Perioperative Pain Management
in Hip and Knee Replacement Surgery

John W. Barrington, MD;
Thomas M. Halaszynski, DMD, MD, MBA;
and Raymond S. Sinatra, MD, PhD
for the Expert Working Group on Anesthesia & Orthopaedics:
Critical Issues in Hip and Knee Replacement Arthroplasty

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Abstract

Many patients who undergo hip or knee replacement surgery today experience high levels of postoperative pain. Data from clinical studies and analyses of hospital records have demonstrated that severe postoperative pain is associated with an increased risk for complications, slowing of the rehabilitation process, delayed return to normal functioning, progression to persistent pain states, prolonged length of hospital stay, elevated rates of readmission, and higher overall costs. Orthopedic surgeons may now play a more active role in reducing the severity of pain following surgery, decreasing both opioid use and the incidence of opioid-related adverse events, and eliminating breakthrough pain and analgesic gaps. The benefits of multimodal regimens that include a combination of agents acting synergistically have been established unequivocally, and many analgesic and anesthetic agents are now available, as well as treatment options that differ according to route of administration. It is therefore possible to individualize treatment based on the type of procedure and patient need. One exciting advance that offers effective, safe, and efficient analgesia for many kinds of surgical procedures is the introduction of an extended-release local anesthetic (liposomal bupivacaine) for infiltration. This new option, which can be administered directly into the knee or hip by an orthopedic surgeon, is an example of the changing paradigm in perioperative analgesia, where commitment, communication, and coordination across all members of the clinical care team—including the surgeon, anesthesiologist, pharmacist, physical therapist, and nursing staff—are fundamental elements of an improved standard of care. An Expert Working Group on Anesthesia & Orthopaedics: Critical Issues in Hip and Knee Replacement Arthroplasty (April 13, 2013; Dallas, Texas) evaluated current approaches to perioperative pain management and proposed new regimens to help achieve optimal outcomes in these procedures.

1. Introduction

Over recent years, data from clinical studies and analyses of hospital records have highlighted the extent of the postoperative pain that is experienced by many patients who undergo hip or knee replacement surgery. It has now been clearly demonstrated that inadequate management of perioperative pain can be associated with a wide range of undesirable effects, including slower rehabilitation, delayed return to activities of daily living, increased financial costs, unnecessary care burdens for families, and progression to a persistent pain state. The evolution of perioperative pain management represents an ongoing search for ways in which to reduce postoperative pain, improve functionality, and reduce morbidity without increasing the incidence of analgesic-related adverse effects. Orthopedic surgeons may now have a more active role to play in this aspect of the overall continuum of care for patients undergoing hip or knee replacement.

Traditionally, opioid analgesics have formed the foundation of perioperative surgical pain management. However, sole reliance on high doses of intravenous (IV) patient-controlled (PCA) or oral opioids (opioid monotherapy) may induce a wide range of negative physiologic effects and associated adverse events that can limit their overall clinical utility. These adverse effects range from annoying to life threatening, and include: pruritus, nausea, vomiting, excessive sedation, respiratory depression, prolonged ileus, development of tolerance, and cognitive dysfunction. Increasing numbers of patients undergoing hip and knee replacement surgery are elderly, and many have significant comorbidities. Opioid-related adverse effects (ORAEs) are generally dose-dependent and occur most frequently in older and obese patients in addition to those presenting with chronic obstructive pulmonary disease, hepatic or renal impairment, and several other comorbidities.[1]

In recent years, more selective approaches to perioperative pain management have been advocated for patients undergoing both hip and knee replacement surgery, including epidural analgesia and regional nerve blockade that can provide effective reduction/elimination of noxious conduction impulse stimu-

lation. However, it remains recognized that these peripheral analgesic approaches may have certain important limitations, for example, although femoral and sciatic nerve blockade (for knee arthroplasty) can provide effective pain relief, these techniques require specific caregiver skill sets of expertise, close perioperative monitoring (patients are tethered to catheters and infusion pumps), and can be associated with rare, yet potentially significant adverse events (infection, pump malfunction, etc.). Other clinically significant adverse events can also occur, including: quadriceps weakness and increased risk of postoperative falls, femoral neuropathy, femoral nerve neuritis, and masking of a compartment syndrome (if not managed promptly can lead to permanent muscle damage).[2]

Despite progress made toward improving pain management delivery systems, together with advanced analgesic options, many patients undergoing hip and knee replacement surgery continue to experience unacceptably high levels of postoperative pain.[3,4] However, evidence has shown that improved management of perioperative analgesia can relieve pain and suffering, lead to earlier patient mobilization, shorten hospital stays, reduce hospital costs, increase patient satisfaction, decrease 30-day readmission rates, and lower mortality rates.[5]

Additional analgesic regimens and non-opioid pain management alternatives are needed to further reduce perioperative pain following orthopedic surgery while reducing reliance on opioids, decreasing opioid dose requirements, and minimizing the incidence of ORAEs. Optimal analgesic regimens would eliminate breakthrough pain, reduce the incidence of analgesic gaps, maintain and improve upon patient safety outcomes, and improve patients' pain therapy experiences.[6] In addition, appropriate perioperative pain management can facilitate patient mobility, reduce healthcare resource utilization, and decrease burdens on health care providers.[6] Such a critical appraisal and action toward improved post-surgical pain management regimens may[6]:

- Achieve economic savings for patients, their families, and health care institutions;
- Raise perioperative patient safety standards;
- Improve the postsurgical pain experience; and
- Enhance patient satisfaction.

Local anesthetic medications used in a range of orthopedic surgical interventions can reduce opioid demands. However, it has typically been necessary to administer local anesthetic agents by continuous infusion to achieve an adequate duration of effect. In addition to local anesthetics in peripheral and neuraxial blockade, an additional safe and effective treatment option for total joint replacement surgery may be achieved with wound infiltration of local anesthetics (ensuring that all layers are infiltrated in a controlled manner). The only drawback associated with wound infiltration has been that single dose administration of local anesthetics (ex., bupivacaine and ropivacaine) offered a limited duration (hours) of analgesic effect. A longer acting and more sustained effective analgesic agent, liposomal bupivacaine, has been developed specifically

for wound infiltration.[7] This recently approved formulation of bupivacaine uses a novel delivery system that combines the well-established benefits of bupivacaine with a time-released delivery system that can result in a markedly prolonged (72 hours) duration of effect. Infiltration analgesia with liposomal bupivacaine may be used in conjunction with or as an alternative to traditional opioids as a first-line pain management therapy during appropriate surgical procedures.

Although availability of new non-opioid analgesic agents and techniques can offer useful clinical benefits when employed alone, without evaluation of institutional administrative and systemic changes, they may be curtailed in providing maximum benefit and may not further advance perioperative pain management. In order to more optimally benefit from novel analgesics and administration protocols, it is imperative that the entire surgical treatment team—surgeons, anesthesiologists, nurses, pharmacists, and physical therapists—understand the concepts and remain committed to adopting newer and improved evidence-based analgesic approaches to perioperative pain management.

2. Need for an Improved Standard of Care
Patient Satisfaction and Performance Standards
Effective treatment of perioperative pain is expected by patients and considered imperative (a basic human right) by hospital administrators, legislative entities, review/credentialing and accrediting organizations. Inadequate and under treatment of surgical pain is well known to be associated with significant morbidity and delay in return to baseline functionality (activities of daily living).[43] Such concern(s) has led to the development of hospital performance standards for healthcare facilities that has evolved from data collected through local and regional patient satisfaction surveys, including information sent to the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS).[8] The quality of perioperative pain management provided to patients by medical and surgical specialists at a particular facility has become one of several key performance markers. In addition, patient reports on how well their pain was controlled are commonly and collectively used as a factor in ranking healthcare facilities. Rankings of facilities can be viewed online by patients, local-to-federal administration agencies, insurance providers, and other healthcare organizing groups.[9] Therefore, selection of one healthcare facility over a nearby hospital may be influenced by published rankings or superiority when providing perioperative surgical pain management. An additional concern of healthcare administrators is the possibility that both government and private medical insurance organizations may implement healthcare reimbursement rates partially on the formal evaluation of surgical pain management, among other performance markers.

Analyses of large-scale retrospective hospital databases continue to be performed to improve understanding and further define the consequences and issues related to impacts from inadequate perioperative pain management, together with effects of ORAEs on surgical care efficacy and healthcare costs. In addition, a more complete understanding of the serious

dilemma that may further escalate incremental therapy and treatment costs associated with ORAEs, provided by computerized surveillance of inpatient records, has revealed that many associated financial burdens are related to such events. For example, surveillance of patient medical records by pharmacists at one institution was able to correlate opioid-related over sedation and respiratory depression with negative clinical consequences and associated medical costs from such events.[10] Although these individual serious events occurred infrequently (1.89 adverse drug events per 1000 surgical cases), the investigators determined that they had a higher incidence (15.9% of all events) in those patients who experienced prior histories of harmful opioid-related excessive sedation and other ORAE's.

Patients experiencing serious opioid adverse events ('opioid outliers') have significant increases in length of hospital stay and an overall cost increase in treatment. An analysis of administrative medical data from 37,031 patients who underwent a common surgical procedure in a hospital system encompassing 26 hospitals revealed that patients who experienced an ORAE had: 55% longer length of hospital admission, 47% higher costs of medical care, 36% increased risk of readmission within 30-days of discharge, and 3.4 times higher risk of inpatient mortality, compared to patients who did not experience an ORAE.[11] Findings from this type of analysis can assist anesthesiologists, surgeons, and administrators in identifying patient populations and specific surgical procedures where non-opioid alternatives for perioperative analgesia may be more prudent and medically necessary.

Physical Consequences of Poorly Controlled Pain

A cascade of harmful clinical consequences for patients, beyond discomfort and suffering, can occur secondary to inadequate pain control (**Figure 1**). Patients may suffer from both direct- and indirect-effects such as: delayed and less robust physical therapy/ambulation, increased anxiety, delays in recovery of normal function and lifestyle, poor sleep, gastrointestinal and urinary dysfunction, and negative psychological consequences (reduced quality of life),[12] all of which can result in increased cost of medical/surgical care.[13,14,15] Following hip and knee surgery, it would be most ideal for patients to actively participate in physical rehabilitation as soon as possible. However, individuals who experience moderate-to-severe pain often refuse to participate or do so less enthusiastically which may delay their surgical recovery.

In addition to the effects listed above, there are a host of other adverse clinical outcomes associated with poorly controlled perioperative pain, including consequences such as: delayed wound healing, increased risk of pulmonary morbidity (including pneumonia) and thrombosis, cardiac and hemodynamic compromise, and increased mortality risk.[12] There are also a number of additional pathophysiologic disturbances that affect the functionality of key organ systems that can have a negative impact on clinical outcomes.

Heart. Cardiac dysfunction secondary to myocardial

infarction, cardiac failure, and cardiac arrhythmia has been determined to account for a significant percentage of postoperative deaths.[16,17,18,19,20] In high risk surgical populations, perioperative ischemia is most likely to occur between postoperative days 1-3.[20] Following surgery, negative physiologic responses to poorly controlled pain may play a prominent role in the development of postoperative myocardial ischemia.[16,17,20,21,22] Release of chemical mediators such as catecholamines, arginine vasopressin (AVP), and aldosterone that have been associated with tissue trauma and postoperative pain can contribute to an increased oxygen demand leading to tachycardia, enhanced myocardial contractility, increased afterload, and hypervolemia. Myocardial dysfunction, cardiac ischemia and acute cardiac failure as described above can be precipitated by increased oxygen demand, together with hypervolemia, especially in patients with poorly compensated coronary artery disease and/or valvular heart disease.[17,20,21,23]

Lungs. Pulmonary function can be negatively impacted upon by surgically induced perioperative pain,[24] and use of opioids for perioperative pain management may exacerbate this problem. During the immediate postoperative period, vital capacity (VC) is the first parameter of pulmonary function to change that could result in: a) significant reductions in VC that are evident within the first 3 hours postoperatively, and b) reduction of VC to 40%-60% of preoperative values.[25,26,27,28] In addition, further negative consequences from pain-induced reductions in VC can include: a) atelectasis (splinting due to pain or opioid induced respiratory depression), b) increased incidence of pneumonia (retention of secretions), c) arterial hypoxemia (narcotic induced),[23,28] d) diminished oxygen supply (pain-induced alterations in pulmonary function), and e) opioid-related respiratory depression (the timing and severity of which are not always predictable). Therefore, during the surgical recovery phase, at a time when myo-
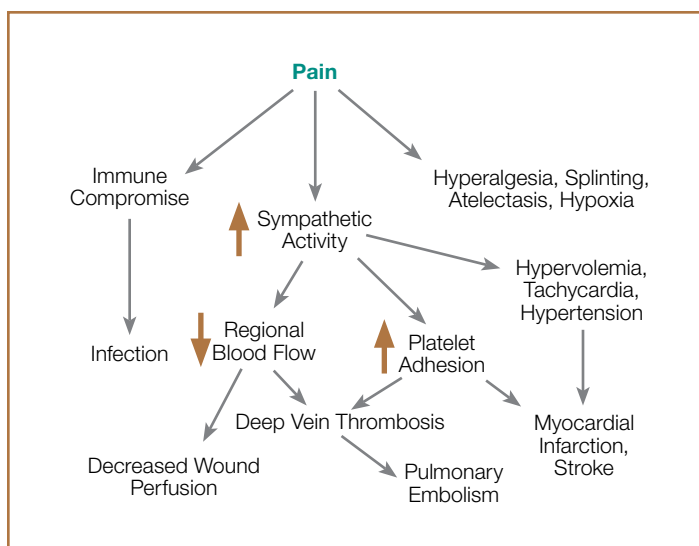

Figure 1. Harmful effects of poorly controlled postsurgical pain.

cardial oxygen requirements are often increased, supply may become inadequate to sustain proper cardiac function.

Vascular system. Inadequately controlled pain can predispose (hypercoagulation and immobility) patients to postsurgical deep venous thromboses (DVT) with the potential for pulmonary embolism. Another contributing factor stems from platelet-fibrinogen activation (development of a hypercoagulable state) that may be stimulated by release of catecholamines and angiotensin in response to surgical stress.[17,22] In addition, moderate-to-severe pain may reduce patient's mobility and can lead to decreased venous blood flow.[17,18,29,30] An issue that can further contribute to the above vascular compromise may occur during hip replacement surgery. For example, damage to venous conduits that return blood from the lower extremity can occur in the course of surgical manipulation of the pelvis. Therefore, when superimposed with additional vascular effects due to perioperative pain, this may lead to an increased incidence of Virchow's triad--hypercoagulability, venous stasis, and endothelial injury leading to the potential development of DVT.[29,30]

Measured plasma levels of norepinephrine (NE) have been found to be significantly elevated in patients who report higher pain scores during the acute surgical recovery phase.[31] High plasma NE levels can lead to vascular constriction that may stimulate platelet adhesion, further reducing peripheral limb perfusion with the potential need for reoperation secondary to graft occlusion.[17,29,30]

Progression of Acute to Chronic Pain
When improperly managed and ineffectively treated for long enough periods of time, perioperative pain can have deleterious short-term consequences, but may also lead to negative consequences lasting several months or longer. It has been shown that a higher than expected percentage of patients recovering from commonly performed procedures can be troubled by persistent somatic and neuropathic chronic pain following surgery.[32,33] Such chronic pain states are often related to poorly controlled perioperative pain and/or extended periods of inadequately treated postoperative pain. Continuous nociceptive input, affecting all levels of the central nervous system, can result in neurochemical and neuroanatomical alterations within the nervous system. Severe acute perioperative pain following insufficient pain medication use, along with improper analgesic agent administration, has been implicated in the development of central sensitization and secondary hyperalgesia.[34] Central sensitization can also set into motion compromising plasticity changes and prolonged enhancement of noxious sensitivity that may prove difficult to reverse.[35,36,37,38]

When inadequately controlled during the perioperative period, humoral and neurochemical alterations that occur in and around the surgical site can also play an important role in the progression of acute perioperative pain to a more persistent pain state. Continued sensitization of peripheral nociceptors and second order spinal neurons, together with elevated levels of various cytokines (e.g. IL-1β, IL-6), tumor necrosis factor, nerve growth factor, nitric oxide, and lymphocytes (including T and NK cells) may all contribute to the development of chronic pain following surgical procedures.[32,39,40,41,42,44]

Therefore, evidence has shown that patients who are most likely to develop persistent/chronic pain conditions include those who suffer from high acute postoperative pain intensity and those who report a greater total amount of time experiencing inadequately treated pain.[45] Furthermore, effective perioperative pain management and close patient observation of pain therapy during recovery and rehabilitation have been portrayed to be important management factors in reducing the incidence of long term/chronic pain conditions for surgical patients.

Nonclinical Impact of Ineffective Perioperative Pain Control
Poorly controlled perioperative pain may reveal significant negative effects on patient wellbeing and satisfaction in addition to an untoward impact on surgical outcome. For example, patients recovering from orthopedic surgery show that increasingly severe postoperative pain can result in greater interference with sleep[46] that can further increase lethargy and negatively affect morale, mood, and motivation to participate in the rehabilitation process. The quality and duration of sleep was most negatively affected when pain scores were greater than 5 on a 0-10 pain scale scoring system.[47] In addition to interfering with sleep, moderate-to-severe postoperative pain experience levels following joint replacement surgery has been found to significantly impair a range of necessary daily functioning activities including: walking ability, general activity levels and motivation, social relationships, and mood.[47]

Both effective and inadequate perioperative pain management has implications for healthcare resource utilization and medical care costs. Under most circumstances, routine care for surgical pain can involve a wide variety of expenses besides medications, physical therapy, and use of opioid analgesics. Perioperative pain management can incur added costs associated with securing, storage, and tracking of the chosen analgesic therapy modality(s). For example, the average cost per patient stay associated with supplies and services for intravenous patient controlled analgesia (IV PCA) and elastomeric pumps often exceed $500. Therefore, if analgesic pump technology could be reduced or eliminated, then healthcare systems could realize savings secondary to nursing time, pharmacy acquisition costs, device maintenance and malfunction, bioengineering costs, etc., since pump delivery systems require medication management, monitoring and maintenance in order to operate properly.

As another example, patients undergoing surgical repair of a hip fracture and who experience higher postoperative pain scores could result in: significantly longer hospital lengths of stay, were much less likely to be ambulating by postoperative day 3, revealed a significantly longer time to ambulate further than bedside-to-chair, and impaired locomotion scores as far out as 6 months postoperatively.[48]

There remains an important association between poorly controlled postoperative pain and incidence of hospital readmission rates following ambulatory surgery that may substantially increase the overall cost of surgical care. In a study by

Coley et al, 20,817 patients who underwent same-day surgery revealed that 313 patients returned to the hospital following discharge.[49] More than one third (38%) of these patients reported pain as the main reason for their return leading to hospital readmission. In those instances of readmission, the average cost due to pain therapy/management was $1,869 per visit.[49]

3. Systematic Causes of Poorly Controlled Pain

Perioperative pain therapy data from patient surveys has revealed that despite improvements in surgical technique and newer analgesic options (i.e. multimodal analgesia) that relatively little progress has been made over the last 20 years with respect toward improving analgesic efficacy. In addition, the overall cost of surgical procedures may be substantially increased by the need to manage analgesic related adverse events. For example, in a study by Oderda et al., the length of hospital stay increased by 0.53 days for patients who experienced an ORAE that resulted in total hospital costs to be increased by 16% (an average of $840).[50] Therefore, evidence has revealed that many surgical patients continue to experience inadequate relief of postsurgical pain.[51,52,53] In 1995, it was reported by Warfield and colleagues that 77% of adults experienced pain after surgery with 80% of these patients describing moderate to severe pain levels.[51] Almost 10 years later, very similar results were reported by Apfelbaum and colleagues with data showing that around 80% of patients experienced acute pain following ambulatory surgery and that 86% of these patients reported having moderate-, severe-, or extreme-postoperative pain (**Figure 2**).[52] Yet again, as recently as 2012, an analysis by the American Society of Anesthesiologists Task Force on Acute Pain Medicine reached very similar conclusions that perioperative pain continues to be undermanaged.[53] These disturbing findings warrant the need to more aggressively determine and search for the answers as to how and why less optimal systematic features of perioperative pain management have continued to persist over this time period and what may account for the lack of improvement in this area of surgical care medicine?

Widespread Reliance on Opioids

One major reason why little progress has been made in controlling pain following orthopedic surgery is due to a continued dependence on opioid analgesics as the mainstay of treatment for perioperative analgesia. Over the past two decades, many surgeons have relied almost exclusively on opioid analgesics for perioperative pain management and relatively large doses are commonly used despite ever-present fears of respiratory depression and other ORAEs. A systematic review of postoperative ORAEs from several controlled observational trials has revealed that the most commonly reported adverse events were from untoward gastrointestinal consequences—nausea, vomiting, ileus, or constipation—that occurred in 31% of patients.[54] Most commonly reported CNS effects were oversedation and somnolence (30.3%) with other common adverse clinical events including: pruritus (18.3%), urinary retention (17.5%), and respiratory events (2.8%).[54] In addition, elderly patients and those individuals treated with higher doses of opioid analgesics were more likely to experience an ORAE.[55,56]

Poor tolerability of patients to the gastrointestinal side effects, as opposed to lack of analgesic efficacy, has become a well known and very significant cause of poorly controlled acute postoperative pain.[54,57] A large retrospective analysis of data from 434,304 surgical procedures was conducted by Suh et al., and determined that 55% of patients required treatment for nausea, vomiting, or constipation following analgesic administration.[58] The use of these analgesic treatment options inducing gastrointestinal dysfunction was almost 5 times more frequent in patients who had received IV opioid medications than in those who had received oral non-opioid analgesics.

Despite marked variability with respect to surgical patient age, weight, and drug tolerance/dependency, opioid analgesics are far too often prescribed according to pre-determined standardized protocols. The concept of "one size fits all" approach toward dosing opioid medications can lead to overdosing and poor tolerance by some patients (the elderly) and potential for sub-therapeutic dosing in others. Surgical orders for postoperative opioid analgesics often specify the same loading dose, bolus dose, lockout interval and 4 hour dose limits for both young and elderly patients alike and often without considerations for the degree of invasiveness of the surgical procedure. Post-surgical IV-PCA orders for patients with chronic opioid dependency are rarely adjusted to compensate for any degree of opioid tolerance, and the same opioid bolus dose is often administered to a naïve individual as would be for a patient who has been taking oxycodone on a daily basis for chronic pain.[59]

Opioid Monotherapy

Opioid analgesics are often prescribed as monotherapy and can be dosed according to the severity of the anticipated postsurgical pain. Unfortunately, the effectiveness of such monotherapeutic treatment with either IV or oral opioids is far too frequently compromised by the extent of ORAEs as there has been an increased incidence of unwanted CNS effects that may become intolerable by many patients.[57,60] Therefore, it is not unusual for such patients to suffer moderate to severe discomfort in silence rather than alerting hospital staff (or "offending" surgeons) with complaints related to their inadequate analgesic regimen.[57,60]

Initially, opioid medications were administered intramuscularly or generally provided on a PRN basis following surgery. However, an important drawback of PRN dosing of analgesic medications is that patients often wait too long to request opioid analgesics for pain relief. In addition, staffing needs may not be able to deliver pain medication as soon as requested and therefore, therapeutic plasma concentrations may not be uniformly maintained.[61] A pain cycle characterized by alternating periods of over sedation with severe pain was a common occurrence with PRN pain medication dosing and this can further affect ambulation and other measures of return to normal functionality.
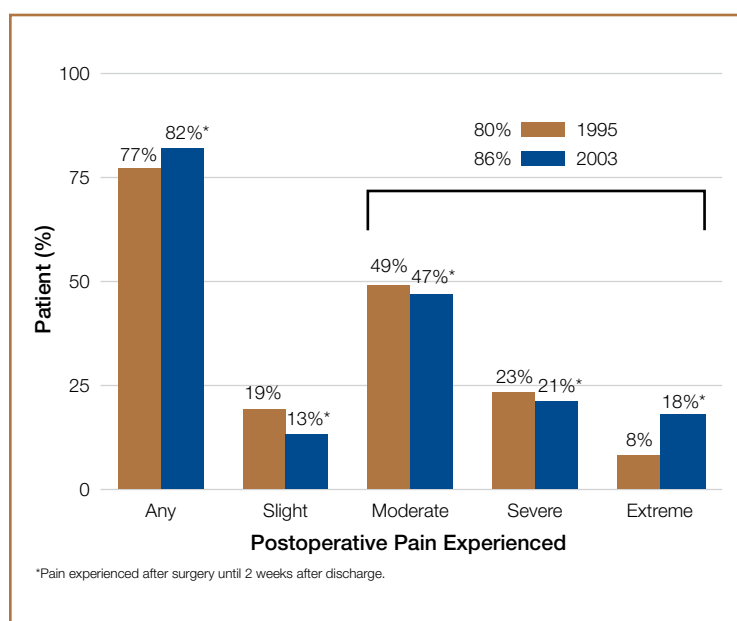
Figure 2. Comparison of Postsurgical Pain Management Over the Last 2 Decades[51,52]

Patient-Controlled Analgesia

IV-PCA was developed to overcome deficiencies associated with intramuscular administration and PRN analgesic dosing and proved effective in helping to reduce or eliminate cycles of increasing pain intensity alternating with delays in analgesic administration. The initial concept was that patients could now be given a PCA system and assured that they would receive excellent control of postoperative pain.[62] However, even though being more efficacious, it soon became evident that the pain relief experienced by these surgical patients receiving IV-PCA fell short of expectations.

Some of the shortcomings of IV-PCA administration were that analgesic dosing was often not properly adjusted for procedure-specific pain and did not take into consideration patient age, comorbidities, prior opioid usage/abuse, or present opioid requirements. In addition, inappropriate PCA analgesic dosing increased the risk of ORAEs in several patients (over-medication) and inadequate pain relief for others (under-medication). Therefore, analgesic regimens with reliance on opioids alone could cause some patients such distress that they would choose to suffer from inadequate postoperative pain management rather than tolerating the ORAEs. In particular, elderly patients may suffer confusion and excessive nausea with opioid analgesics such that they would forget or subconsciously chose not to activate the bolus dosing button often enough to achieve effective perioperative analgesia (elect not to activate bolusing system for fear of increasing the level of ORAEs).[1]

Another major risk associated with use of IV-PCA pump systems was oversedation that could lead to potentially fatal narcotic-induced respiratory depression.[12] In addition, mistakes in programming analgesic PCA systems could be a frequent cause of over-sedation, but such events could occur even when the pump was properly programmed secondary to the knowledge that patient response to opioid analgesics can widely vary.[63] In a study of postsurgical patients receiving postoperative PCA therapy by Overdyk et al, they detected respiratory depression in 41% of patients and revealed frequent desaturation and bradypnea during patient-controlled analgesia.[64]

A common risk associated with opioid IV-PCA therapy is activation of the analgesic bolus component of the system by well meaning healthcare providers and family members. This phenomenon known as 'PCA by proxy' could also result in over sedation of surgical patients along with an increased incidence of other ORAEs.[63,65]

Regarding issues surrounding healthcare resource utilization, one system-related event that must be addressed by administrative medical care providers that occurs frequently is the use of analgesic delivery systems that are complex, invasive, or involve multiple steps for medication acquisition and administration, IV-PCA programming, delivery and management. For example, when administering opioid analgesics using a PCA pump, infiltration of an IV line can often be a commonly reported event that will diminish postoperative pain management and result in subcutaneous drug deposition capable of leading to increased patient pain and discomfort. There can be as many as 125 steps encompassing 6 to 8 different healthcare personnel involved in simply acquiring, setting-up, administering, and maintaining PCA systems. The average patient may need to have their IV restarted 2.3 times in order to maintain an intravenous site for PCA delivery along with significant potential for error including: incorrect PCA programming, device malfunctions, and over- or under-dosing errors.[66,67,68,69] In addition, risks associated with mis-programming of PCA pumps should not be underestimated. For example, over an 8-year period from 1995 to 2003 the Joint Commission found that 21% of sentinel events relating to medication errors involved opioids.[68] Although only 2% of opioid medication errors resulted in patient harm, when a PCA pump was involved, chances for patient harm increased 3.5-fold. Now, there remains a heightened realization of the increased frequency (type and cause) of these events and importance of severity of PCA versus non-PCA medication errors in the database due to results of increased incidence of fatalities.[68]

Analgesic Gaps

Despite clinical and pharmacologic advances in analgesic treatment modalities, perioperative pain management has continued to be compromised by periods of inadequate pain relief known as analgesic gaps.[70,71,72] Such analgesic gaps can occur passively as when a patient emerges in pain because plasma levels of analgesic medication(s) are inadequate. This type of analgesic gap typically occurs if opioids (or neuraxial blockade) are either withheld, administration rates slowed, or administered at sub-therapeutic levels in which adequate levels of analgesic medication are not maintained. Analgesic gaps will

compromise pain management, may take several minutes or even hours to re-establish pain control, and patients will generally remember this untoward experience.

Some surgeons have abandoned use of short-acting opioids as the primary method of postoperative analgesia and chose instead to employ non-steroidal anti-inflammatory drugs (NSAID's) and acetaminophen for pain management that may result in analgesic gaps. However, both hydrocodone and oxycodone (provide 3 to 4 hours of pain relief) continue to be widely prescribed, but have a relatively short duration of effect that can predispose patients to analgesic gaps, especially when prescribed on a PRN basis. Therefore, patients who are administered short-acting pain medications that must be requested or taken frequently can often experience repeated analgesic gaps following major surgery. In an effort to prevent analgesic gaps associated with use of short-acting agents, sustained-release formulations of morphine or oxycodone are increasingly being prescribed.[73] However, these long-acting agents are not appropriate in some patients or under certain surgical circumstances.

Analgesic gaps may also occur during times of medication transition or with increases in levels of activity. For example, a patient could be comfortable for several hours until a change in medication administration occurs (transition from an IV to an oral analgesic) or with changes in activity levels (moving from a bed to a chair) that places added stress(s) on the surgical area exacerbating a sudden increase in pain intensity. When patients are surveyed, they tend to remember these brief spikes in pain intensities and can rank overall pain relief and satisfaction lower than it would have been otherwise if the analgesic gap had not occurred.

Disparities in quality of health care according to patient age, gender, ethnicity, or race can also contribute indirectly to analgesic gaps. Improvements in the overall health of Americans over the past few decades is not shared equally among all racial groups, and this can be seen particularly in the management of acute pain in both the emergency room and postsurgical care setting.[68,74,75] In addition, elderly and cognitively impaired patients may do poorly with PCA systems as it is not uncommon to find that these patients may experience severe pain simply because they are unable to comprehend PCA device instructions or not able to locate and/or activate the PCA button for medication delivery (they do not understand when they should activate the PCA or they mistake it for a nursing call button).[66]

Technology failures with epidural and peripheral nerve block catheters can also bring about analgesic gaps. For example, epidural catheter placement is known to function suboptimally in about 30-40% of cases.[76] Under these circumstances, patients can experience the return of surgical pain when an epidural catheter becomes dislodged during patient movement, physical therapy, or ambulation. In addition, since most commonly administered epidural analgesic solutions are highly diluted, the dose of medication that is delivered into the epidural space can rapidly become sub-therapeutic if the catheter has become dislodged or is no longer functioning properly. Infusion-related medication errors may also occur with an epidural or peripheral nerve blockade, particularly if there is a kink of the infusion catheter or insufficient solution remaining in the medication bag. In addition, infusion pump devices may become unplugged and/or pump batteries can lose their charge. Finally, since all infusion pumps require caregiver input, there remains the ever present potential for using the wrong solution of medication and/or infusion pump setting errors.[66,72] Therefore, if an interventional technique is not providing consistent and effective pain relief, it is prudent for the surgical team or nurse to contact the anesthesiologist or pain management team to determine whether replacement of the catheter, adjustments in catheter position, administration of bolus dose of medication is warranted, or use of an alternative analgesic option needs to be considered.

4. Evolving Paradigm in Postsurgical Pain Management

Multimodal Analgesia

Expert opinion and physiological evidence has shown that more optimal management of perioperative pain can no longer be achieved using a single drug or analgesic technique. It is becoming well known that generation of the pain cascade(s) during the perioperative period involves multiple pathways. Therefore, in order to achieve more efficacious control of perioperative pain (interrupting multiple pain pathways), a "balanced" or multimodal analgesic approach is necessary. What must now be considered a more effective strategy for management of perioperative pain involves a combination of agents and techniques that work independently, additively and synergistically in both the peripheral and central nervous systems. By using a combination of analgesic modalities (agents, techniques, etc.) in this way, it has become possible to administer lower doses of individual medications, reduced reliance on opioid mono-therapy, provide autonomy to postoperative patient care, and ameliorate dose-dependent adverse effects to identify a few distinct advantages to previous (reliance on a single agent or technique) pain management scenarios.

Opioid analgesics (despite potential for ORAEs) will continue to be used clinically and remain a vital component to perioperative care of surgical patients. However, the goal should be to administer these agents as needed in combination with other pain reducing treatment modalities while avoiding reliance on opioid agents alone, reducing the impression of narcotic use as the pain management foundation, and to use as little opioid medication as possible by substituting other more effective analgesic options.[77] Under many surgical scenarios, dose of opioid medications required can be reduced significantly by administering non-opioid agents as part of a multimodal regimen (patient- and procedure-specific). Today there are several other analgesic/anesthetic agents available, all capable of influencing the pain cascade by various mechanisms (transduction, transmission, conduction, etc.) from the periphery to the central nervous system and back. Therefore, with so many different analgesic options and various routes of administration, it is now possible to tailor and individualize perioperative analgesic treatment plans based

on individualized patient need along with degree of surgical trauma and invasiveness.

There are several analgesic agents and techniques that can be considered as alternatives to utilization of opioid drugs as the foundation of perioperative pain management. Multimodal analgesia can include: a host of non-opioid analgesics, peripheral neural blockade (PNB; usually performed by the anesthesiology team), local anesthetic infiltration (usually administered by the surgeon), and opioids along with creative combinations of the above treatment options. The choices above, in addition to several other non-opioid analgesic options, can be especially beneficial in those who are at risk for experiencing severe surgical pain, those who are highly sensitive to opioid medications, opioid naïve patients and those with history of narcotic abuse, patients concerned about opioid-related adverse affects, and circumstances where surgical interventions dictate an absolute or relative contraindication to more traditional analgesic treatment options.

Advances in PNB interventional methods, along with introduction of ultrasound guidance and stimulating catheters have resulted in improved efficacy and reliability of PNB techniques for pain management (increased acceptance and use). Techniques of wound site infusion with local anesthetics and use of gas charged elastomeric pumps for prolonged wound site infiltration can provide effective relief from painful orthopedic procedures. In addition, these same pumps or use of electronic programmable pumps connected to PNB catheters can also provide extended duration of analgesia during the acute perioperative phase. Richman et al. performed a meta-analysis from 19 randomized clinical trials comparing efficacy of continuous PNB (using local anesthetics) against oral or parenteral opioid analgesia in patients undergoing lower extremity surgery. The investigators determined that PNB provided superior postoperative analgesia with significantly fewer GI adverse side-effects.[78] An additional study has examined the efficacy of continuous epidural infusion, continuous "3-in-1 block", and IV PCA after total knee arthroplasty[79] and reported: superior pain relief, fewer adverse effects, and faster knee rehabilitation in patients receiving alternative postoperative pain therapy (epidural infusion, and 3-in-1 block) compared with those who received opioid IV-PCA.

Non-opioid analgesics such as acetaminophen (which controls pain perception) and NSAIDs/COX-2 inhibitors (which control peripheral pain suppression and inflammation) have until recently only been available in oral formulations. Some formulations, however, are now available in injectable forms that can provide effective pain relief while reducing opioid dose requirements.[80,81] However, these injectable non-opioid analgesics may be contraindicated in certain patients who have GI dysfunction (gastric bleeding) along with hepatic and/or renal disease(s).[1] The medications above in addition to other non-opioid analgesic alternatives are being incorporated into preemptive and multimodal perioperative pain management regimens with the goal toward achieving improved and more efficacious analgesic effects while focused on reducing morbidity.

The Changing Collaboration Between Orthopedics and Anesthesia

Introduction and implementation of medical, pharmacological and technical breakthroughs along with innovative patient care therapies in perioperative pain management will often require institutional systematic changes (policy, procedures, and protocols). In order to be effective in establishing new protocols for pain management in hip and knee replacement surgery, adoption also requires a duplication of the above protocol to include commitment, communication, and coordination among all members of the clinical team including: surgical and anesthesia teams, pharmacist, physical therapist, hospital administrators, along with nursing and administrative staffs. In addition, for adoption of an innovative patient treatment modality to be synthesized into an accepted multimodal pain care regimen(s), it will require that evidence-based and scientific data become coordinated enough to show procedure- as well as a patient-specific advantages, easily incorporated into the current healthcare culture, expertise by specific team members to coordinate and perform implementation, and acceptance by all perioperative team players. Perioperative teams must answer a few important questions for new perioperative pain management strategies to be successfully implemented:

- "What objective is trying to be accomplished?"
- "What change(s) can be made that will result in an improvement?"
- "How can such change(s) toward an improvement be measured?"

Liposomal bupivacaine, a long acting, sustained release local anesthetic preparation was introduced into clinical practice not as replacement for current perioperative pain treatment modalities, but intended to function as a foundation or cornerstone of modern multimodal analgesic regimen(s). Inclusion of this medication into perioperative analgesia will help to close analgesic gaps in the control of acute pain. Liposomal bupivacaine infiltration blocks nociceptive pain in the periphery, the site of initiation of surgical trauma. Using this protocol, the surgeon administers liposomal bupivacaine and anesthesiologist employ's other anesthetics and complimentary analgesic modalities (peripheral nerve and/or neuraxial blockade) to achieve complete management of acute surgical pain. It remains vital that the surgeon communicate all details of liposomal bupivacaine administration (dose and concentration) to the anesthesiologist who will then coordinate complementary analgesic agents and plans throughout the postoperative course of treatment.

Using liposomal bupivacaine as a component synthesized into multimodal perioperative anesthetic regimens; both surgical and anesthesia care teams now play a synergistic role in perioperative pain management of the surgical patient. There is a greater need for collaboration and communication between teams to avoid patient harm and optimize the chosen pain management plan. Therefore, the two disciplines must coordinate time requirements, dosage and concentration for

this medication to maximize (i.e. peak effect) and function in harmony to achieve superior analgesic potential. As an example of one approach expressing how collaboration between surgical and anesthesia teams may work together in harmony for maximum patient benefit during knee replacement surgery using liposomal bupivacaine injection into the surrounding surgical site, the following scenario is outlined below:

To eliminate the *immediate* post-surgical analgesic gap: The surgical team can inject immediate-acting bupivacaine into the joint (taking care not to overlap timing intervals nor exceed recommended local anesthetic dosage limits). In addition, the intraoperative anesthesia team could place a neuraxial blockade or "single shot" peripheral nerve block (femoral +/- sciatic) along with modification of the intraoperative anesthetic (reducing or eliminating general anesthetic agents and/or opioid analgesics). If the patient is not a candidate for neuraxial anesthesia, a short-acting nerve block can be provided without an indwelling catheter that could be in the form of a single-shot femoral nerve or an adductor canal block. The adductor canal block seems to be gaining popularity, as there is evidence of reduced motor blockade of the quadriceps muscle with this approach.[82]

Patients with chronic pain can be especially challenging to manage and present opportunities for individualized interventions that involve both surgeon and anesthesiologist.[83] One course that can be considered in such patients, for example, is combination of a conduction block with a nociceptive block, via administration of liposomal bupivacaine. Essential issues that need to be addressed collaboratively by the surgeon and anesthesiologist in that situation are the total dose and timing of pain medications that the patient will receive.

One current practice that now appears to be under some degree of scrutiny is the use of peripheral blocks with catheters. The premise of catheter use in the management of perioperative pain has been to accomplish extended release and duration of effect of local anesthetic. Decreasing the use of catheters, however, may reduce the rate of falls by eliminating quadriceps weakness, and a similar extended duration of effect can now be achieved by administering liposomal bupivacaine.

Shared responsibility for administration of perioperative analgesia between the surgeon and anesthesiologist might also result in improved efficiency with respect to the use of operating room time. At most hospitals, it is standard procedure to perform intrathecal anesthesia in the operating room, due to the potential for hemodynamic compromise from administration of local anesthetics into the subarachnoid space. If liposomal bupivacaine is going to be infiltrated by the surgeon during the course of the procedure, however, a lower dose of the spinal anesthetic would be required, and this smaller dose with a lower risk for hypotension could be administered in a properly equipped preoperative area outside of the operating room.

Perioperative analgesic plans must focus on individualized treatment according to patients' medical, physiologic, social, and physical needs to achieve optimal success. A coordination of intraoperative healthcare teams remains vital toward

such a goal. In addition, addressing a patients' psychological needs, managing anxiety, and setting appropriate postoperative expectations must also be part of the overall treatment plan.[1] Therefore, not only will surgical team collaboration prove successful for perioperative outcomes, but patient education remains an important component of these individualized treatment plans.[12] Patient expectations must be addressed and remain reasonable as patients need to be involved in pain management plans and made aware of what is realistically possible. They need to be made aware and understand that being completely pain-free after total joint replacement is not a realistic goal, but, patients need to be educated that:

- They should not experience severe or very severe pain;
- Maintaining pain at a mild level (at most a moderate level) is a reasonable goal; and
- Degree of pain relief will be balanced with the goal of minimizing any side effects of analgesic medication(s).

5. Practical Application of New Concepts in Hip and Knee Surgery

Infiltration of the surgical site with long acting local anesthetics represent an exciting recent advance to multimodal perioperative pain management that offers effective, safe, and efficient analgesia for many kinds of surgical procedures. Liposomal bupivacaine incorporates bupivacaine HCl with DepoFoam, a proprietary drug delivery technology that uses multi-vesicular liposomes to encapsulate the bupivacaine and release it over an extended period of time.[84] Liposomal bupivacaine has been FDA approved for injection/infiltration directly into the surgical site (proper infiltration taking approximately 7 minutes).[85] Since local infiltration techniques are simple, reliable, and repeatable procedures, the potential for variability or operator (most often the surgeon) error is usually low. Proper infiltration technique involves a slow injection into soft tissues of the surgical site, with frequent aspiration to identify any incidence of blood aspiration with a goal to minimize the risk of intravascular injection. For optimal analgesic efficacy, it is important to inject all soft-tissue layers and be certain that as much of the medication remains within tissue planes, although some medication will be seen in the surgical wound.

As an example, combining liposomal bupivacaine infiltration into the surgical wound prior to closure along with intraoperative intrathecal or epidural analgesia (using plain local anesthetic) is one strategy that surgeons and anesthesiologists can employ to gain highly effective multimodal analgesia. In the example above, liposomal bupivacaine infiltration blocks peripheral nerve endings and peripheral nerves adjacent to the surgical site while the neuraxial blockade provides interruption from the surgical injury to the central nervous system. Long acting (72hrs.) liposomal bupivacaine blocks axonal transmission from peripheral nerve fibers along their course from the periphery to the spinal cord in contrast to the shorter duration of effect from the neuraxial blockade local anesthetics. Therefore, a combination of liposomal bupivacaine infiltration plus peripheral or epidural neural blockade will result in additive
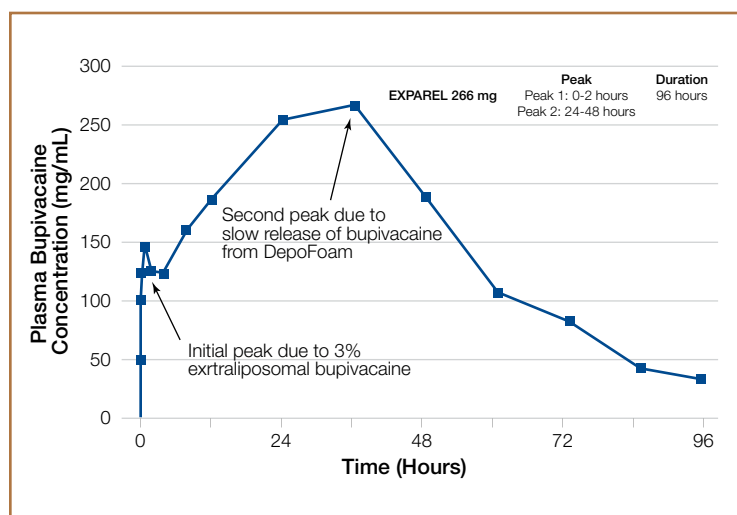
Figure 3. Pharmacokinetics of Liposomal Bupivacaine[86]

analgesia by blocking nociceptor activation, as well as signaling (transduction) and conduction from noxious nerve fibers to the central nervous system. This approach will impact upon and reduce the incidence of analgesic gaps that can occur with the use of either technique alone. However, combining infiltration of liposomal bupivacaine in addition to a peripheral nerve block and/or a neuraxial blockade (especially an epidural) using bupivacaine may increase the risk of local anesthetic systemic toxicity, so care must be taken to avoid excessive plasma levels of local anesthetic.

Pharmacokinetics of liposomal bupivacaine. Clinical pharmacokinetics of liposomal bupivacaine are characterized by short-term and first-order release of local anesthetic molecules, followed by zero-order kinetic release over a variable length of time depending upon the type of surgical procedure (**Figure 3**).[86] Following bupivacaine release from DepoFoam particles, the rate of systemic absorption depends upon the total dose of drug administered, route of medication injection, and vascularity of the surgical/administration site.[85]

The gradual release of bupivacaine from the remaining DepoFoam particles explains its extended duration of effect. After most of the drug has been released, there is an additional 10- to 12-hour half-life duration of local anesthetic effect. Therefore: 1) by the end of day two (48 hours), 60% to 70% of the bupivacaine containing DepoFoam vesicles have degraded, 2) sometime into post-injection day two, there remains an additional 10-12 hours of analgesic effect, 3) by 72 hours, most all of the liposomal bupivacaine vesicles have degraded along with a reduction in tissue plasma levels of bupivacaine and analgesic clinical effectiveness begins to dissipate.

Pharmacokinetic properties of liposomal bupivacaine were examined in a prospective, open-label, crossover study in 8 healthy volunteers. All subjects within the investigation received a subcutaneous injection of 20 mL of 0.5% plain bupivacaine HCl (100mg), then 1 week later, the same volunteers received 20 mL of a 2% liposomal bupivacaine (400mg) in-

jection. The mean maximal plasma concentration of bupivacaine between the 2 injection protocols (difference between plain bupivacaine and liposomal formulation) was not statistically significant (0.87 and 0.83 mcg/mL, respectively). However, the terminal half-life of plain bupivacaine was only 131 minutes compared to reports of 1294 minutes (21.6 hours) with the liposomal bupivacaine (P<.01).[84]

Impact of liposomal bupivacaine on outcomes. The efficacy and safety of liposomal bupivacaine has been established in more than 21 clinical investigations, including 10 double-blind, randomized, controlled trials that collectively involved 823 patients undergoing a range of surgical procedures (including soft tissue and orthopedic surgeries).[87] The above studies demonstrated that a single dose of liposomal bupivacaine could provide continuous and effective analgesia at the site of surgical injury for up to 72 hours.[87] In another review of pooled data analysis from nine studies representing five different surgical procedures, these randomized, controlled trials also showed that patients receiving liposomal bupivacaine required 35% less opioids than those patients receiving bupivacaine HCl (12.2 mg versus 19.0 mg; P<.0001).[88]

Even though there have been only a few published studies with liposomal bupivacaine in orthopedics, it is being used in total joint replacement as well as some other orthopedic surgeries. In addition, favorable outcomes were reported from one phase 3, randomized, placebo-controlled trial that enrolled patients undergoing bunionectomy. Patients in the study received either 120 mg of liposomal bupivacaine by wound infiltration or placebo.[89] Patient pain scores rated on a numerical rating scale (0-10) was significantly less in those treated with liposomal bupivacaine compared to those patients receiving placebo at both 24 (P=.0005) and 36 hours (P<.02). In those patients treated with liposomal bupivacaine, only 1% of them used opioid rescue medication during the first 24 hour period following surgery compared to 7.2% of the patients in the placebo group (P<0.04). In addition, the median time to first opioid use was 7.2 hours in the liposomal bupivacaine group versus 4.3 hours in the placebo group (P<.0001).

Much of the current clinical data investigating effects of liposomal bupivacaine on outcomes (i.e. perioperative analgesia) have been identified in the general surgery patient population. When compared to standard opioid-based analgesic regimens in an open-label, single-center, sequential-cohort study of adults undergoing open colectomy, a liposomal bupivacaine–based multimodal analgesic regimen resulted in less opioid consumption (57 mg versus 115 mg; P=.025), a shorter length of hospital stay (2.0 days versus 4.9 days; P=.004), and lower total hospital costs ($8766 versus $11,850; P=.027) (**Figure 4**).[90]

Opioid-reducing attributes of a multimodal analgesic regimen using liposomal bupivacaine were confirmed in another general surgery patient population undergoing ileostomy reversal.[91] In this open-label multicenter study, sequential co-

horts of patients received either IV opioid PCA or multimodal analgesia including intraoperative liposomal bupivacaine. The mean total dosage of postsurgical opioid analgesic use in the multimodal analgesic group was 20 mg, compared with 112 mg in the opioid analgesic group of patients (P<.01). The average total cost of hospitalization in the multimodal group was $6,482 versus $9,282 in the IV opioid PCA group (P=.01), while the median postsurgical length of stay was 3.0 days in the multimodal group, compared to 5.1 days in the opioid PCA group (P<.001).[91]

Very similar results were seen in another study on patients undergoing ileostomy reversal. In this single-center, open-label study, patients received postsurgical multimodal analgesia that included intraoperative administration of liposome bupivacaine or IV PCA with either morphine or hydromorphone.[92] Intravenous opioid analgesics along with oral opioids plus acetaminophen were available to all patients. The mean opioid dose requested by patients in the multimodal group was 38 mg (morphine equivalent) compared with 68 mg in the IV PCA group (P=.004). The median time to first opioid use was 1.1 hours and 0.7 hours in the multimodal analgesia group and IV opioid PCA group respectively (P=0.035). Postsurgical length of stay and geometric mean hospitalization costs were not significantly different between the 2 groups of patients.

An indwelling femoral nerve catheter and pump are often used for extending the duration of local anesthesia following total knee replacement. The effectiveness of this approach, however, is variable, and quadriceps weakness is common. Inclusion of liposomal bupivacaine as part of the infiltration mixture allows for elimination of the nerve block and pump. A recent comparative study, presented at the most recent American Academy of Orthopaedic Surgery Annual Meeting, demonstrated that wound infiltration with liposomal bupivacaine compares favorably to continuous femoral nerve block, with equivalent analgesia, reduced total narcotic consumption, and no quadriceps weakness.[93]

A prospective case controlled study in 1,000 hip or knee arthroplasty procedures, presented at the same conference, also showed an average cost saving with liposomal bupivacaine of $1,250 per patient.[94] The predominant factor contributing to this saving was the elimination of femoral nerve catheters. The study also showed a significant decrease in falls from 1.2% of patients to 0.2% (P=0.002).
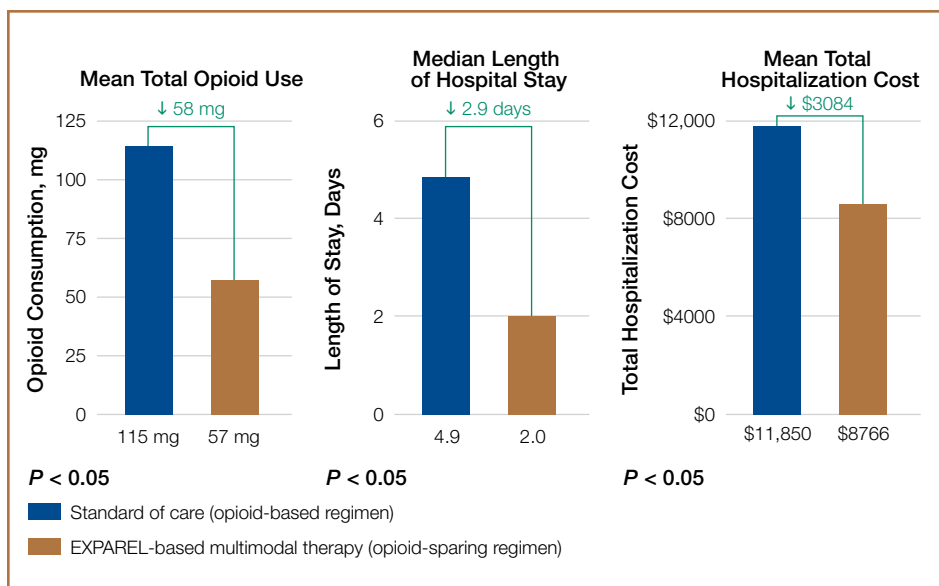
Dosing of liposomal bupivacaine. The dosage of liposomal bupivacaine should be guided by the instruction insert and based upon incision size or type of sur-

gery, but the maximum dosage should not exceed 266 mg (20 mL of undiluted drug). Depending upon nerve innervation density of the surgical site, liposomal bupivacaine can be administered undiluted or volume expanded by diluting with preservative-free normal (0.9%) sterile saline up to 0.89 mg/mL (i.e., 1:14 dilution by volume, for a total of 280 mL) for injection. The diluted medication (20 mL of undiluted drug mixed with normal saline) should be used within 4 hours of syringe preparation.[85]

It is not possible to convert different formulation dosing of free bupivacaine HCl formulations to liposomal bupivacaine as different formularies of bupivacaine are not bioequivalent at the same milligram strength. Liposomal bupivacaine is intended for single-dose administration only.[85] Although liposomal bupivacaine can be used in patients with more than one surgical site, the total dose of liposomal bupivacaine across all sites should not exceed 266 mg.[85] The safety of liposomal bupivacaine has currently been evaluated at doses ranging from 66 mg to 532 mg.[85]

Administration of both liposomal bupivacaine and bupivacaine HCl during the same procedure increases the overall exposure of the patient to free bupivacaine. Furthermore, if bupivacaine HCl is injected immediately before the liposomal bupivacaine at a milligram dose that exceeds 50% of the liposomal bupivacaine dose, the pharmacokinetic and physicochemical properties of the liposomal bupivacaine may be affected.[85] Coadministration of liposomal bupivacaine and bupivacaine HCl is not recommended at this time.

Infiltration technique. Attention to the proper infiltration technique of liposomal bupivacaine is essential when administering the medication. One important consideration when using any local anesthetic is the potential for accidental or an inadvertent intravascular injection. Injection of a local anes-

Mean Total Opioid Use — ↓ 58 mg — Opioid Consumption, mg — 115 mg, 57 mg — *P* < 0.05

Median Length of Hospital Stay — ↓ 2.9 days — Length of Stay, Days — 4.9, 2.0 — *P* < 0.05

Mean Total Hospitalization Cost — ↓ $3084 — Total Hospitalization Cost — $11,850, $8766 — *P* < 0.05

■ Standard of care (opioid-based regimen)
■ EXPAREL-based multimodal therapy (opioid-sparing regimen)

Figure 4. Standard Opioid-Based Analgesic Regimen vs Liposomal Bupivacaine–Based Multimodal Regimen in Patients Undergoing Open Colectomy[90]

thetic directly into the bloodstream may result in adverse CNS and/or cardiovascular events.[95] Therefore, in order to reduce risks of local anesthetic intravascular injection, it is imperative that thorough training in safe, directed, and effective methods of local anesthetic infiltration be followed.[95]

There are several methods that have been shown to reduce the potential risk of accidental intravascular injection such as: 1) intentional and continuous moving of the needle during infiltration, 2) intermittent syringe aspiration or plunger withdrawal, and 3) total syringe withdrawal prior to infiltration into an adjacent site. The continuous moving-needle infiltration technique may also facilitates a more even dispersal of local anesthetic into surrounding tissues and also leads to less tissue distention because no single tissue area would be infiltrated with excessively large volumes of medication.[95]

Safety of liposomal bupivacaine. When administered at the correct dosage and correctly infiltrated, liposomal bupivacaine has been shown to be generally very well tolerated.[96] Adverse reactions to liposomal bupivacaine have been reported to include: dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%) in a small number of patients,[97] and infiltration into the surgical site does not appear to have any untoward effect on either wound healing or risk of wound infection.[7]

The safety data found within the label insert is based on the use of up to 266 mg of liposomal bupivacaine[85] as higher doses may be associated with a dose-dependent risk of cardiac toxicity, including life-threatening arrythmias and depressed myocardial contractility. Results from 4 phase-1 bupivacaine extended-release studies (n = 169) and 10 bupivacaine extended-release wound infiltration studies (n = 1459) were pooled and assessed while investigating ECG and/or Holter monitor findings along with any reported incidence(s) of cardiovascular AEs.[98] These studies included liposomal bupivacaine administration at doses as high as 600 mg, however, no clinically relevant ECG changes and/or cardiac adverse events were observed.[98] When co-administering liposomal bupivacaine and bupivacaine HCl, the total bupivacaine dose should not exceed 3 mg/kg and the bupivacaine plasma level should not exceed 2-4 µg/mL.[85] Therefore, communication between anesthesiologist administering bupivacaine hydrochloride (i.e. femoral nerve blockade) and surgeon infiltrating liposomal bupivacaine (within the knee joint capsule surgical site) must remain open and cognizant of maximum bupivacaine dose and serum levels so as to not exceed the predetermined concentration levels.

It remains important to note that 150 mg of bupivacaine hydrochloride is equivalent to 133 mg of free bupivacaine, and 266 mg of liposomal bupivacaine will, over time (72 hours), all be considered free bupivacaine as it is being released. In the liposomal formulation, 97% of the bupivacaine is encapsulated in multivesicular liposomes, and is released over an extended period of time.[99] The remaining 3% of bupivacaine is not contained within the liposomes, and this fraction accounts for the early effect on local pain receptors.

CNS reactions associated with all local anesthetics, includ-ing liposomal bupivacaine, are characterized by excitation and/or depression. However, excitation may be transient and depression may be followed rapidly by drowsiness leading to unconsciousness with respiratory arrest as the first indication of an adverse reaction. In addition, restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, and convulsions may also occur along with other more minor effects such as nausea, vomiting, chills, and constriction of the pupils.

Several studies have suggested a cytotoxic effect of bupivacaine on articular chondrocytes and there have been many additional case reports of patients developing glenohumeral chondrolysis following placement of a continuous intraarticular bupivacaine infusion.[100] Therefore, liposomal bupivacaine is not recommended for intraarticular injection due to the risk of chondrocyte toxicity.

Secondary to chemical make-up and physical properties of the bupivacaine encapsulated into liposomal spheres, liposomal bupivacaine should not be admixed or come into contact with certain types of other medications. For example, other non–bupivacaine-based local anesthetics (i.e. lidocaine), if administered together, may cause the liposomal spheres to prematurely break down and lead to an immediate release of bupivacaine locally. However, if use of the local anesthetic lidocaine is considered clinically necessary, administration of liposomal bupivacaine infiltration should be delayed for at least 20 minutes following lidocaine injection. As another example, liposomal bupivacaine should not be permitted to come into contact with antiseptics. There exists a similar potential for disruption of lipid layers of the DepoFoam leading to an unpredictable release of bupivacaine when contacting un-dried topical antiseptics.[85] Therefore, when topical antiseptics, such as povidone iodine and chlorhexidine are applied, the site should be permitted to dry before infiltration of liposomal bupivacaine is administered into the surgical site.

The compatability of liposomal bupivacaine with other drugs is dependent on the compatability of the drug itself, as well as the compatability of the liposome and the liposomal components. In recent studies, liposomal bupivacaine demonstrated compatibility with both diluents and implanted materials, including silicone, stainless steel, titanium, polypropylene, and expanded polytetrafluoro-ethylene.[101] Clinically meaningful interactions between liposomal bupivacaine and other local anesthetics, including lidocaine, ropivacaine, mepivacaine, or bupivacaine HCl (at liposomal bupivacaine:bupivacaine HCl ratios <2:1), were observed. There were no clinically meaningful interactions, however, between liposomal bupivacaine and epinephrine, corticosteroids, antibiotics, non-steroidal anti-inflammatory drugs, tranexamic acid, or opioid analgesics.

A Proposed Multimodal Regimen for Total Hip Arthroplasty

As described earlier, opioid medications (including IV PCA delivery) may have significant limitations and can adversely affect certain patient populations (i.e. elderly patients) more so than others. Therefore, reduced reliance and decreased dosing of opioid analgesics in cognitively impaired patients for perioper-

ative pain management in total hip arthroplasty may be preferred and result in more optimal outcomes. As an example, by incorporating a multimodal analgesic regimen using liposomal bupivacaine infiltration into perioperative pain management where a neuraxial block was performed for intraoperative anesthesia (with or without intrathecal morphine 0.1 mg to 0.3 mg) has been proposed (**Figure 5**). In the example above, intraoperative spinal (using local anesthetics alone) and infiltration of liposomal bupivacaine prior to surgical site closure has indicated that the need for postoperative IV-PCA may be significantly reduced or eliminated for these patients recovering from total hip replacement.

A perioperative multimodal analgesic regimen begins with the appropriate premedication consisting of: celecoxib, and/or pregabalin, and/or a glucocorticoid, and/or intraoperative administration of adjunctive analgesia with IV acetaminophen or IV NSAID are suitable. An option for intraoperative surgical anesthesia with this approach could consist of a spinal using bupivacaine mixed with morphine 0.15 mg to 0.2 mg (dose of morphine is usually higher for patients recovering from knee arthroplasty than from a total hip replacement). It must be remembered that there is often a dose response with spinal morphine, so the higher the morphine dose, the greater the potential risk of side effects.

An ideal approach of an optimal comprehensive multimodal regimen would ensure that perioperative opioid requirements are kept to a minimum with the goal to reduce the adverse events profile(s). With a focus on this objective and goal to determine if short- and long-term influences from perioperative pain management may impact surgical outcomes, there are other anesthesia/analgesic options. In addition to the alternative approach of liposomal bupivacaine infiltration into the hip surgical site/wound tissue layers, administration of IV PCA opioids for the first postsurgical night followed by quick conversion to adjunctive reliance on non-opioid analgesics (IV acetaminophen and ketorolac, supplemented as necessary with oral opioids for breakthrough pain) may prove effective.

A Proposed Multimodal Regimen for Partial and Total Knee Arthroplasty

A similar perioperative analgesic regimen could be used in those patients presenting for total knee arthroplasty (**Figure 6**). Knee replacement surgery can often be considered more painful than hip replacement procedures requiring more total analgesics during the postoperative period. For knee replacement surgery, premedication would be the same as in hip replacement surgery (celecoxib and/or pregabalin and/or a glucocorticoid) and surgical anesthesia could also consist of a neuraxial blockade with local anesthetics mixed with an opioid adjunct. A higher dose of neuraxial opioid (morphine 0.2 to 0.3 mg for a knee) is usually required for knee arthroplasty. In
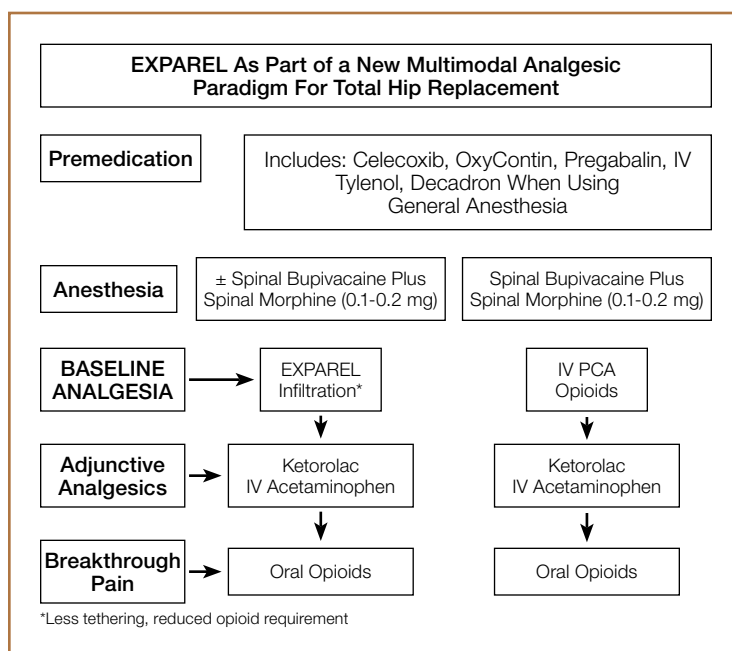
Figure 5. Liposomal Bupivacaine as Part of a Multimodal Analgesic Regimen for Patients Undergoing Total Hip Replacement
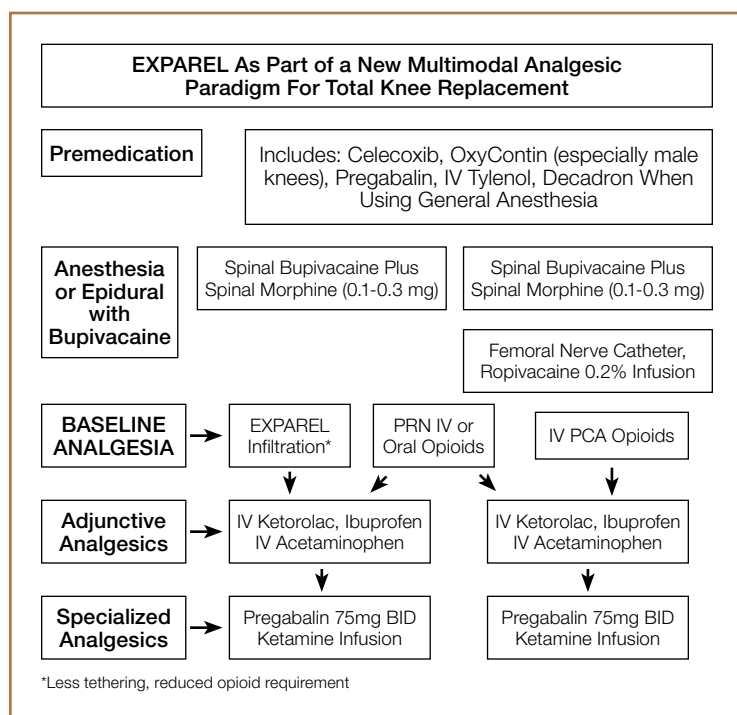
IV, intravenous; PCA, patient-controlled analgesia

addition, liposomal bupivacaine could be infiltrated into the tissue layers of the surgical site to achieve a more prolonged postoperative analgesic period.

An alternative perioperative analgesic regimen could consist of a femoral nerve blockade/catheter using plain local anesthetics (use during the immediate postoperative period) and liposomal bupivacaine infiltrated into tissue layers of the surgical site to achieve an extended duration of analgesic relief. In either of the selected anesthesia/analgesic plans, additional analgesia using IV or oral opioids can be provided as needed to treat analgesic gaps in addition to other adjunctive analgesia with IV acetaminophen and IV NSAID's. In addition, since knee replacement surgery is typically a more painful procedure (compared to hip replacement procedures), additional postoperative analgesia with pregabalin twice daily and a ketamine infusion should also be considered.

Anticipating and Planning for Postsurgical Pain

There are time periods when patients undergoing hip or knee replacement surgery(s) are at risk for inadequately controlled postoperative pain such as: when emerging from surgery, while in the PACU, when being transported within the hospital, and when being transitioned to home care management. When emerging from surgery, some patients can experience pain secondary to deficiencies of intraoperative analgesia.

Pain in the PACU can be a common problem secondary to under-utilization of analgesic medications or incomplete or absent regional blockade. In patients that have not received liposomal bupivacaine, one option would be to titrate analgesic medications such as IV opioids, IV acetaminophen,

EXPAREL As Part of a New Multimodal Analgesic Paradigm For Total Knee Replacement

Premedication — Includes: Celecoxib, OxyContin (especially male knees), Pregabalin, IV Tylenol, Decadron When Using General Anesthesia

Anesthesia or Epidural with Bupivacaine — Spinal Bupivacaine Plus Spinal Morphine (0.1-0.3 mg) | Spinal Bupivacaine Plus Spinal Morphine (0.1-0.3 mg) ; Femoral Nerve Catheter, Ropivacaine 0.2% Infusion

BASELINE ANALGESIA → EXPAREL Infiltration* | PRN IV or Oral Opioids | IV PCA Opioids

Adjunctive Analgesics → IV Ketorolac, Ibuprofen IV Acetaminophen | IV Ketorolac, Ibuprofen IV Acetaminophen

Specialized Analgesics → Pregabalin 75mg BID Ketamine Infusion | Pregabalin 75mg BID Ketamine Infusion

*Less tethering, reduced opioid requirement

Figure 6. Liposomal Bupivacaine as Part of a Multimodal Analgesic Regimen for Patients Undergoing Total Knee Replacement

BID, twice a day; IV, intravenous; PCA, patient-controlled analgesia; PRN, as needed

opioids have been extensively used for more than 2 decades, these particular agents when used alone do not provide a useful balance between efficacy and tolerability in most acute pain management settings. Because ORAEs have been determined to be dose-dependent, surgeons, anesthesiologists, and patients alike all share the same dilemma: sub-therapeutic opioids can be well tolerated yet provide inadequate pain relief, while higher opioid doses are more effective, but they can often elicit clinically significant adverse events. Therefore, alternative and additional analgesic regimen options that reduce opioid requirements will be embraced.

Multimodal analgesic regimens using a combination of medications and techniques have been shown to reduce reliance upon and avoid complications associated with high opioid consumption. However, additional research is still needed since our understandings toward pain as a complex phenomenon is only beginning to be formulated. Therefore, surgical pain medicine is currently best addressed when simultaneously targeting analgesic relief toward the host of known pain pathways responsible for the initiation, development, transmission, and potential wind-up of perioperative pain.

Sustained release liposomal bupivacaine is a newer addition to the analgesic armamentarium. With evolving evidence-based data, it may be determined that liposomal bupivacaine will prove pivotal and important as a major component of a multimodal regimen for perioperative pain management along with objective measures signaling the opportunity toward reduced dependence on opioids as the foundation of the pyramid for surgical pain treatment. Introduction of liposomal bupivacaine may also serve to be a heralding paradigm shift in which surgeons, working collaboratively with anesthesiology colleagues, will play a more significant role in perioperative pain management. In addition, perioperative healthcare providers must maintain an objective goal to reduce or eliminate pain and mediators responsible for pain development along with efforts to interrupt the cascade of events that have the potential to evolve into chronic postoperative pain. Therefore, with a focus on procedure- and patient-specific analgesic modalities (liposomal bupivacaine, neuraxial, and regional anesthetic techniques) and combating perioperative pain at multiple levels within the pain cascade (transduction, transmission, perception, etc.), results of post-surgical pain management experiences for patients will prove to emerge and yield superior surgical outcomes.

or IV ketorolac. An alternative approach to consider would be a repeat bolus of local anesthetic through an existing regional nerve block catheter or replacement of the nerve block if necessary. Pain in the PACU in patients treated with liposomal bupivacaine could be related to incomplete neuraxial blockade. For patients experiencing breakthrough pain in the PACU, regardless of whether they have received liposomal bupivacaine, the anesthesiologist should consider: 1) Titration of analgesic medication in relation to pain intensity; 2) Single dose neuraxial opioid (ex. spinal morphine, epidural hydromorphone, or fentanyl); or 3) Single-dose peripheral nerve blockade.

6. Summary

Despite improvements in pain management delivery systems and the emergence of more advanced analgesic options, more than 80% of patients undergoing surgical procedures today experience postoperative pain. It is now known that inadequate relief of postoperative pain following hip and knee replacement surgery can have profound clinical consequences, and can add to the already high economic burden of treatment by extending recovery time and length of hospital stay. Thus, the need for improved approaches to perioperative pain management in this setting is clear and compelling.

Overall effectiveness of any form of analgesic therapy consists of a balance between analgesic options, scientific knowledge, expertise, and perioperative team collaboration (efficacy, side effect profile, tolerability, expectations, etc.). Although

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