce postoperative hyperalgesia.[128]

Perioperative use of pregabalin has been shown to decrease the incidence of chronic pain after TKA.[129] A preoperative dose of 300 mg was likely too high because several patients became sedated (which is the most common adverse effect of this class of drugs). Randomized controlled trials have determined that lower doses of pregabalin are more useful, avoiding excessive sedation, particularly in the elderly patients.

Ketamine

Ketamine is a well-known agent used by anesthesiologists for both general anesthesia and sedation for the past 3 decades. Ketamine's mechanism of action is as a noncompetitive *N*-methyl-D-aspartate receptor antagonist. With the discovery of the *N*-methyl-D-aspartate receptor and its links to nociceptive pain transmission and central sensitization, there is a renewed interest in using ketamine as a potential antihyperalgesic agent. Although high doses (>2 mg/kg) of ketamine have been implicated in causing psychomimetic effects (excessive sedation, cognitive dysfunction, hallucinations, nightmares), subanesthetic or low doses (<1 mg/kg) of ketamine have demonstrated significant analgesic efficacy without these adverse effects. Furthermore, there is no evidence to indicate that low-dose ketamine exerts any adverse effect on respiration, cardiovascular function, nausea, vomiting, urinary retention, and constipation/postoperative ileus.

Recent systematic reviews have concluded that low-dose ketamine as the sole analgesic agent reduces pain after intravenous, intramuscular, and subcutaneous administration. In contrast, there is little evidence to support low-dose epidural ketamine by itself for postoperative analgesia.[130] There is a growing body of evidence that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to opioids, local anesthetics, and other analgesic agents.[112] Ketamine in combination with either parenteral or epidural opioids not only reduces postoperative opioid consumption but also prolongs and improves analgesia.[131] Although extensive data are lacking, there are suggestions that low-dose ketamine infusions during the perioperative period may reduce the incidence of chronic pain.[132]

Strategies to Decrease the Risk of Falls After TKA

A critical component of optimizing joint function after knee arthroplasty is postoperative ambulation and flexion.[133–135] This

importance stems from the effects of immobilization on muscles and synovial joints, including muscular and cartilage atrophy, ligament weakening, and adhesion formation.[136] Because these damaging changes begin immediately after surgery, physical therapy, which is heavily dependent on ambulation, is usually initiated as soon as possible (often in the afternoon the day of surgery).[137,138] It is generally accepted that joint pain limits patients' ability to ambulate,[56] and therefore, providing potent analgesia is a high priority during physical therapy sessions.

Within the first decade of widespread use, case reports within the surgical literature suggested a link between continuous FNBs and falls.[139,140] Doubt was cast on the importance of these case reports when a large retrospective study revealed little difference in the rate of falls between no regional analgesic and single-injection FNBs (incidence, 0.8%–1.6%).[10] However, given the limitations of the database used for this retrospective investigation, single-injection and continuous PNBs could not be differentiated,[141] and it remains unknown what percentage, if any, of the "peripheral nerve blocks" included a perineural local anesthetic infusion.

Unfortunately, additional studies that were able to distinguish between the 2 techniques have found an association between continuous, but not single-injection, FNBs and falls. One retrospective study found that TKA patients without any regional analgesic or a single-injection FNB had similar risks of falling, but the addition of a continuous FNB increased the OR of falling to 4.4 ($P = 0.04$).[142] Two meta-analyses involving psoas compartment and femoral catheters after knee and hip arthroplasty reported ORs of 3.9 and higher than 5.5 over single-injection blocks and perineural infusions of less than 12 hours.[90,143] Lastly, a retrospective study reported no falls in patients at a single institution in the 3 years before the implementation of a continuous PNB program, compared with a 2.7% incidence in the 4 years after the program's implementation.[144] Taken together, these investigations suggest that continuous PNBs involving the femoral nerve may be associated with an increased risk of falling over a single-injection or no nerve block after knee arthroplasty.

Remaining unknown is the underlying cause of this difference in fall risk.[141] Although joint proprioception, sensory ability, and motor strength are all decreased during perineural infusion, to what degree each contributes to the risk of falling is undetermined. Nevertheless, various risk factors for falling have been identified, other than continuous PNBs, including increasing age,[10,142] general anesthetic (vs spinal),[10] major comorbidities (eg, anemia risk still increased even after transfusion),[10,145] obesity (body mass index, >30 kg/m^2),[142] and male sex.[10] Various steps have been demonstrated to decrease the risk of falling, including medical (eg, delirium prevention, nutrition, minimization of medications) and physical (eg, bed rails, nonslip flooring, decreasing bed height, access to call light) interventions.[146] Interventions specifically within the purview of anesthesiologists include educating health care providers regarding continuous PNBs (eg, physical therapists, nurses, surgeons),[47] requesting a knee immobilizer during ambulation,[147] educating patients and their families,[148] and possibly having both patients and nursing staff sign "contracts" prohibiting unassisted ambulation.[149]

There are various steps that will minimize the effects of continuous PNBs on the lower extremity. The first involves the choice of local anesthetic. When delivered via perineural catheters in various anatomic locations, ropivacaine appears to provide similar analgesia to bupivacaine as long as the dose is increased by approximately 50%.[150–154] In addition, although the evidence

Preoperative Holding Area
- Acetaminophen: 1000 mg PO
- Celecoxib: 400 mg PO (if 18-64 years old and GFR > 50 ml/min)
- Consider Gabapentin 600 mg or Pregabalin 100 mg PO
- Consider Oxycodone (immediate release): 5-10 mg PO

Intraoperative
- Preferred spinal anesthetic (not required) with sedation
- Consider peripheral nerve blockade (single injection vs continuous infusion)
- Consider surgeon administered periarticular infiltration of local anesthetic
- Consider IV ketamine injection of 0.5 mg/kg +/- ketamine infusion of 0.1 mg/kg/hour
- Dexamethasone: 4 mg IV
- Granisetron: 0.1 mg IV *OR* Ondansetron: 4 mg IV, +/- Droperidol: 0.625 mg IV
- Fentanyl: up to 250 mcg IV, +/- Hydromorphone: up to 1 mg IV PRN for analgesia

PACU
- Fentanyl: 25 mcg IV PRN *OR* Hydromorphone: 0.2 mg IV PRN for pain ≥ 4
- Acetaminophen: 1000 mg PO or IV (if last dose ≥ 6 hours)
- Ketamine: 10 mg IV once PRN for pain ≥ 4
- Oxycodone (IR): 5 mg PO for pain ≤ 4 *OR* 10 mg PO for pain ≥ 5 (one dose prior to discharge)

Floor Care
- Acetaminophen: 1000 mg PO every 6 hours (650 mg for age > 75)
- Ketorolac: 15 mg IV every 6 hours for 4 doses (if GFR > 50 ml/min) or other NSAID
- Tramadol: 50-100 mg PO *OR* Oxycodone: 5-10 mg PO *OR* Hydromorphone: 2-4 mg PO (PRN pain)
- Fentanyl: 25 mcg IV PRN for *breakthrough* pain ≥ 7; up to 3 doses
- +/- Continuous peripheral nerve catheter infusion

Abbreviations: PACU, Post Anesthesia Care Unit; IV, intravenous; PO, per os; PRN, pro re nata (as necessary); GFR, glomerular filtration rate; all pain scores listed refer to the numeric rating scale (0 to 10).

FIGURE 2. Sample multimodal analgesia total joint pathway. All pain scores listed refer to the numeric rating scale. GFR indicates glomerular filtration rate; PACU, postanesthesia care unit; PO, per os (by mouth); PRN, pro re nata (as necessary).

regarding motor block is mixed,[150–152,154,155] there is strong evidence that the duration of bupivacaine is 2 to 3 times that of ropivacaine.[155] Therefore, if ropivacaine is used for a perineural infusion and negatively influences mobilization, the infusion pump may be paused until resolution of the undesirable effects, allowing for more effective titration compared with a bupivacaine infusion. Minimizing local anesthetic dose/mass will also decrease unwanted adverse effects. This can be accomplished by minimizing the basal infusion rate while providing patient-controlled bolus doses to reinforce analgesia for breakthrough pain.[156–159] It also remains unknown if the addition of a single-injection or continuous SNB increases the risk of falling[76–78,160–162]; although until illuminating data are published, it seems prudent to minimize local anesthetic dose/mass just as for femoral perineural infusion.[163]

Unfortunately, although some practitioners have tried to decrease quadriceps weakness by decreasing local anesthetic concentration, data from multiple randomized controlled investigations demonstrate that it is dose, not concentration (or basal rate), that determines continuous block effects.[163,164] Relatedly, providing local anesthetic as automatic, repeated bolus doses does not change block effects compared with a continuous basal infusion, as long as the total dose remains constant.[156,165,166] Similarly, no additive has demonstrated improved analgesia and/or decreased motor block, including epinephrine[167–169] and clonidine.[170–172]

One of the most promising fall-reduction interventions is converting continuous femoral to adductor canal nerve blocks, owing to the demonstrated reduction of induced quadriceps weakness.[57,173] At the time of this writing, 6 RCTs were published comparing continuous femoral and adductor canal nerve blocks,[9,57,63,70,72,173] with 3 demonstrating increased ability of standing, sitting, ambulating, and climbing stairs for subjects with an adductor canal infusion.[9,57,63,70] Regardless, although there is a hypothetical reduction in fall risk with adductor infusion, this association remains solely theoretical and requires additional study because no RCT to date demonstrates a reduction in falls between the 2 catheter locations.[9,57,63,70,72,73]

Lastly, new applications of existing technologies providing post-TKA analgesia may provide similar or superior analgesia to continuous peripheral nerve blockade without increasing the risk of falling. For example, ultrasound-guided percutaneous peripheral nerve stimulation offers the promise of blocking pain signals at the level of the spinal cord, without inducing a motor, sensory, or proprioception block.[174,175] Similarly, there is evidence that cryoneurolysis of the superficial, sensory-only anterior femoral cutaneous and infrapatellar saphenous nerves provides post-TKA analgesia without any weakening of the quadriceps femoris muscle.[176,177] In addition, several nonpharmacologic approaches have been investigated for post-TKA analgesia. These encompass neuromuscular electrical stimulation, which is electrical stimulation of muscles to produce contraction, and transcutaneous electrical nerve stimulation, as well as cooling therapies and compression, which show promise in the management of post-TKA pain. Additional research is required to define the analgesic efficacy of these modalities along with the incidence of complications and comparisons with other post-TKA analgesic techniques.

DISCUSSION

Clinical pathways are tools created to organize care of a well-defined group of patients while maintaining high-quality, efficient care during a well-defined, limited episode of care. A collaboration of experts from ASRA and ESRA has reviewed the existing literature and presents in this review the components of a comprehensive, up-to-date, and evidence-based clinical pathway. This review is intended to assist individuals and institutions in designing a pathway for TKA that is based on existing evidence and expert recommendation and may be customized according to individual settings (Fig. 2).

Multimodal analgesia involves the concurrent use of more than 1 class of medication to target different mechanisms of analgesia and has been advocated to improve analgesia through additive or synergistic effects while reducing opioid-induced adverse effects.[108,109] The goal is to reduce or eliminate the use of opioids, which are well recognized as having many unacceptable adverse effects. Many contemporary pathways include PNBs and/or peripheral nerve catheters. Although there is considerable disagreement on the optimal PNB or combination of nerve blocks, we can conclude that single-injection and continuous ACBs induce less quadriceps weakness compared with their femoral counterparts. Conversely, there are limited data suggesting that femoral blocks and catheters provide superior analgesia. Therefore, health care providers must determine the relative importance of analgesia versus quadriceps strength and mobilization ability. More studies are needed to determine what role periarticular infiltrative techniques will play in a multimodal pathway. The promise of simplicity may entice providers to rely on these less invasive local anesthesia–based alternatives as stand-alone or as part of multimodal regimens to treat TKA postoperative pain.

Unfortunately, adequately powered prospective RCTs comparing neuraxial versus general anesthesia in TKA patients are lacking. Recent population-based data suggest, however, that neuraxial anesthesia may be associated with superior results for most but not all outcomes compared with general anesthesia. It is noteworthy that some clinical investigations provide evidence of good outcomes when general anesthesia is being used, suggesting that individual practice patterns can achieve adequate results with either technique. Although no definitive answer is available regarding the best anesthetic practice for TKA, little, if any, evidence exists that neuraxial is inferior to a general anesthetic. Thus, in the absence of contraindications and assessment of associated risk, neuraxial anesthesia may represent a preferable approach in the treatment of patients undergoing TKA, although highly specialized practices maintain excellent outcomes with either approach. Studies elucidating the mechanisms by which neuraxial anesthesia may produce advantageous results, as well as investigations regarding evaluating the long-term outcome of these patients, are urgently needed to enhance our knowledge on this topic further.

REFERENCES

1. Kurtz SM, Ong KL, Lau E, et al. International survey of primary and revision total knee replacement. *Int Orthop*. 2011;35:1783–1789.
2. Johnson RL, Kopp SL. Optimizing perioperative management of total joint arthroplasty. *Anesthesiol Clin*. 2014;32:865–880.
3. Chan EY, Fransen M, Parker DA, Assam PN, Chua N. Femoral nerve blocks for acute postoperative pain after knee replacement surgery. *Cochrane Database Syst Rev*. 2014;5:CD009941.
4. Sarai RS, Kopp SR, Knox MR, Coleman GT, Kotze AC. In vitro levamisole selection pressure on larval stages of *Haemonchus contortus* over nine generations gives rise to drug resistance and target site gene expression changes specific to the early larval stages only. *Vet Parasitol*. 2015;211:45–53.
5. Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med*. 2015;16:2277–2283.
6. Lavand'homme P, Thienpont E. Pain after total knee arthroplasty: a narrative review focusing on the stratification of patients at risk for persistent pain. *Bone Joint J*. 2015;97-B:45–48.

7. Kopp SL, Berbari EF, Osmon DR, et al. The impact of anesthetic management on surgical site infections in patients undergoing total knee or total hip arthroplasty. *Anesth Analg*. 2015;121:1215–1221.
8. Memtsoudis SG, Liu SS. Do neuraxial techniques affect perioperative outcomes? The story of vantage points and number games. *Anesth Analg*. 2014;119:501–502.
9. Zhang W, Hu Y, Tao Y, Liu X, Wang G. Ultrasound-guided continuous adductor canal block for analgesia after total knee replacement. *Chin Med J (Engl)*. 2014;127:4077–4081.
10. Memtsoudis SG, Danninger T, Rasul R, et al. Inpatient falls after total knee arthroplasty: the role of anesthesia type and peripheral nerve blocks. *Anesthesiology*. 2014;120:551–563.
11. Harsten A, Kehlet H, Toksvig-Larsen S. Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial. *Br J Anaesth*. 2013;111:391–399.
12. Liu J, Ma C, Elkassabany N, Fleisher LA, Neuman MD. Neuraxial anesthesia decreases postoperative systemic infection risk compared with general anesthesia in knee arthroplasty. *Anesth Analg*. 2013;117:1010–1016.
13. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes S, Callaghan JJ. Differences in short-term complications between spinal and general anesthesia for primary total knee arthroplasty. *J Bone Joint Surg Am*. 2013;95:193–199.
14. Stundner O, Chiu YL, Sun X, et al. Comparative perioperative outcomes associated with neuraxial versus general anesthesia for simultaneous bilateral total knee arthroplasty. *Reg Anesth Pain Med*. 2012;37:638–644.
15. Guay J, Choi PT, Suresh S, et al. Neuraxial anesthesia for the prevention of postoperative mortality and major morbidity: an overview of cochrane systematic reviews. *Anesth Analg*. 2014;119:716–725.
16. Macfarlane AJ, Prasad GA, Chan VW, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? *Clin Orthop Relat Res*. 2009;467:2379–2402.
17. Memtsoudis SG, Sun X, Chiu YL, et al. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology*. 2013;118:1046–1058.
18. Chang CC, Lin HC, Lin HW. Anesthetic management and surgical site infections in total hip or knee replacement: a population-based study. *Anesthesiology*. 2010;113:279–284.
19. Zorrilla-Vaca A, Grant MC, Mathur V, Li J, Wu CL. The impact of neuraxial versus general anesthesia on the incidence of postoperative surgical site infections following knee or hip arthroplasty: a meta-analysis. *Reg Anesth Pain Med*. 2016;41:555–563.
20. Memtsoudis SG, Sun X, Chiu YL, et al. Utilization of critical care services among patients undergoing total hip and knee arthroplasty: epidemiology and risk factors. *Anesthesiology*. 2012;117:107–116.
21. Perlas A, Chan VW, Beattie S. Anesthesia technique and mortality after total hip or knee arthroplasty: a retrospective, propensity score-matched cohort study. *Anesthesiology*. 2016;125:724–731.
22. Fleischut PM, Eskreis-Winkler JM, Gaber-Baylis LK, et al. Variability in anesthetic care for total knee arthroplasty: an analysis from the anesthesia quality institute. *Am J Med Qual*. 2015;30:172–179.
23. Liu J, Yuan W, Wang X, et al. Peripheral nerve blocks versus general anesthesia for total knee replacement in elderly patients on the postoperative quality of recovery. *Clin Interv Aging*. 2014;18:341–350.
24. Napier DE, Bass SS. Postoperative benefits of intrathecal injection for patients undergoing total knee arthroplasty. *Orthop Nurs*. 2007;26:374–378.
25. Chu CP, Yap JC, Chen PP, Hung HH. Postoperative outcome in chinese patients having primary total knee arthroplasty under general anaesthesia/intravenous patient-controlled analgesia compared to spinal-epidural anaesthesia/analgesia. *Hong Kong Med J*. 2006;12:442–447.
26. Kudoh A, Takase H, Takazawa T. A comparison of anesthetic quality in propofol-spinal anesthesia and propofol-fentanyl anesthesia for total knee arthroplasty in elderly patients. *J Clin Anesth*. 2004;16:405–410.
27. Williams-Russo P, Sharrock NE, Haas SB, et al. Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement. *Clin Orthop Relat Res*. 1996;331:199–208.
28. Williams-Russo P, Sharrock NE, Mattis S, et al. Cognitive effects after epidural vs general anesthesia in older adults. *JAMA*. 1995;271:44–50.
29. Sharrock NE, Go G. Fibrinolytic activity following total knee arthroplasty under epidural or general anesthesia. *Reg Anesth*. 1992;17(3)(suppl):94.
30. Jørgensen LN, Rasmussen LS, Nielsen PT, et al. Antithrombotic efficacy of continuous extradural analgesia after knee replacement. *Br J Anaesth*. 1991;66:8–12.
31. Mitchell D, Friedman RJ, Baker JD 3rd, et al. Prevention of thromboembolic disease following total knee arthroplasty. Epidural versus general anesthesia. *Clin Orthop Relat Res*. 1991;269:109–112.
32. Sharrock NE, Haas SB, Hargett MJ, et al. Effects of epidural anesthesia on the incidence of deep-vein thrombosis after total knee arthroplasty observational. *J Bone Joint Surg Am*. 1991;73:502–506.
33. Nielsen PT, Jørgensen LN, Albrecht-Beste E, et al. Lower thrombosis risk with epidural blockade in knee arthroplasty. *Acta Orthop Scand*. 1990;61:29–31.
34. Nielson WR, Gelb AW, Casey JE, et al. Long-term cognitive and social sequelae of general versus regional anesthesia during arthroplasty in the elderly. *Anesthesiology*. 1990;73:1103–1109.
35. Cozowicz C, Poeran J, Memtsoudis SG. Epidemiology, trends, and disparities in regional anaesthesia for orthopaedic surgery. *Br J Anaesth*. 2015;115(suppl 2):ii57–ii67.
36. Adhikary SD, Liu WM, Memtsoudis SG, Davis CM 3rd, Liu J. Body mass index more than 45 kg/m(2) as a cutoff point is associated with dramatically increased postoperative complications in total knee arthroplasty and total hip arthroplasty. *J Arthroplasty*. 2016;31:749–753.
37. Memtsoudis SG, Rasul R, Suzuki S, et al. Does the impact of the type of anesthesia on outcomes differ by patient age and comorbidity burden? *Reg Anesth Pain Med*. 2014;39:112–119.
38. Pumberger M, Memtsoudis SG, Stundner O, et al. An analysis of the safety of epidural and spinal neuraxial anesthesia in more than 100,000 consecutive major lower extremity joint replacements. *Reg Anesth Pain Med*. 2013;38:515–519.
39. Memtsoudis SG, Stundner O, Rasul R, et al. Sleep apnea and total joint arthroplasty under various types of anesthesia: a population-based study of perioperative outcomes. *Reg Anesth Pain Med*. 2013;38:274–281.
40. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK. Executive summary: regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:102–105.
41. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64–101.
42. Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg*. 1998;87:88–92.
43. Capdevila X, Barthelet Y, Biboulet P, et al. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology*. 1999;91:8–15.
44. Memtsoudis SG, Poeran J, Cozowicz C, et al. The impact of peripheral nerve blocks on perioperative outcome in hip and knee arthroplasty-a population-based study. *Pain*. 2016;157:2341–2349.

45. Duncan CM, Moeschler SM, Horlocker TT, Hanssen AD, Hebl JR. A self-paired comparison of perioperative outcomes before and after implementation of a clinical pathway in patients undergoing total knee arthroplasty. *Reg Anesth Pain Med*. 2013;38:533–538.
46. Hebl JR, Kopp SL, Ali MH, et al. A comprehensive anesthesia protocol that emphasizes peripheral nerve blockade for total knee and total hip arthroplasty. *J Bone Joint Surg Am*. 2005;87(suppl 2):63–70.
47. Ilfeld BM. Continuous peripheral nerve blocks: a review of the published evidence. *Anesth Analg*. 2011;113:904–925.
48. Horlocker TT, Hebl JR, Kinney MA, Cabanela ME. Opioid-free analgesia following total knee arthroplasty—a multimodal approach using continuous lumbar plexus (psoas compartment) block, acetaminophen, and ketorolac. *Reg Anesth Pain Med*. 2002;27:105–108.
49. Horn JL, Pitsch T, Salinas F, Benninger B. Anatomic basis to the ultrasound-guided approach for saphenous nerve blockade. *Reg Anesth Pain Med*. 2009;34:486–489.
50. Lundblad M, Forssblad M, Eksborg S, Lonnqvist PA. Ultrasound-guided infrapatellar nerve block for anterior cruciate ligament repair: a prospective, randomised, double-blind, placebo-controlled clinical trial. *Eur J Anaesthesiol*. 2011;28:511–518.
51. Westergaard B, Jensen K, Lenz K, et al. A randomised controlled trial of ultrasound-guided blockade of the saphenous nerve and the posterior branch of the obturator nerve for postoperative analgesia after day-case knee arthroscopy. *Anaesthesia*. 2014;69:1337–1344.
52. Runge C, Borglum J, Jensen JM, et al. The analgesic effect of obturator nerve block added to a femoral triangle block after total knee arthroplasty: a randomized controlled trial. *Reg Anesth Pain Med*. 2016;41:445–451.
53. Borglum J, Johansen K, Christensen MD, et al. Ultrasound-guided single-penetration dual-injection block for leg and foot surgery: a prospective, randomized, double-blind study. *Reg Anesth Pain Med*. 2014;39:18–25.
54. Manickam B, Perlas A, Duggan E, et al. Feasibility and efficacy of ultrasound-guided block of the saphenous nerve in the adductor canal. *Reg Anesth Pain Med*. 2009;34:578–580.
55. Lund J, Jenstrup MT, Jaeger P, Sorensen AM, Dahl JB. Continuous adductor-canal-blockade for adjuvant post-operative analgesia after major knee surgery: preliminary results. *Acta Anaesthesiol Scand*. 2011;55:14–19.
56. Grevstad U, Mathiesen O, Valentiner LS, Jaeger P, Hilsted KL, Dahl JB. Effect of adductor canal block versus femoral nerve block on quadriceps strength, mobilization, and pain after total knee arthroplasty: a randomized, blinded study. *Reg Anesth Pain Med*. 2015;40:3–10.
57. Jaeger P, Zaric D, Fomsgaard JS, et al. Adductor canal block versus femoral nerve block for analgesia after total knee arthroplasty: a randomized, double-blind study. *Reg Anesth Pain Med*. 2013;38:526–532.
58. Espelund M, Fomsgaard JS, Haraszuk J, Mathiesen O, Dahl JB. Analgesic efficacy of ultrasound-guided adductor canal blockade after arthroscopic anterior cruciate ligament reconstruction: a randomised controlled trial. *Eur J Anaesthesiol*. 2013;30:422–428.
59. Jaeger P, Nielsen ZJ, Henningsen MH, et al. Adductor canal block versus femoral nerve block and quadriceps strength: a randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. *Anesthesiology*. 2013;118:409–415.
60. Kwofie MK, Shastri UD, Gadsden JC, et al. The effects of ultrasound-guided adductor canal block versus femoral nerve block on quadriceps strength and fall risk: a blinded, randomized trial of volunteers. *Reg Anesth Pain Med*. 2013;38:321–325.
61. Jaeger P, Grevstad U, Henningsen MH, et al. Effect of adductor-canal-blockade on established, severe post-operative pain after total knee arthroplasty: a randomised study. *Acta Anaesthesiol Scand*. 2012;56:1013–1019.
62. Kim DH, Lin Y, Goytizolo EA, et al. Adductor canal block versus femoral nerve block for total knee arthroplasty: a prospective, randomized, controlled trial. *Anesthesiology*. 2014;120:540–550.
63. Sztain JF, Machi AT, Kormylo NJ, et al. Continuous adductor canal versus continuous femoral nerve blocks: relative effects on discharge readiness following unicompartment knee arthroplasty. *Reg Anesth Pain Med*. 2015;40:559–567.
64. Bendtsen TF, Moriggl B, Chan V, Pedersen EM, Borglum J. Defining adductor canal block. *Reg Anesth Pain Med*. 2014;39:253–254.
65. Bendtsen TF, Moriggl B, Chan V, Pedersen EM, Borglum J. Redefining the adductor canal block. *Reg Anesth Pain Med*. 2014;39:442–443.
66. Bendtsen TF, Moriggl B, Chan V, Borglum J. The optimal analgesic block for total knee arthroplasty. *Reg Anesth Pain Med*. 2016;41:711–719.
67. Wong WY, Bjorn S, Strid JM, Borglum J, Bendtsen TF. Defining the location of the adductor canal using ultrasound. *Reg Anesth Pain Med*. 2017;42:241–245.
68. Hanson NA, Allen CJ, Hostetter LS, et al. Continuous ultrasound-guided adductor canal block for total knee arthroplasty: a randomized, double-blind trial. *Anesth Analg*. 2014;118:1370–1377.
69. Jenstrup MT, Jaeger P, Lund J, et al. Effects of adductor-canal-blockade on pain and ambulation after total knee arthroplasty: a randomized study. *Acta Anaesthesiol Scand*. 2012;56:357–364.
70. Shah NA, Jain NP. Is continuous adductor canal block better than continuous femoral nerve block after total knee arthroplasty? Effect on ambulation ability, early functional recovery and pain control: a randomized controlled trial. *J Arthroplasty*. 2014;29:2224–2229.
71. Ilfeld BM, Turan A, Ball ST. Not all "continuous femoral nerve blocks" are equivalent. *J Arthroplasty*. 2015;30:896–897.
72. Machi AT, Sztain JF, Kormylo NJ, et al. Discharge readiness after tricompartment knee arthroplasty: adductor canal versus femoral continuous nerve blocks—a dual-center, randomized trial. *Anesthesiology*. 2015;123:444–456.
73. Neal JM, Salinas FV, Choi DS. Local anesthetic-induced myotoxicity after continuous adductor canal block. *Reg Anesth Pain Med*. 2016;41:723–727.
74. Ilfeld BM, Madison SJ. The sciatic nerve and knee arthroplasty: to block, or not to block—that is the question. *Reg Anesth Pain Med*. 2011;36:421–423.
75. Abdallah FW, Brull R. Is sciatic nerve block advantageous when combined with femoral nerve block for postoperative analgesia following total knee arthroplasty? A systematic review. *Reg Anesth Pain Med*. 2011;36:493–498.
76. Wegener JT, van Ooij B, van Dijk CN, et al. Value of single-injection or continuous sciatic nerve block in addition to a continuous femoral nerve block in patients undergoing total knee arthroplasty: a prospective, randomized, controlled trial. *Reg Anesth Pain Med*. 2011;36:481–488.
77. Pham Dang C, Gautheron E, Guilley J, et al. The value of adding sciatic block to continuous femoral block for analgesia after total knee replacement. *Reg Anesth Pain Med*. 2005;30:128–133.
78. Morin AM, Kratz CD, Eberhart LH, et al. Postoperative analgesia and functional recovery after total-knee replacement: comparison of a continuous posterior lumbar plexus (psoas compartment) block, a continuous femoral nerve block, and the combination of a continuous femoral and sciatic nerve block. *Reg Anesth Pain Med*. 2005;30:434–445.
79. Hunt KJ, Bourne MH, Mariani EM. Single-injection femoral and sciatic nerve blocks for pain control after total knee arthroplasty. *J Arthroplasty*. 2009;24:533–538.
80. Abdallah FW, Chan VW, Gandhi R, et al. The analgesic effects of proximal, distal, or no sciatic nerve block on posterior knee pain after total knee arthroplasty: a double-blind placebo-controlled randomized trial. *Anesthesiology*. 2014;121:1302–1310.

81. Safa B, Gollish J, Haslam L, McCartney CJ. Comparing the effects of single shot sciatic nerve block versus posterior capsule local anesthetic infiltration on analgesia and functional outcome after total knee arthroplasty: a prospective, randomized, double-blinded, controlled trial. *J Arthroplasty*. 2014;29:1149–1153.
82. Abdallah FW, Madjdpour C, Brull R. Is sciatic nerve block advantageous when combined with femoral nerve block for postoperative analgesia following total knee arthroplasty? A meta-analysis. *Can J Anaesth*. 2016;63:552–568.
83. Park JH, Restrepo C, Norton R, et al. Common peroneal nerve palsy following total knee arthroplasty: prognostic factors and course of recovery. *J Arthroplasty*. 2013;28:1538–1542.
84. Fredrickson MJ, Kilfoyle DH. Neurological complication analysis of 1000 ultrasound guided peripheral nerve blocks for elective orthopaedic surgery: a prospective study. *Anaesthesia*. 2009;64:836–844.
85. Barrington MJ, Watts SA, Gledhill SR, et al. Preliminary results of the Australasian Regional Anaesthesia Collaboration: a prospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications. *Reg Anesth Pain Med*. 2009;34:534–541.
86. Jeng CL, Torrillo TM, Rosenblatt MA. Complications of peripheral nerve blocks. *Br J Anaesth*. 2010;105(suppl 1):i97–i107.
87. Nercessian OA, Ugwonali OF, Park S. Peroneal nerve palsy after total knee arthroplasty. *J Arthroplasty*. 2005;20:1068–1073.
88. Dwyer T, Drexler M, Chan VW, Whelan DB, Brull R. Neurological complications related to elective orthopedic surgery: part 2: common hip and knee procedures. *Reg Anesth Pain Med*. 2015;40:443–454.
89. Jacob AK, Mantilla CB, Sviggum HP, et al. Perioperative nerve injury after total knee arthroplasty: regional anesthesia risk during a 20-year cohort study. *Anesthesiology*. 2011;114:311–317.
90. Ilfeld BM, Duke KB, Donohue MC. The association between lower extremity continuous peripheral nerve blocks and patient falls after knee and hip arthroplasty. *Anesth Analg*. 2010;111:1552–1554.
91. Johnson RL, Duncan CM, Ahn KS, et al. Fall-prevention strategies and patient characteristics that impact fall rates after total knee arthroplasty. *Anesth Analg*. 2014;119:1113–1118.
92. Buvanendran A, Kroin JS, Della Valle CJ, Moric M, Tuman KJ. Local drug infiltration analgesia during knee surgery to reduce postoperative pain in rats. *Reg Anesth Acute Pain*. 2016;41:374–379.
93. Rawal N. Current issues in postoperative pain management. *Eur J Anaesthesiol*. 2016;33:160–171.
94. Surdam JW, Licini DJ, Baynes NT, Arce BR. The use of exparel (liposomal bupivacaine) to manage postoperative pain in unilateral total knee arthroplasty patients. *J Arthroplasty*. 2015;30:325–329.
95. Bergese SD, Ramamoorthy S, Patou G, et al. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *J Pain Res*. 2012;5:107–116.
96. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. *Knee*. 2012;19:530–536.
97. Collis PN, Hunter AM, Vaughn MD, et al. Periarticular injection after total knee arthroplasty using liposomal bupivacaine vs a modified ranawat suspension: a prospective, randomized study. *J Arthroplasty*. 2016;31:633–636.
98. Schroer WC, Diesfeld PG, LeMarr AR, Morton DJ, Reedy ME. Does extended-release liposomal bupivacaine better control pain than bupivacaine after total knee arthroplasty (TKA)? A prospective, randomized clinical trial. *J Arthroplasty*. 2015;30:64–67.
99. Ilfeld BM, Malhotra N, Furnish TJ, Donohue MC, Madison SJ. Liposomal bupivacaine as a single-injection peripheral nerve block: a dose-response study. *Anesth Analg*. 2013;117:1248–1256.
100. Hadzic A, Minkowitz HS, Melson TI, et al. Liposome bupivacaine femoral nerve block for postsurgical analgesia after total knee arthroplasty. *Anesthesiology*. 2016;124:1372–1383.
101. Rawal N. American Society of Regional Anesthesia and Pain Medicine 2010 Gaston Labat Lecture: perineural catheter analgesia as a routine method after ambulatory surgery—effective but unrealistic. *Reg Anesth Pain Med*. 2012;37:72–78.
102. Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg*. 2006;203:914–932.
103. Raines S, Hedlund C, Franzon M, et al. Ropivacaine for continuous wound infusion for postoperative pain management: a systematic review and meta-analysis of randomized controlled trials. *Eur Surg Res*. 2014;53:43–60.
104. Rawal N. Epidural technique for postoperative pain: gold standard no more? *Reg Anesth Pain Med*. 2012;37:310–317.
105. Andersen LO, Kehlet H. Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: a systematic review. *Br J Anaesth*. 2014;113:360–374.
106. Samad TA, Sapirstein A, Woolf CJ. Prostanoids and pain: unraveling mechanisms and revealing therapeutic targets. *Trends Mol Med*. 2002;8:390–396.
107. Buvanendran A, Mitchell K, Kroin JS, Iadarola MJ. Cytokine gene expression after total hip arthroplasty: surgical site versus circulating neutrophil response. *Anesth Analg*. 2009;109:959–964.
108. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg*. 1993;77:1048–1056.
109. Wu CL, Raja SN. Treatment of acute postoperative pain. *Lancet*. 2011;377:2215–2225.
110. Weisberg DF, Becker WC, Fiellin DA, Stannard C. Prescription opioid misuse in the United States and the United Kingdom: cautionary lessons. *Int J Drug Policy*. 2014;25:1124–1130.
111. Young A, Buvanendran A. Recent advances in multimodal analgesia. *Anesthesiol Clin*. 2012;30:91–100.
112. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol*. 2009;22:588–593.
113. Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. *Anesthesiol Clin North America*. 2005;23:185–202.
114. Joshi GP, Schug SA, Kehlet H. Procedure-specific pain management and outcome strategies. *Best Pract Res Clin Anaesthesiol*. 2014;28:191–201.
115. Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. *JAMA*. 2003;290:2411–2418.
116. Dorr LD, Raya J, Long WT, Boutary M, Sirianni LE. Multimodal analgesia without parenteral narcotics for total knee arthroplasty. *J Arthroplasty*. 2008;23:502–508.
117. Ranawat AS, Ranawat CS. Pain management and accelerated rehabilitation for total hip and total knee arthroplasty. *J Arthroplasty*. 2007;22:12–15.
118. Grant GM, Mehlisch DR. Intranasal ketorolac for pain secondary to third molar impaction surgery: a randomized, double-blind, placebo-controlled trial. *J Oral Maxillofac Surg*. 2010;68:1025–1031.
119. Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Ther*. 2005;12:46–55.
120. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage*. 2007;34:183–189.

121. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg*. 2007;104:1545–1556.

122. Munsterhjelm E, Munsterhjelm NM, Niemi TT, et al. Dose-dependent inhibition of platelet function by acetaminophen in healthy volunteers. *Anesthesiology*. 2005;103:712–717.

123. Oscier CD, Milner QJ. Peri-operative use of paracetamol. *Anaesthesia*. 2009;64:65–72.

124. Looke TD, Kluth CT. Effect of preoperative intravenous methocarbamol and intravenous acetaminophen on opioid use after primary total hip and knee replacement. *Orthopedics*. 2013;36:25–32.

125. Sinatra RS, Jahr JS, Reynolds LW, et al. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology*. 2005;102:822–831.

126. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg*. 2010;110:1170–1179.

127. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain*. 2005;115:254–263.

128. Field MJ, Holloman EF, McCleary S, Hughes J, Singh L. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. *J Pharmacol Exp Ther*. 1997;282:1242–1246.

129. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg*. 2010;110:199–207.

130. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain*. 1999;82:111–125.

131. Cengiz P, Gokcinar D, Karabeyoglu I, Topcu H, Cicek GS, Gogus N. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: a prospective, randomized double-blind placebo-controlled trial. *J Coll Physicians Surg Pak*. 2014;24:299–303.

132. Remerand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg*. 2009;109:1963–1971.

133. Gilbey HJ, Ackland TR, Wang AW, et al. Exercise improves early functional recovery after total hip arthroplasty. *Clin Orthop Relat Res*. 2003;408:193–200.

134. Ryu J, Saito S, Yamamoto K, Sano S. Factors influencing the postoperative range of motion in total knee arthroplasty. *Bull Hosp Jt Dis*. 1993;53:35–40.

135. Shoji H, Solomonow M, Yoshino S, D'Ambrosia R, Dabezies E. Factors affecting postoperative flexion in total knee arthroplasty. *Orthopedics*. 1990;13:643–649.

136. Akeson WH, Amiel D, Abel MF, Garfin SR, Woo SL. Effects of immobilization on joints. *Clin Orthop Relat Res*. 1987;219:28–37.

137. Enloe LJ, Shields RK, Smith K, Leo K, Miller B. Total hip and knee replacement treatment programs: a report using consensus. *J Orthop Sports Phys Ther*. 1996;23:3–11.

138. Ishiguro S, Asano N, Yoshida K, et al. Day zero ambulation under modified femoral nerve block after minimally invasive surgery for total knee arthroplasty: preliminary report. *J Anesth*. 2013;27:132–134.

139. Feibel RJ, Dervin GF, Kim PR, Beaule PE. Major complications associated with femoral nerve catheters for knee arthroplasty: a word of caution. *J Arthroplasty*. 2009;24:132–137.

140. Kandasami M, Kinninmonth AW, Sarungi M, Baines J, Scott NB. Femoral nerve block for total knee replacement—a word of caution. *Knee*. 2009;16:98–100.

141. Ilfeld BM. Single-injection and continuous femoral nerve blocks are associated with different risks of falling. *Anesthesiology*. 2014;121: 668–669.

142. Wasserstein D, Farlinger C, Brull R, Mahomed N, Gandhi R. Advanced age, obesity and continuous femoral nerve blockade are independent risk factors for inpatient falls after primary total knee arthroplasty. *J Arthroplasty*. 2013;28:1121–1124.

143. Johnson RL, Kopp SL, Hebl JR, Erwin PJ, Mantilla CB. Falls and major orthopaedic surgery with peripheral nerve blockade: a systematic review and meta-analysis. *Br J Anaesth*. 2013;110:518–528.

144. Finn DM AR, Ilfeld BM, Madison SJ, et al. Association between the use of continuous peripheral nerve blocks and risk of falling following knee and hip arthroplasty. *Medsurg Nurs*. In press.

145. Sharma S, Iorio R, Specht LM, Davies-Lepie S, Healy WL. Complications of femoral nerve block for total knee arthroplasty. *Clin Orthop Relat Res*. 2010;468:135–140.

146. Clyburn TA, Heydemann JA. Fall prevention in the elderly: analysis and comprehensive review of methods used in the hospital and in the home. *J Am Acad Orthop Surg*. 2011;19:402–409.

147. Muraskin SI, Conrad B, Zheng N, Morey TE, Enneking FK. Falls associated with lower-extremity-nerve blocks: a pilot investigation of mechanisms. *Reg Anesth Pain Med*. 2007;32:67–72.

148. Ilfeld BM, Esener DE, Morey TE, Enneking FK. Ambulatory perineural infusion: the patients' perspective. *Reg Anesth Pain Med*. 2003;28: 418–423.

149. Sinha SKAJ, Arumugam S, Schutzer S, Lewis C. Effectiveness of a prevention strategy for in-hospital falls following total joint arthroplasty [abstract]. *Reg Anesth Pain Med*. 2011:A–24.

150. Borghi B, Facchini F, Agnoletti V, et al. Pain relief and motor function during continuous interscalene analgesia after open shoulder surgery: a prospective, randomized, double-blind comparison between levobupivacaine 0.25%, and ropivacaine 0.25% or 0.4%. *Eur J Anaesthesiol*. 2006;23:1005–1009.

151. Casati A, Borghi B, Fanelli G, et al. Interscalene brachial plexus anesthesia and analgesia for open shoulder surgery: a randomized, double-blinded comparison between levobupivacaine and ropivacaine. *Anesth Analg*. 2003;96:253–259.

152. Casati A, Vinciguerra F, Cappelleri G, et al. Levobupivacaine 0.2% or 0.125% for continuous sciatic nerve block: a prospective, randomized, double-blind comparison with 0.2% ropivacaine. *Anesth Analg*. 2004;99:919–923.

153. Eroglu A, Uzunlar H, Sener M, Akinturk Y, Erciyes N. A clinical comparison of equal concentration and volume of ropivacaine and bupivacaine for interscalene brachial plexus anesthesia and analgesia in shoulder surgery. *Reg Anesth Pain Med*. 2004;29:539–543.

154. Heid F, Muller N, Piepho T, et al. Postoperative analgesic efficacy of peripheral levobupivacaine and ropivacaine: a prospective, randomized double-blind trial in patients after total knee arthroplasty. *Anesth Analg*. 2008;106:1559–1561.

155. Borgeat A, Kalberer F, Jacob H, Ruetsch YA, Gerber C. Patient-controlled interscalene analgesia with ropivacaine 0.2% versus bupivacaine 0.15% after major open shoulder surgery: the effects on hand motor function. *Anesth Analg*. 2001;92:218–223.

156. Charous MT, Madison SJ, Suresh PJ, et al. Continuous femoral nerve blocks: varying local anesthetic delivery method (bolus versus basal) to minimize quadriceps motor block while maintaining sensory block. *Anesthesiology*. 2011;115:774–781.

157. Fredrickson MJ, Abeysekera A, Price DJ, Wong AC. Patient-initiated mandatory boluses for ambulatory continuous interscalene analgesia: an

effective strategy for optimizing analgesia and minimizing side-effects. *Br J Anaesth*. 2011;106:239–245.

158. Ilfeld BM, Morey TE, Enneking FK. Infraclavicular perineural local anesthetic infusion: a comparison of three dosing regimens for postoperative analgesia. *Anesthesiology*. 2004;100:395–402.
159. Ilfeld BM, Thannikary LJ, Morey TE, Vander Griend RA, Enneking FK. Popliteal sciatic perineural local anesthetic infusion: a comparison of three dosing regimens for postoperative analgesia. *Anesthesiology*. 2004;101:970–977.
160. Cappelleri G, Ghisi D, Fanelli A, et al. Does continuous sciatic nerve block improve postoperative analgesia and early rehabilitation after total knee arthroplasty? A prospective, randomized, double-blinded study. *Reg Anesth Pain Med*. 2011;36:489–492.
161. Cook P, Stevens J, Gaudron C. Comparing the effects of femoral nerve block versus femoral and sciatic nerve block on pain and opiate consumption after total knee arthroplasty. *J Arthroplasty*. 2003;18:583–586.
162. Sato K, Adachi T, Shirai N, Naoi N. Continuous versus single-injection sciatic nerve block added to continuous femoral nerve block for analgesia after total knee arthroplasty: a prospective, randomized, double-blind study. *Reg Anesth Pain Med*. 2014;39:225–229.
163. Ilfeld BM, Moeller LK, Mariano ER, et al. Continuous peripheral nerve blocks: is local anesthetic dose the only factor, or do concentration and volume influence infusion effects as well? *Anesthesiology*. 2010;112: 347–354.
164. Bauer M, Wang L, Onibonoje OK, et al. Continuous femoral nerve blocks: decreasing local anesthetic concentration to minimize quadriceps femoris weakness. *Anesthesiology*. 2012;116:665–672.
165. Brodner G, Buerkle H, van Aken H, et al. Postoperative analgesia after knee surgery: a comparison of three different concentrations of ropivacaine for continuous femoral nerve blockade. *Anesth Analg*. 2007;105:256–262.
166. Madison SJ, Monahan AM, Agarwal RR, et al. A randomized, triple-masked, active-controlled investigation of the relative effects of dose, concentration, and infusion rate for continuous popliteal-sciatic nerve blocks in volunteers. *Br J Anaesth*. 2015;114:121–129.
167. Kaloul I, Guay J, Cote C, Fallaha M. The posterior lumbar plexus (psoas compartment) block and the three-in-one femoral nerve block provide similar postoperative analgesia after total knee replacement. *Can J Anaesth*. 2004;51:45–51.
168. Partridge BL. The effects of local anesthetics and epinephrine on rat sciatic nerve blood flow. *Anesthesiology*. 1991;75:243–250.
169. Weber A, Fournier R, van Gessel E, Riand N, Gamulin Z. Epinephrine does not prolong the analgesia of 20 mL ropivacaine 0.5% or 0.2% in a femoral three-in-one block. *Anesth Analg*. 2001;93: 1327–1331.
170. Casati A, Vinciguerra F, Cappelleri G, et al. Adding clonidine to the induction bolus and postoperative infusion during continuous femoral nerve block delays recovery of motor function after total knee arthroplasty. *Anesth Analg*. 2005;100:866–872, table of contents.
171. Ilfeld BM, Morey TE, Enneking FK. Continuous infraclavicular perineural infusion with clonidine and ropivacaine compared with ropivacaine alone: a randomized, double-blinded, controlled study. *Anesth Analg*. 2003;97:706–712.
172. Ilfeld BM, Morey TE, Thannikary LJ, Wright TW, Enneking FK. Clonidine added to a continuous interscalene ropivacaine perineural infusion to improve postoperative analgesia: a randomized, double-blind, controlled study. *Anesth Analg*. 2005;100:1172–1178.
173. Elkassabany NM, Antosh S, Ahmed M, et al. The risk of falls after total knee arthroplasty with the use of a femoral nerve block versus an adductor canal block: a double-blinded randomized controlled study. *Anesth Analg*. 2016;122:1696–1703.
174. Ilfeld BM, Grant SA, Gilmore CA, et al. Neurostimulation for postsurgical analgesia: a novel system enabling ultrasound-guided percutaneous peripheral nerve stimulation. *Pain Pract*. 2016.
175. Ilfeld BM, Grant SA. Ultrasound-guided percutaneous peripheral nerve stimulation for postoperative analgesia: could neurostimulation replace continuous peripheral nerve blocks? *Reg Anesth Pain Med*. 2016;41: 720–722.
176. Ilfeld BM, Preciado J, Trescot AM. Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves. *Expert Rev Med Devices*. 2016;13:713–725.
177. Dasa V, Lensing G, Parsons M, et al. Percutaneous freezing of sensory nerves prior to total knee arthroplasty. *Knee*. 2016;23:523–528.