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Current and Novel Formulations of Bupivacaine for Formal Nerve Block Intended for Total Knee Arthroplasty

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CURRENT AND NOVEL FORMULATIONS OF BUPIVACAINE FOR FEMORAL NERVE BLOCK INTENDED FOR TOTAL KNEE ARTHROPLASTY

by

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Abstract

Total knee arthroplasty is a surgical procedure in which the knee joint is replaced with an artificial joint to relieve pain and improve range of motion. The prevalence of total knee arthroplasty is increasing in the U.S. and this type of surgery is associated with significant post-operative pain. The anesthetic management for total knee arthroplasty by Certified Registered Nurse Anesthetists (CRNA) can greatly impact the patient's recovery process from total knee arthroplasty. A comprehensive literature review of data on the administration of Bupivacaine, a local anesthetic, for total knee arthroplasty has been compiled. . Current literature on a new form of Bupivacaine, Liposomal Bupivacaine, has also been reviewed and discussed. Methods of compilation included resources from the Harley French Library at the University of North Dakota include: PubMed, CDC, and clinicaltrials.gov. Dissemination of the findings from this literature review will present the positive and negative effects of using Bupivacaine for postoperative pain relief after total knee arthroplasty and information about the current uses and prospective anesthetic treatments with Liposomal Bupivacaine.

Keywords: total knee arthroplasty, femoral nerve block, Bupivacaine, Liposomal Bupivacaine

Introduction

Total Knee Arthroplasty (TKA), better known as a knee replacement, is a rapidly growing orthopedic surgery in the United States. In fact, the Journal of Bone and Joint Surgery reported that the rate of total knee arthroplasty has doubled from 1999 to 2008 (Losina, Thornhill, Rome, Wright, & Katz, 2012). Increasing incidence of osteoarthritis (OA), particularly in the knee joint, can be attributed to an elderly population growth and increasing rates of obesity. Osteoarthritis, therefore, has contributed greatly to the incidence of this surgical procedure. A single predominant factor explaining this phenomenon, however, has not been identified (Losina et al., 2012). Lack of preventative medicine and limited medical management of knee osteoarthritis has led to the increased utilization of surgical management for this irreversible disease process.

This scholarly project will include a thorough review of the literature on the use of Bupivacaine and Liposomal Bupivacaine (a relatively new and novel local anesthetic) for femoral nerve block as a method of perioperative analgesia for total knee arthroplasty. The focus of the review will include the use of these agents for perioperative analgesia administered in conjunction with general and neuroaxial anesthesia for TKA.

Certified Registered Nurse Anesthetists (CRNAs) collaborate with surgeons regularly to create a plan of care for the effective and efficient anesthetic management of perioperative pain. Bupivacaine has been utilized for many years as a local anesthetic agent to decrease the

sensation of pain during TKAs. However, as medicine has progressed, new local anesthetics have been developed for peripheral nerve block; one of them being the transformation of Bupivacaine to Liposomal Bupivacaine. While this new pharmacological technology is still undergoing clinical trials for use in femoral nerve blockade, it is important for Certified Registered Nurse Anesthetists to be abreast of new medication advances and their potential for improving patient care. This review of the literature specifically will look at the older forms of Bupivacaine as well as the new and novel form of Bupivacaine, Liposomal Bupivacaine.

Purpose

The purpose of this scholarly project is to review the literature pertaining to anesthetic treatments of total knee arthroplasty with Bupivacaine. This project will serve as a conduit to inform CRNA's of current trends in the use of Bupivacaine for femoral nerve blocks intended for TKAs. This review will focus on the newest form of Bupivacaine, Liposomal Bupivacaine, which is currently in part one of two clinical trials for approval from the FDA for the use in femoral nerve blocks for TKA surgeries. It is the intent that the information obtained through this literature review will provide CRNAs with new and important knowledge regarding the use of Bupivacaine for femoral nerve block. Increased knowledge will allow the CRNA to choose local anesthetic agents better suited to each individual patient, therefore improving patient care. The results of this literature review were presented to CRNAs and student registered nurse anesthetists (SRNAs) at the biannual North Dakota Association of Nurse Anesthetists (NDANA) educational meeting in April 2013.

Significance

Osteoarthritis (OA) is a common form of arthritis often involving the knee joint. In fact, it is estimated that over 9 million adults have symptomatic knee OA (Lawrence et al., 2008). Advancing age and high BMIs, or obesity, are contributing factors (Losina et al., 2012). Osteoarthritis may be treated pharmacologically using non-steroidal pain medications and therapy, but often surgical joint replacement is necessary. Total knee arthroplasty (TKA) is an alternative management for knee osteoarthritis that can permanently relieve joint pain and restore a patient's activity level.

Certified registered nurse anesthetists (CRNAs) provide anesthesia for surgery and play a significant role in postoperative pain management. TKAs are known to result in severe postoperative pain (Allen, Liu, Ware, Nairn, & Owens, 1998). Appropriate management of this pain is of key importance to CRNA's and other anesthesia professionals. Femoral nerve blockade utilizing Bupivacaine (local anesthetic) is a technique that can be used to significantly help reduce this pain. Understanding the various formulations available for peripheral nerve blockade as a pain management technique is important for CRNAs and imperative to safe, quality patient care.

This project will address the uses of Bupivacaine, a local anesthetic, for perioperative pain management in patients undergoing TKA. Bupivacaine was approved for use in the 1960's, and within five years was limited in its dosage and uses due to adverse side effects (Ruetsch, Boni, & Borgeat, 2001). It is frequently used today despite its narrow therapeutic safety window because of its pharmacodynamic superiority in duration of action.

A new form of Bupivacaine, Liposomal Bupivacaine, will be discussed in this scholarly review. It is a sustained-release local anesthetic that has the potential to provide postoperative

analgesia for up to 72 hours with a decreased likelihood of systemic toxicity (Bergese et al., 2012). Liposomal Bupivacaine is currently in a clinical trial for use with femoral nerve block for TKA which is expected to be completed in July 2013. Liposomal Bupivacaine was approved for surgical wound infiltration in 2011 by the U.S. Food and Drug Administration (Chahar & Cummings, 2012)

Theoretical Framework

Katharine Kolcaba's "Theory of Comfort" was used as a conceptual framework for this paper. Comfort is a desired positive outcome in the perioperative setting. Kolcaba defines comfort as the immediate state of being strengthened by having the human needs for relief, ease and transcendence (types of comfort) addressed physically, pyschospiritually, socioculturally, and environmentally (contexts in which comfort is experienced) (Kolcaba & Wilson, 2002, p. 166)

Relief, the first state of comfort described by Kolcaba, can be clinically measured by having an identifiable discomfort lessened. For example, relief is experienced by a patient when their pain decreases. Kolcaba describes other discomforts such as feeling cold, postoperative nausea and vomiting, or anxiety. These are physical and psychological discomforts which can be expressed by patients and assessed and treated by nurses. They are measurable distresses and treatment outcomes for these discomforts can be clearly evaluated.

Ease, the second type of comfort identified by Kolcaba, is defined as the patient's sense of contentment about their diagnosis, treatment and prognosis. Nurses can improve a patient's sense of well-being by establishing a strong nurse to patient relationship, keeping open lines of communication and providing emotional support.

Transcendence is overcoming discomfort that could not be previously relieved. It is defined

by Kolcaba as a feeling that one can rise above problems or pain (Kolcaba & Wilson, 2002, p. 167). Nurses can promote transcendence with patients by encouraging resiliency with health hindrances. Motivation and the use of distraction techniques to help patients through distress that cannot be immediately alleviated is another way to achieve transcendence.

Kolcaba makes the claim that nurses should take a holistic approach to addressing a patient's discomfort. Kolcaba states that physical, emotional and environmental stressors compound each other to make the patient's state of mind worse. They are not separate entities; all discomforts will not just affect the physical condition of a patient, but also their mental, spiritual and sociocultural well-being.

Comfort is a major concern of CRNAs and anesthesia professionals during all the phases of the perioperative setting. Pain is a source of patient anxiety preoperatively (Kolcaba & Wilson, 2002). Pain should be reduced as much as possible intraoperatively and postoperatively to decrease the use of narcotic pain medication and complications after surgery and to decrease length of hospital stay. CRNAs and other anesthesia professionals have the opportunity to use Bupivacaine, a local anesthetic, to reduce pain intraoperatively and postoperatively in patients undergoing total knee arthroplasty. When administered as a peripheral nerve block, Bupivacaine can eliminate the pain and anxiety that may be created during the perioperative period.

Using a local anesthetic, such as Bupivacaine, for femoral nerve block to prevent and treat pain addresses all three types of discomfort described by Kolcaba's Theory of Comfort. The patient will ideally emerge from anesthesia with no pain in their operative leg. Choosing the appropriate local anesthesia agent will significantly determine the duration of that pain. Early mobilization is the standard of care in the rehabilitation of TKA patients. In fact, it is encouraged as early as four to six hours after surgery (Ibrahim, Khan, Nizam, & Haddad, 2013). Pain relief

will ease this process. Transcendence occurs when a patient can work through their limitations. Pain relief using local anesthetic via peripheral nerve block will help to bridge acute pain that occurs with TKA surgery until discomfort is tolerable.

Definitions

Pain: an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage (Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy, 1979). Pain can be classified according to pathophysiology (somatic, visceral or neuropathic), etiology (postoperative or oncologic), or by location in the body (abdominal pain or headache). Pain provides sensory information that alerts the body to respond to injury (Morgan, Mikhail, & Murray, 2006).

Total Knee Arthroplasty: Surgical replacement of malformed or degenerated knee joint with prosthetic implant (Jaffe & Samuels, 2009, p. 1014).

Local Anesthetics: A local anesthetic is a drug that can be injected into the epidural pace, subarachnoid space, skin or nerves for peripheral nerve blockade to induce the absence of pain sensation (Morgan et al., 2006, p. 270). Local anesthetics can also cause motor blockade (Morgan et al., 2006, p. 268).

Peripheral Nerve Block: Peripheral nerve block, also called regional nerve blockade, is the injection of local anesthetic near a nerve or specific plexus of nerves that requires the positioning of a needle in the perineural sheath followed by the injection of local anesthetic to provide sensory and motor blockade (Morgan et al., 2006, p. 325).

Femoral Nerve Block: Peripheral nerve block used to provide anesthesia for the anterior thigh, knee, and a small part of medial foot (Morgan et al., 2006, p. 344). It is commonly used for postoperative pain relief following knee surgery.

Process

The research for this project was compiled using the electronically accessible library from the University of North Dakota's Harley E. French Library of the Health Sciences. A comprehensive review of the literature was completed between the months of October 2012 through March 2013. Cochrane library, PubMed, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were employed to perform the search. Keywords or medical subject headings (MeSH) used included: Bupivacaine, Liposomal Bupivacaine, femoral nerve block and total knee arthroplasty. During the search various keywords were combined and/or interchanged to see if they would yield different results. The search resulted in studies that were performed on humans and a current clinical research trial on Liposomal Bupivacaine. Foundational research on the use of Bupivacaine and pain were included in this literature project.

The outcomes of this independent project were presented using a power point presentation at the North Dakota American Association of Nurse Anesthetists (NDANA) educational meeting on April 19th, 2013. CRNAs and student registered nurse anesthetists (SRNAs) who practice and study in the state of North Dakota listened to the dissemination of this literature review. Additionally, the findings of this paper were presented to SRNAs at a Midwestern nurse anesthesia program.

Darla Adams, CRNA, PhD, the program director for the Nurse Anesthesia Track at the University of North Dakota, was faculty advisor on this independent project. She approved the initial project proposal, provided critique and evaluation of the paper, and offered direction until the final draft was submitted to the graduate office.

Review of the Literature

Total knee arthroplasty (TKA) is a common surgical procedure used to treat osteoarthritis in adult patients. Osteoarthritis is compounded by advancing age and obesity, among other things. Total knee arthroplasty is associated with significant perioperative pain for the patient requiring careful management by CRNAs and other anesthesia professionals. Peripheral nerve blocks using Bupivacaine and the new, long-acting Liposomal Bupivacaine can play a significant role in the management of both intraoperative and postoperative pain in total knee arthroplasty patients. The review of literature for this project will focus on the multimodal management of total knee arthroplasty pain utilizing Bupivacaine and Liposomal Bupivacaine.

Prevalence of Osteoarthritis and Total Knee Arthroplasty

Many Americans suffer from stiff, aching and painful joints. The most common cause for these symptoms is osteoarthritis. Osteoarthritis is defined as the normal wear and tear on joints that results in the breakdown of the cartilage between the bones (Losina et al., 2012). As the cartilage wears away, the bones rub against each other and this leads to arthralgia, or joint pain. A national health and examination survey done in 2008 by the National Institutes of Health determined that 12.1% of the U.S. population ages 25-74 years of age have clinically diagnosed osteoarthritis (Lawrence, et al., 2008). A common location for osteoarthritis and arthralgia is the knee. Osteoarthritis of the knee cannot be cured; it is a progressive disease that will get worse over time. However, the symptoms can be treated medically to delay the necessity of surgery.

When medications, changes in lifestyle, and physical therapy no longer suppress the symptoms of osteoarthritis in the knee, patients with severe pain may require surgery to replace the knee joint. A total knee arthroplasty (TKA) is the replacement of the knee joint to eliminate

joint pain. The prevalence of TKA has been dramatically increasing over the past fifteen years. The Journal of Bone and Joint Surgery stated that in 2008, 615,050 patients had TKA surgery (Losina, et al., 2012). The number of patients requiring total knee surgery is rapidly increasing. The Centers for Disease Control and Prevention (CDC) reported in 2009 that the number of TKAs performed in the U.S. had jumped to 676, 000 surgeries (Centers for Disease Control and Prevention, [CDC], 2012). This reflects a difference of 60,950 patients in one year. This increase in patients undergoing TKA accounts for a large percentage of the total surgical procedures annually. The CDC estimates that from 1999-2010, total and/or partial knee replacements for patients eighteen years and older accounted for 28.7% of all hospital procedures in the U.S. (CDC, 2010).

While a single definitive cause has not been identified to explain the growing number of patients having knee surgery, a combination of health factors are believed to contribute. "With the aging of the population, rising prevalence of obesity, and lack of definitive treatments to prevent the disease or halt its progression, the public impact of osteoarthritis continues to grow" (Neogi, 2012, p. 95). It is anticipated that the necessity for surgical treatment for these patients will continue as will the need to effectively manage the pain associated with TKA.

Causes of Pain Associated With Total Knee Arthroplasty

A total knee arthroplasty (TKA) is the replacement of the knee joint with a prosthetic implant (Jaffe & Samuels, 2009, p. 1014). Before the surgeon makes an incision on the knee, a tourniquet is applied to the surgical thigh. This is done to aid surgical exposure by decreasing the amount of blood loss during the case and creating a dry surgical field. After the tourniquet is applied and inflated, incision will be made by the surgeon and the intra-articular tissues are removed. The surgeon then removes bone from the femur and tibia at the level of the joint line to make space

for the prosthesis. After the prosthesis is placed, tracking of the knee will be assessed by the surgeon. The tourniquet will be released to allow for hemostasis.

Extensive tissue damage and discomfort experienced from application of a tourniquet to the thigh yields TKA's as a very painful orthopedic procedure. The direct pressure placed on the soft tissues and nerves by the tourniquet cause pain to the lower leg (Tai et al., 2011). As the tourniquet is released, limb swelling caused by rapid hyperpefusion to the lower leg also contributes to the pain experienced by the patient (Tai et al., 2011). Surgical incisions also damage soft tissue and sever nerves. It was stated in Knee Surgery and Related Research Journal in 2012 that approximately half of the patients who undergo a TKA present with extreme pain after surgery (Korean Knee Society, 2012). The prevalence of TKA's and high rates of postoperative pain are alarming; focused attention on methods to reduce its occurrence and safe recovery is a concern from an anesthetic stand point.

Inappropriate postsurgical pain can lead to dangerous complications during the recovery process. Postsurgical pain negatively affects the endocrine, pulmonary, cardiac, and gastrointestinal systems. The immediate endocrine response of the human body to pain is the release of the hormones cortisol, glucagon, growth hormone, and circulating catecholamines. The increased levels of these hormones in the body results in immunosuppression, increased metabolic demands, and strain on the cardiovascular system (Korean Knee Society, 2012). Severe pain also leads to immobilization (the primary cause of thrombus formation), decreased pulmonary function (leading to atelectasis and pneumonia), and gastrointestinal complications (such as ileus). Methods to decrease these pathological processes are a primary concern for anesthesia practitioners when managing TKA cases. Current guidelines for the management of postoperative pain after TKA recommend the use of femoral nerve block as an effective adjunct

to postoperative pain (The New York School of Regional Anesthesia, 2009). An understanding of the innervations and anatomy of the lower leg has led to the use of local anesthetics to prohibit nerve conduction of pain through the femoral nerve in an attempt to decrease pain transmission and the above mentioned postoperative complications.

Pertinent Anatomy and Peripheral Nerve Block for Total Knee Arthroplasty

The knee is innervated by the lumbar plexus and lumbosacral plexus located in the pelvis (Brown, 2006, p. 91). The goal of anesthesia for TKA is to block sensory and motor sensation intraoperatively and provide analgesia postoperatively. Blocking the femoral nerve will prevent pain sensation in the anterior aspect of the thigh, knee and medial aspect of the leg below the knee, all of which are areas needed for TKA (Storm, 2012, p. 157). Bupivacaine, a long-acting local anesthetic, can be used for lower leg sensory blockade and can provide postoperative analgesia for up to 12 hours after surgery when administered as a femoral nerve block in TKA patients (Bergese et al., 2012). While this is the longest-acting local anesthetic available for postoperative pain relief at this time, patients often still have significant pain that lasts for days after their femoral nerve block has worn off. The pain experienced by patients could interfere with their recovery process. Bupivacaine also has dangerous systemic side effects that have limited its dose and use among anesthesia providers.

Bupivacaine

Local anesthetics are drugs that produce reversible conduction blockade of impulses along peripheral nerve pathways after regional anesthesia administration (Stoelting & Hillier, 2006). Metabolism of the local anesthetic results in spontaneous and complete return of the nerve conduction with no evidence of structural damage to nerve fibers as a result of the drug's effects (Stoelting & Hillier, 2006, p. 179).

Bupivacaine is a potent local anesthetic used in femoral nerve block for the treatment of TKAs. While it does have a slow onset to sensory deficit, approximately 50 minutes (Fanelli et al., 1998), it provides the longest duration of action of all local anesthetics currently approved by the FDA. It is estimated to provide 240-480 minutes of dense sensory analgesia after administration (Stoelting & Hillier, 2006, p. 181). It provides varying levels of continued analgesia for up to 6-12 hours, depending on the individual patient (Bergese et al., 2012). The high potency and slow metabolism of Bupivacaine is the determinant of its efficacy and duration of action.

While this accounts for its favorability towards providing the longest postoperative pain relief, there are drawbacks to its safety profile for the same reason. The slow metabolism of Bupivacaine means that there will be sustained increases of the drug in the plasma, putting the patient at risk for systemic toxicity (Stoelting & Hillier, 2006, p. 185). Over the past several years of its use as a local anesthetic for peripheral nerve blockade for TKA's, a well-documented association has been made between high plasma concentrations of Bupivacaine and cardiovascular and neurological changes (Bergese et al., 2012, p.1). These side effects can be as serious as seizures, coma, cardiac or respiratory arrest (Lui & Chow, 2010). Concerns exist regarding Bupivacaine's safety and effectiveness, prompting numerous comparative studies against other local anesthetics available for use. The findings of several studies have motivated researchers to look for less toxic alternatives.

A foundational study comparing Bupivacaine used for femoral and sciatic peripheral nerve blocks to Mepivacaine, Lidocaine, and Tetracaine was reviewed for this independent project. Investigators for this study used thirty-five patient participants having lower leg surgery whom received bilateral femoral and sciatic nerve blocks. The individual patient was used as their own

control group by blocking one leg with Bupivacaine and the other leg with one of the following local anesthetics: Lidocaine (six patients), Mepivacaine (five patients), Mepivacaine plus Tetracaine (four patients), or Tetracaine (twenty patients). The results from this study concluded that the duration of action of Bupivacaine was two to three times longer than that of lidocaine, Mepivacaine or Tetracaine from the time of injection to regression of sensation and then to complete return of sensation (Moore, Bridenbaugh, Bridenbaugh, & Tucker, 1970). While this study clearly showed that Bupivacaine had the longest duration of action, it was a small sample group size for a prospective study. The authors do not disclose whether subjects were randomly chosen, or describe details of the study design (double-blind study, etc.). This study was published just after Bupivacaine was authorized for use in the U.S. in 1965 (Ruetsch et al., 2001). The soon to follow reports of cardiovascular and central nervous system toxicity led to restrictions on its use. Guidelines directed towards prevention of systemic toxicity were developed by the FDA (Ruetsch et al., 2001).

Local anesthetics have evolved since the study mentioned above. Ropivacaine, for example, was developed and quickly became a local anesthetic of choice due to its comparable duration of action to Bupivacaine, with decreased cardiotoxic side effects. A recent study done by the International Anesthesia Research Society (2008) compared the pharmacodynamics and pharmacokinetics of Bupivacaine vs Ropivacaine and their equal volume mixtures with Lidocaine for femoral and sciatic blocks. This study was spurred by a disturbing correlation associating Bupivacaine with patient seizures and cardiac arrest due to high plasma concentrations of the drug. This particular study was a controlled, double-blind, randomized study combining data from eighty-two patients that compared the time of onset, efficacy, and plasma concentrations of Bupivacaine, Bupivacaine plus Lidocaine, Ropivacaine, and

Ropivacaine plus Lidocaine (Cuvillon et al., 2009). The results were a conundrum. The mixtures of Bupivacaine with Lidocaine and Ropivacaine with Lidocaine had a significantly faster onset of sensory analgesia than individually administered Bupivacaine and Ropivacaine when used for femoral and sciatic block. However, femoral and sciatic blocks using Bupivacaine or Ropivacaine provided longer duration of action postoperatively. The purpose of combining Bupivacaine and Ropivacaine with Lidocaine was to evaluate if combining a smaller amount of Bupivacaine or Ropivacaine (more concentrated local anesthetics) with Lidocaine (less concentrated) would decrease plasma concentration levels and therefore decrease the likelihood of systemic toxicity. The results of this study determined that the effects of having a lower concentration of Bupivacaine or Ropivacaine mixed with Lidocaine did not decrease the likelihood of systemic toxicity (Cuvillon et al., 2009). This study established that the combining of local anesthetics has an additive effect. "If the toxicities of local anesthetics are additive, then the apparent safety of reducing the concentration of Bupivacaine or Ropivacaine may be offset by the additional toxicity of Lidocaine (Cuvillon et al., 2009, page number). The results of this study were compared using a two-tailed t test with a P value of <0.05%.

Another prospective, randomized, double-blind study done by the Department of Anesthesiology in Milan, Italy (1998) investigated the use of 0.75% Ropivacaine, 0.5% Bupivacaine, and 2% Mepivacaine for onset and duration during sciatic and femoral nerve block. This study had forty-five patient participants with a similar ASA physical status undergoing lower extremity surgery with the use of a tourniquet. Data on the time of onset for sensory and motor block on the operative limb, resolution of motor block, onset of postsurgical pain and time of first analgesic requirement were collected. It was determined from this information that Ropivacaine had a shorter onset than Bupivacaine. In fact, the study demonstrated that

Bupivacaine had a fifty minute onset of action for sensory and motor blockade, where as Ropivacaine had a fifteen minute onset (Fanelli et al., 1998, p. 599). Results from this study also determined that the 0.75% Ropivacaine and 0.5% Bupivacaine provided prolonged analgesia with a significant decrease in analgesic requirements compared to 2% Mepivacaine. "Because quick onset of the block and prolonged postoperative analgesia are important goals in regional anesthesia, results of the present study suggest that 0.75% Ropivacaine is the most suitable choice of local anesthetic for combined sciatic-femoral block, providing an onset similar to Mepivacaine and post operative analgesia intermediate between Bupivacaine and Mepivacaine." (Fanelli et al., 1998, p. 600). Limitations of this study included that only hallux valgus repair procedures were utilized and a small number of participants were studied.

Liposomal Bupivacaine

Patients can experience pain that lasts for many days after total knee arthroplasty (Golf, Daniels, & Onel, 2011, p. 785). Traditional Bupivacaine provides pain relief for approximately 6 - 12 hours postoperatively, leaving the patient to rely on other pain control methods such as systemic opioids (Dasta et al., 2012, p. 5). Liposomal Bupivacaine is a new formulation of Bupivacaine; it not only holds the promise to provide a longer duration of action than current long-acting local anesthetics (greater than Bupivacaine and Ropivacaine), but also to do so with decreased plasma concentration levels and risk of systemic toxicity. This makes it an effective treatment for post operative pain with less chance of systemic toxicity. In fact, Liposomal Bupivacaine will last significantly longer than traditional Bupivacaine, therefore providing longer postoperative pain relief over the acute recovery period, when patients need it the most (Dasta et al., 2012, p. 5).

Liposomal Bupivacaine is a local anesthetic that has been incorporated into a new

pharmacological technology which provides 72-96 hours of postoperative analgesia without cardiovascular or central nervous toxicity side effects (Stoelting & Hillier, 2006, p. 179). Liposomal Bupivacaine's novel new drug design, the DepoFoam® delivery system, is the reason for this pharmacological advancement (Naseem et al., 2012, p. 2). It is described by Naseem at al. in the Journal of Clinical Pharmacology as "microscopic, spherical, lipid-based particles composed of a honeycomb of numerous, nonconcentric, internal aqueous chambers containing the encapsulated drug. Each chamber is separated from adjacent chambers by lipid membranes. In vivo, the DepoFaom® particles release the drug over an extended period of time by erosion and/or reorganization of the particle lipid membranes (Naseem et al., 2012, p.2). In essence, Liposomal Bupivacaine diffuses out of liposomal membranes in a slow-release fashion. This extends its duration of action and keeps plasma concentrations of this potent local anesthetic at a safer level for humans.

Liposomal Bupivacaine was approved for use in the U.S. by the FDA in 2011 for surgical wound infiltration (Chahar & Cummings, 2012). A randominized, placebo-controlled trial of DepoFoam® was done by Golf, Daniels, and Onel (2009) for wound infiltration in bunionectomies. The researchers found that patients whom received Liposomal Bupivacaine by means of wound infiltration had a significantly decreased need for opioid pain medication in the first twenty-four hours after surgery. They also found that patients who received wound infiltration with Liposomal Bupivacaine had less pain at thirty-six hours after surgery than those whom received the placebo. The authors described Liposomal Bupivacaine as being well tolerated. There were no serious adverse events during this study. The most common side effects described were nausea, vomiting, dizziness, headache, and generalized puritis (Golf et al., 2011, p. 783). There was no evidence of poor surgical healing after the use of Liposomal Bupivacaine

on follow up visits four to six weeks after surgery (Golf et al., 2011, p. 784). The conclusion of this article supported the fact that Liposomal Bupivacaine provided extended pain relief post surgically with decreased use of opioid medication and a safe side effect profile.

A similar study done on the use of Liposomal Bupivacaine for wound infiltration with hemorroidectomy patients had similar results. This was a multicenter, randominized, double-blind, placebo-controlled trial done in 2009. Pain scores, first dose of opioid medication, and safety data were monitored. The results concluded that pain scores were lower for the first 72 hours after surgery for those whom received Liposomal Bupivacaine versus the placebo (Gorfine, Onel, Patou, & Krivokapic, 2011). The researchers also determined that 59% of patients remained opioid free the first twelve hours after surgery and the overall consumption of opioid pain medication was reduced (Gorfine et al., 2011). No significant adverse effects were reported.

Wound infiltration with Liposomal Bupivacaine for TKA has also been investigated. A randominized, double-blind, dose-ranging study done between 2007 and 2009 on Liposomal Bupivacaine was completed by Bramlett, Onel, Viscusi, and Jones (2012). The authors revealed that the highest dose of this local anesthetic provided postoperative analgesia ranging from twelve hours to as much as five days. Opioid pain medication use was also decreased. The most common side effect reported was nausea. This study compared patient outcomes of those receiving Liposomal Bupivacaine and Bupivacaine. There were two deaths associated with the study that could have been related to the administration of Bupivacaine and Liposomal Bupivacaine. One patient received traditional Bupivacaine and suffered a pulmonary embolism, and another patient received Liposomal Bupivacaine and experienced hemorrhagic cystitis (Bramlett, Onel, Viscusi, & Jones, 2012).

In September, 2012, the U.S. National Institutes of Health approved a research study on the safety, efficacy, and pharmacokinetics of Liposomal Bupivacaine for patients undergoing TKA with general anesthesia or spinal anesthesia and concurrent femoral block. It has not been completed but is designed as a multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose ranging study to evaluate single injection femoral nerve block with Liposomal Bupivacaine for postsurgical analgesia in subjects undergoing TKA (U.S. National Institutes of Health, 2013).

This study is designed to be carried out in a two part fashion. The goal of part one of this research is to determine the optimal dose of Liposomal Bupivacaine to be used for femoral nerve block. One hundred subjects will be randomly chosen to receive one of three doses of a single-dose injection of Liposomal Bupivacaine via femoral nerve blockade: 67mg, 133mg, or 266mg. Some of these patients will also receive a 20ml placebo dose of preservative free normal saline. The purpose of part one of this study is to evaluate the dose of Liposomal Bupivacaine compared to the placebo dose to determine the extent and duration of analgesic effect. Once this information is obtained, part two of the study will begin. Part two of the research will study the efficacy and safety of the "best" dose determined by part one.

The study has four main focuses. First, to document patient pain scores via the numeric rating score (NRS) while at rest for the first 72 hours postoperatively. Second, to document the total postsurgical consumption of opioids. Third, to document the time to first opioid rescue and lastly to monitor the safety data of Liposomal Bupivacaine. This study was started in September 2012 and is expected to be completed in June 2013. Outcome measures and final data from the study are estimated to be posted to the public by the U.S. National Institutes of Health in July 2013.

Discussion

Local anesthetics administered as femoral nerve block are used as part of a comprehensive perioperative pain management plan for patients undergoing total knee arthroplasty. Bupivacaine is the longest acting local anesthetic that is approved by the FDA and currently in use for femoral nerve blockade. However, the duration of action of this medication does not outlast the pain patients experience during the recovery process. Inadequate pain relief can lead to a host of recovery difficulties and unpleasant experiences for the patient; and the cardiotoxic and neurotoxic side effects can be detrimental (Korean Knee Society, 2012). Therefore, current guidelines recommend using opioid medications up to ninety six hours post-operatively to promote healing and quicker mobilization (Bramlett et al., 2012), p. 530). It must be taken into consideration that opioid pain medications carry their own risks. This has lead to the search for improved multimodal therapies.

The introduction of Liposomal Bupivacaine, essentially Bupivacaine placed into new DepoFoam® technology, allows for the extended release of the local anesthetic. It has been safely used in the infiltration of postsurgical wounds since it was approved by the FDA in 2011. It is currently undergoing clinical trials to be used as an agent for femoral nerve blockade in TKA patients. This medication holds promise for decreasing the amount of pain TKA patients experience post-operatively, decreasing the amount of overall opioid use, and providing an improved safety profile when compared to traditional Bupivacaine.

Outcome

The intent of this literature review was to provide CRNA's with current information about the use of Bupivacaine for femoral nerve block for TKA. The advancement of local anesthetic technology resulting in the novel local anesthetic Liposomal Bupivacaine is also discussed in this

literature review. This information was disseminated to CRNAs and University of North Dakota SRNAs at the North Dakota Association of Nurse Anesthetists on April 19th, 2013. It was also presented to nurse anesthesia students at a Midwestern University.

The responses to the presentations were positive. The attendees were aware of the cardiotoxic and neurotoxic side effects associated with Bupivacaine. Most attendees stated that they were currently using Ropivacaine for a long-acting local anesthetic for femoral nerve blocks with TKA patients. Based on the response from those attending the presentation, it was evident that the majority were unfamiliar with the new drug Liposomal Bupivacaine or with DepoFoam® technology. Attendees were excited about the new information and the potential future opportunity to use it clinically. There were questions regarding the density of sensory and motor block of Liposomal Bupivacaine. The dissemination of this material was well received and informative to the anesthesia professionals in attendance at the North Dakota Association of Nurse Anesthetist conference.

Interpretation

Pain experienced after TKA is often intense, lasting for days after the procedure. It can hinder the recovery process and leave patients at risk for postoperative complications. Femoral nerve blocks are frequently used in conjunction with general or neuroaxial anesthesia to alleviate this pain. However, current local anesthetics used for femoral nerve blocks only bridge the acute pain felt by patients in the first six to twelve hours postoperatively.

Bupivacaine is the longest acting local anesthetic currently approved by the FDA for femoral nerve block administration by anesthesia providers (Stoelting & Hillier, 2006, p. 181). The interpretation and analysis of Bupivacaine for femoral nerve block clearly shows that it useful and effective based on its long duration of action. However, it does not last long enough to

relieve acute pain past twelve hours and its side effects are undesirable. Serious cardiotoxic and neurotoxic side effects have discouraged its use by many anesthesia providers (Bergese et al., 2012, p.1). This has lead to the continuous search for postoperative pain relief that is safer and will last longer into the recovery process.

Recently a new and novel formulation of Bupivacaine has been introduced into the clinical practice. It is currently being used for surgical wound infiltration and is providing pain relief for up to 72 hours (Stoelting & Hillier, 2006, p. 179). This medication was approved for skin infiltration by the FDA in 2011 and has shown to have a safer index of use (Naseem et al., 2012, p.5).

Liposomal Bupivacaine is currently undergoing clinical research to be used for pain relief in femoral nerve block with total knee arthroplasty patients. If approved for clinical use Liposomal Bupivacaine may bridge the gap between acute pain and tolerable pain for patients undergoing painful knee joint replacement. The length of local anesthetic action greatly exceeds Bupivacaine, and could significantly reduce postoperative pain for TKA patients (Gorfine, Onel, Patou, & Krivokapic, 2011)..

Implications for Nursing

It is the goal of Certified Registered Nurse Anesthetists to administer the safest and most effective postoperative analgesia possible to patients. Femoral nerve blocks are frequently used in conjunction with general or neuroaxial anesthesia to alleviate the pain associated with total knee arthroplasty. Successful management of this pain allows for a reduction in opioid medication consumption and the negative side effects (nausea and vomiting) associated with their use. Unfortunately, to date, successful pain relief utilizing femoral nerve blocks is limited by the duration of action of the widely used local anesthetics, even with the longest acting local

anesthetic approved for use (Bupivacaine). It is imperative that CRNAs are aware of the uses and limitations of traditional Bupivacaine as well as the potential uses for the promising new formulation, Liposomal Bupivacaine. Liposomal Bupivacaine may be used in the future by CRNAs to provide extended pain relief without the dangerous, undesirable side effects of traditional Bupivacaine.

The information in this review significantly impacts nursing education and research. Many of the CRNAs who were present during the dissemination of this project were not even aware of the development of Liposomal Bupivacaine. This review provided much need education and informed anesthesia providers of the new pharmacological technology currently being clinically tested for use in femoral nerve blocks for TKA patients. It also made them aware that Liposomal Bupivacaine is already in use for postsurgical wound infiltration.

The research of this topic provided a wealth of information on Bupivacaine and Liposomal Bupivacaine. This straightforward topic revealed research that described the current pros and cons of traditional Bupivacaine. The literature review also clearly described Liposomal Bupivacaine's profile, current uses with FDA approval, and clinical trials for future use. Research was clearly lacking on the use of Liposomal Bupivacaine for femoral nerve block because of the lack of FDA approval. Following FDA approval more research will be needed to clearly identify the clinical usefulness of this agent. Anesthesia providers who perform femoral nerve blocks will benefit from the knowledge gained by future research regarding Liposomal Bupivacaine.

Summary/Conclusions

Bupivacaine is a local anesthetic that has been used clinically for almost fifty years for a variety of anesthetic procedures including femoral and sciatic nerve block for TKA. Bupivacaine has some excellent characteristics such as dense motor block and sensory analgesia, long duration of action, low cost, and familiarity to CRNAs. Unfortunately, Bupivacaine also has some significant disadvantages associated with it. Dangerous side effects, such as cardiotoxicity and neurotoxicity can be life threatening to patients. In fact, according to Lui and Chow (date), Bupivacaine is known to reach high plasma concentration levels in the body that can lead to seizures, cardiac arrest, and respiratory failure (citation).

While Bupivacaine is primarily utilized for its long duration of action, this benefit may not outweigh the risks of its use. Although it limits the initial pain experienced by patients undergoing TKA, the severe pain that patients experience can last for days, well beyond the duration of action of traditional Bupivacaine. Bupivacaine will provide between 6 –to12 hours of sensory analgesia or pain control (Bergese et al., 2012). The adverse side effects associated with Bupivacaine account for the current trend of CRNAs and other anesthesia providers turning to Ropivacaine for femoral nerve block (Fanelli et al., 1998, p. 599).

Although traditional Bupivacaine has several significant disadvantages that discourage anesthesia providers from using it, it still has clinical value when used safely. The new and novel drug formulation, Liposomal Bupivacaine, has been designed to eliminate the negative safety profile associated with traditional Bupivacaine. Liposomal Bupivacaine was created using DepoFoam® technology which allows for the slow, incremental release of Bupivacaine into the body (Naseem et al., 2012), p. 2). Consistent, small doses of Bupivacaine are released at the

injection site to provide sensory analgesia for up to 72 hours, without the risk of systemic toxic side effects (seizures, cardiotoxicity or neurotoxicity (Stoelting & Hillier, 2006, p. 179).

Liposomal Bupivacaine has been used successfully since 2011 for surgical wound infiltration (Chahar & Cummings, 2012). Clinical research is currently being completed for its use in peripheral nerve blocks; specifically, femoral nerve block for total knee arthroplasty. These clinical trials are looking at pain score ratings, safety data, and the need for supplemental opioid pain medications. It is anticipated that Liposomal Bupivacaine will be found to successfully diminish postoperative TKA pain for longer periods of time resulting in a reduction in opioid use. This information will be released to the public and the FDA in July 2013.

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