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MINIREVIEW

Neurological structures and mediators of pain sensation in anterior cruciate ligament reconstruction

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ABSTRACT

Anterior cruciate ligament (ACL) tears is a devastating injury and one of the most common knee injuries experienced by athletes in the United States. Although patients reach maximal subjective improvement by one-year following ACL reconstruction, many patients often experience moderate to severe post-operative pain. Opioids, intra-articular injections, and regional anesthesia have been previously implemented to mediate post-operative pain. However, chronic opioid usage has become an epidemic in the United States. Alternative analgesic modalities, such as nerve blocks, have been implemented in clinical practice to provide adequate pain relief and minimize opioid usage. Periarticular injections targeted towards local neurological structures performed concomitantly with nerve blocks provides superior pain relief and satisfaction than isolated nerve blocks. Therefore, it is imperative for physicians to understand local neurological anatomy around the knee joint in order to provide adequate analgesia while minimizing opioid consumption. This purpose of this investigation is to summarize (1) neurogenic origins of pain generators and mediators in sites affected by ACL reconstruction and autograft harvest sites and (2) analgesia utilized in ACL reconstruction.

1. Introduction

Anterior cruciate ligament (ACL) tears are one of the most common traumatic knee injuries experienced by athletes in the United States (Sanders et al., 2016). Following ACL reconstruction, patients reach maximal subjective improvement by one-year post-operatively (Agarwalla et al., 2018); however, many patients often experience moderate to severe post-operative pain (Lynch et al., 2019). The incidence of pain following ACL reconstruction varies between technique and graft choice; however, 76% of patients with bone-patellar tendon-bone autografts experienced pain on post-operative day zero while 43% of patients with hamstring autografts experienced pain at the same point in time (Okoroha et al., 2016a). As ACL reconstruction shifts towards the outpatient setting (Mall et al., 2014), it is imperative to appropriately manage pain since controlled perioperative pain may improve satisfaction and outcomes (Kocher et al., 2002). Opioids, intra-articular injections, and regional anesthesia have been previously implemented to improve post-operative pain following ACL reconstruction (Lynch et al., 2019). Although these analgesic modalities are efficacious, each has inherent advantages and limitations that have prevented establishment of a standard protocol for pain management following ACL reconstruction.

Femoral nerve blockade (FNB) has traditionally been used following ACL reconstruction due to its efficacy as an analgesic (Runner et al., 2018; Secrist et al., 2016; Woods et al., 2006). Although FNB reduces pain and opioid consumption following knee surgery, it is associated with quadriceps weakness and nerve palsies (Chan et al., 2014; Krych et al., 2015; Luo et al., 2015), which may delay limb mobilization and prolong recovery times (Krych et al., 2015; Luo et al., 2015). Early mobilization is imperative as it has been associated with improved outcomes following ACL reconstruction regardless of treatment modality (Secrist et al., 2016).

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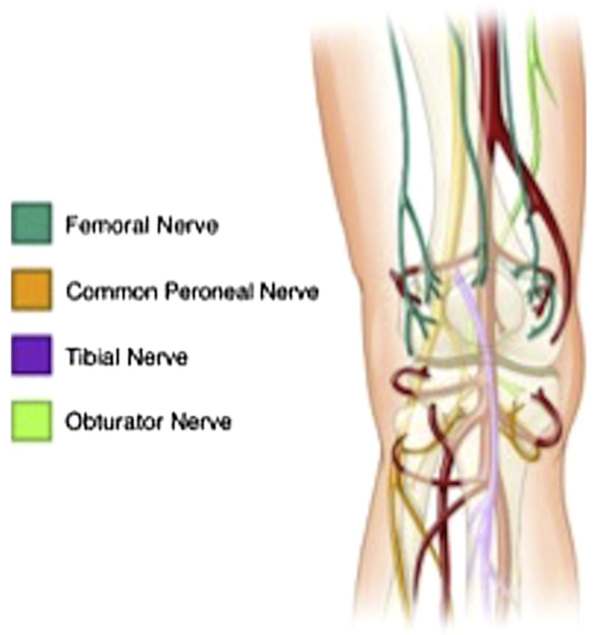

Fig. 1. Neurovascular anatomy of the knee joint. Deep branches of femoral nerve (turquoise); common peroneal nerve (orange); tibial nerve (purple); obturator nerve (green). Left: anterior view in relation to blood supply of popliteal artery (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

More recently, adductor canal blockade (ACB) has been proposed as an alternative regional anesthetic that provides sensory blockade while preserving quadriceps muscle strength (Abdallah et al., 2016). Furthermore, local infiltration analgesia (LIA), where non-narcotic painkillers are injected locally, may provide an alternative analgesic modality or supplementation to traditional nerve blocks. LIA may be injected into the joint space, donor autograft sites, or targeted to local neurological structures and has been effective in pain management following ACL reconstruction (Fauno et al., 2015; Koh et al., 2012; Kristensen et al., 2014; Kurosaka et al., 2018; Okoroha et al., 2016b).

Regional or local anesthesia have demonstrated significant efficacy in providing targeted pain relief; however, it is imperative to review mediators and generators of pain sensation in ACL reconstruction and graft harvest sites in order to optimize pain control with traditional nerve blocks and local infiltrative analgesia. This purpose of this investigation is to summarize (1) neurogenic origins of pain generators and mediators in sites affected by ACL reconstruction and autograft harvest sites and (2) analgesia utilized in ACL reconstruction.

1.1. ACL and knee joint neurovascular anatomy

The infrapatellar branch of the saphaneous nerve originates at the knee joint and provides sensory innervation to the skin surrounding the patella, medial to the knee, and the patellar ligament (Pekala et al., 2017). However, the infrapatellar branch of the saphaneous nerve exists variably amongst patients (Burckett-St Laurant et al., 2016), rarely exists as a solitary nerve (Kalthur et al., 2015) and contributes to a deep nerve plexus (Gardner, 1948). The neurovascular anatomy of the knee joint is provided in Fig. 1.

The nerve to the vastus medialis exists the adductor canal and delivers several branches to the knee. The most proximal branch supplies the anterior capsule superior to the patella, while the remaining branches supply the medial capsule (Burckett-St Laurant et al., 2016). Both the saphaneous nerve and the nerve to the vastus medialis form a plexus that gives rise to the anterior and medial genicular nerves, which innervate the deep anteromedial joint capsule (Burckett-St Laurant et al., 2016). Furthermore, Burkett-St. Laurant et al. observed that no terminal branches of the obturator nerve innervated the knee joint capsule (Burckett-St Laurant et al., 2016). However, it has previously been shown that branches of the obturator nerve contribute to knee innervation in 11% of cases (Horner and Dellon, 1994). These branches of the obturator nerve join segments of the saphaneous nerve to create the subsartorial plexus (Burckett-St Laurant et al., 2016).

The ACL is innervated by the nerve fibers from the posterior articular branches of the tibial nerve as it penetrates the joint capsule posteriorly and courses along with the synovial vessels that surround and penetrate the ACL (Kennedy et al., 1982). Many of these nerve fibers have vasomotor function, and contain sensory receptor endings in which they can respond to various chemical and inflammatory mediators to induce a painful sensation (Kennedy et al., 1982; McDougall, 2006).

1.2. Autograft harvest sites

There are three common autograft sites used for ACL reconstruction: bone-patellar-bone, hamstring (Gracillis or Semitendinosus) and quadriceps tendons. The bone-patellar-bone autograft is harvested from the inferior portion of the patella and tibial tuberosity and is primarily innervated by the infrapatellar nerve branch of the saphenous nerve. The infrapatellar branch of the patellar nerve is of particular importance when harvesting hamstring tendon autografts. It has been shown that a vertical incision significantly increases the risk of injury to the nerve in comparison to the oblique or horizontal incisions (Grassi et al., 2018). Furthermore, the infrapatellar branch of the saphaneous nerve is commonly injured with patellar tendon autograft harvest (Cohen et al., 2018). The quadriceps tendon may also be harvested and is innervated by the muscular branches of the femoral nerve. Harvest of the quadriceps tendon is not associated with complication of nerve injury in ACL reconstruction.

Pain from harvesting a bone-patellar tendon-bone autograft is mediated by nociceptors within the patellar tendon, retinaculum, fat pad, synovium and periosteum. It was speculated that biochemical irritants, such as glycosamines and chondroitin sulfate, that are released as a result of tendon injury sensitizes nociceptors on the infrapatellar fat pad that lies posterior to the patellar tendon, as well as the surrounding synovium, tissues and patellar tendon to mediate pain (Khan et al., 2000). Pain is also mediated via the free nerve endings (type IV) in the knee joint, which are located in the tendons of semitendinosus, gracilis and sartorius muscles, the lateral and medial patellar retinaculum, the patellar ligament and meniscofemoral ligaments (Grzegorzewski et al., 2015).

1.3. Central processes

Once stimulated, nerve endings from the nociceptors in the ACL and knee joint enter the dorsal spinal cord in the lumbosacral region, synapse with interneurons that further modulate the sensory input or ascend with the spinothalamic, spinomesencephalic and spinoreticular tracts towards the brain (McDougall, 2006). Pain sensation can either be dampened or intensified prior to entering the sensory cortex. The mechanism of how the brain is able to recognize these signals has yet to be clearly elucidated.

2. ACL pain sensation

2.1. Nociception

Various sensory receptors are located on the nerve fibers branching off of the posterior articular branches of the tibial nerve.

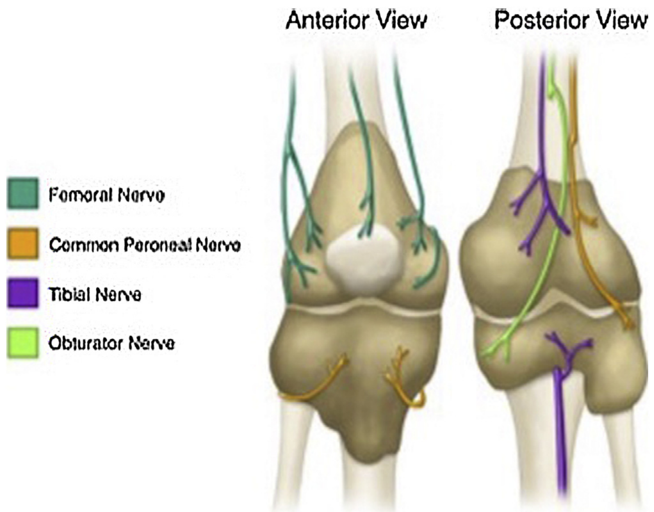

Fig. 2. Distribution of nerves along the knee joint and capsule. Deep branches of femoral nerve (turquoise); common peroneal nerve (orange); tibial nerve (purple); obturator nerve (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Haus and Halata (1990) studied twenty-one human ACLs and microscopically identified free nerve endings as well as terminal sensory nerve structures (both myelinated and unmyelinated) in the synovium as well as within the ACL. Pain fibers typically are of small diameter and can either by unmyelinated (type IV) or unmyelinated with a free nerve ending (type III). These small fibers provide pain sensation and nociception and supply the local vasculature (Haus and Halata, 1990). Furthermore, these pain fibers function as local effectors by releasing neuropeptides that induce vasoactive function in the vasculature in reaction to inflammation or trauma. These nerve fibers course along with the synovial and peri-ligamentous vessels that surround the ACL and extend towards the infrapatellar fat pad. However, most of the fibers associated with ACL are found endogenously and are equally dispersed throughout the ACL (Kennedy et al., 1982).

Previous investigations reviewed the locations of nociceptors and pain fibers throughout the knee joint, including cruciate and collateral ligaments, the menisci, synovium, periosteum and subchondral bone (Freeman and Wyke, 1967; Marinozzi et al., 1991; McDougall, 2006; O'Connor, 1984; Serre et al., 1999). These structures as well as the joint capsule are collectively innervated by branches of the femoral, common peroneal, tibial and obturator nerves. The distribution of these nerves over the knee joint is provided in Fig. 2. In animal models, approximately 80% of afferent fibers in the knee joint were nociceptive - indicating the high teleologic importance of sensing abnormality in the knee (Freeman and Wyke, 1967; Marinozzi et al., 1991). Collectively, these areas influence our sensation of pain when injuries occur in the knee. During states of physical injury and/or inflammation, local blood vessels have increased permeability to substances such as plasma proteins, which promote fluid flow into the interstitium (McDougall, 2006). This results in increased intra-articular pressure that affects nociceptors and articular afferent nerve fibers, which then mediate pain and altered biomechanics.

2.2. Pain mediators

After injury, there is a chemical inflammatory response in which neuropeptides are released that modulate pain and ultimately assist with the healing process. These mediators may arise from nerve fibers, damaged collagen (glycosamines), endothelium or immunocytes, and can then cause sensitization or excitation of sensory receptors (i.e. nociceptors) (McDougall, 2006). These neuropeptides, such as substance P and vasoactive intestinal peptide (VIP), are elevated during inflammation and cause nociceptor sensitization and subsequent pain response. Calcitonin gene-related peptide (CGRP) is another mediator that plays a role in central neurotransmission of pain. As pain is relayed from knee joint afferents, increased levels of CGRP induce spinal cord neurons to fire more rapidly (McDougall, 2006). McDougall et al. (2006) suggested that treating osteoarthritic knees with a VIP antagonist may reduce pain levels; thus, highlighting the potential use of neuropeptide antagonists as treatment for pain secondary to osteoarthritis. Prostaglandins (PG) are another important mediator in inflammation that induce pain by sensitizing nociceptors in joints and augmenting afferent firing rate (Schaible and Schmidt, 1988).

2.3. Ion channels in nociception

Several ion channels exist on nociceptors, which can be activated directly or via a coupling mechanism. Voltage-gated sodium channels primarily cause depolarization of the afferent nerve terminal and propagate the action potential to the central nervous system. Chronic inflammation and nociceptive input via mediators upregulated the gene expression of sodium channels on nociceptors in various tissues (Black et al., 2004; Gould et al., 1998; McDougall, 2006). Furthermore, many nociceptors contain mechano-gated ion channels that are sensitive to shear stress that may be applied from external forces (Heppelmann and McDougall, 2005). The stress creates a conformational change in these ion channels and causes it to open and depolarize. As the intensity of the stimulus increases, the probability of these channels opening proportionally increases (Heppelmann and McDougall, 2005).

2.4. Mechanoreceptors

In addition to pain sensation, large myelinated mechanoreceptors such as Ruffini, Vater-Pacini, and Golgi-like tension receptors are found at the attachments of and on the surface of the ACL (Kennedy et al., 1982). Similar to nociceptors, many of these mechanoreceptors are located around the knee joint. Interestingly, mechanoreceptors exists in varying locations along the anterior cruciate ligament. Ruffini receptors are sensitive to stretching and are located on the surface of the ACL; Vater-Pacini receptors detect rapid movements and are found at each of the ends of the ACL, and Golgi-like receptors which detect tension are located near the attachment sites of the ACL (Hogervorst and Brand, 1998). These mechanoreceptors detect postural changes in the knee and assist with knee proprioception. Deformations within the ACL will elicit a response from the efferent muscle spindles and create a slight reflex of the muscles surrounding the knee (Grigg and Hoffman, 1984; Schutte et al., 1987). After ACL injury, this reflex arc is disrupted and muscle weakness – most notably quadriceps femoris – is evident (Zimny et al., 1986).

2.5. Effects of local anesthetics

Local anesthetics, such as Lidocaine, Bupivacaine, or Ropivacaine function by binding to the intracellular portion of the voltage-gated sodium channels in nerve axons. By inhibiting the influx of sodium ions, local anesthetics prevent depolarization and subsequent conduction of pain signals. Bupivacaine is preferred in nerve blocks due to its favorable pharmacokinetics of a quick onset and long-acting capability as well as low cost (Buys et al., 2017). Liposomal bupivacaine (Exparel, Pacira Pharmaceutical Incorporated, Parsippany, New Jersey, USA) is a lipid encapsulated form of bupivacaine that allows for depo administration of the drug into soft tissue (Springer et al., 2018). The lipids allow for the slow release of anesthetic over

Table 1
Complications following femoral nerve blockade.

- Infection
- Residual sensory deficit
- Quadriceps muscle weakness
- Loss of knee extension

the course of 72-h, which may allow for longer duration of analgesia following operative management.

3. Clinical management of pain in ACL reconstruction

3.1. Opioid usage in ACL reconstruction

By one year post-operatively, 4.71% of patients continued filling opioid medications (Anthony et al., 2017). Additionally, patients who fill opioid prescriptions within 1–3 months prior to ACL reconstruction and those younger than 25 years of age at the time of surgery were at a significantly higher risk of prolonged opioid use (Anthony et al., 2017). It has been shown that patients who are prescribed opioid medications in the post-operative period have a higher risk of lower outcomes following orthopaedic procedures (Holman et al., 2014; Lee et al., 2014; Zywiel et al., 2011). Furthermore, chronic opioid analgesic usage is epidemic affecting the United States (Levin et al., 2016; Murthy, 2016). The effects on opioid usage on complications following ACL reconstruction have yet to be described; however, opioid use may cause nausea, vomiting, sedation, respiratory depression, and death (Leroux et al., 2019). Death related to opioid use has increased nearly three-fold from 2002 to 2015(Gause et al., 2018). Therefore, surgeons and healthcare systems should acknowledge risk factors for prolonged post-operative opioid usage and implement other modalities of pain control to patient following ACL reconstruction.

3.2. Nerve blocks in ACL reconstruction

Femoral nerve block has commonly been used to manage post-operative pain following ACL reconstruction; however, it is associated with quadriceps weakness and nerve palsies (Krych et al., 2015; Luo et al., 2015). Restoring quadriceps function is imperative to returning athletes to sport without an increased risk of ACL re-injury. Patients who were unable to achieve 90% symmetry in quadriceps muscle strength by 12 months post-operatively had a significantly higher re-injury rate by 2-years post-operatively (Grindem et al., 2016). Furthermore, FNB is associated with a higher rate of knee extension loss and subsequent lysis of adhesions (Bailey et al., 2019). Complications following femoral nerve block are provided in Table 1. Adductor canal blockade has been identified as an alternative nerve block that results in equally effective pain control and reduced quadriceps muscle weakness in the immediate and short-term post-operative period (Bailey et al., 2019; Lynch et al., 2019). However, the quadriceps muscle strength was equivalent between FNB and ACB by 6 months post-operatively (Bailey et al., 2019). ACB may be an advantageous alternative nerve block in providing pain relief while preserving quadriceps muscle strength.

3.3. Local infiltrative anesthesia

Local infiltrative anesthesia with a short-acting agent or multi-drug cocktail has been proposed an alternative form of regional anesthesia (Okoroha et al., 2016b). LIA is associated with lower pain and opioid consumption in comparison to FNB (Kurosaka et al., 2018). Furthermore, periarticular injections is associated with less pain than intraarticular injections following ACL reconstruction (Koh et al., 2012). This finding suggests that targeted anesthetics towards the neurological structures surrounding the knee joint provides more efficacious pain relief than a generalized intraarticular injection. Nerve blocks with LIA provides a possible targeted analgesic regimen that may provide pain relief, preserve quadriceps function, minimize opioid usage, and maximize outcomes.

4. Conclusions

Branches of the posterior tibial, saphaneous nerves, and the nerve to the vastus medialis innervate the ACL and the surrounding joint capsule. These structures, specifically the infrapatellar branch of the saphaneous nerve, are at risk for iatrogenic injury during ACL reconstruction. Therefore, it is imperative that physicians are mindful of these structures during operative management. Furthermore, nociceptors and pain fibers are located throughout the knee joint within the cruciate ligaments, menisci, synovium, periosteum, subchondral bone, retinaculum, as well as the patellar ligament. The relative densities of these receptors in each structure is unknown; however, of these areas, they collectively play a role in pain sensation of the knee after surgery.

As the opioid epidemic becomes more prevalent in the United States (Levin et al., 2016; Murthy, 2016), it is imperative that physicians and health care systems investigate and implement alternative forms of analgesia following ACL reconstruction. Femoral nerve blockage provides adequate pain relief; however, it is associated with quadriceps weakness (Krych et al., 2015; Luo et al., 2015), which may increase the rate of re-injury following return to sport (Grindem et al., 2016). Adductor canal blockage has recently been shown as an alternative nerve block that provides equivalent pain relief while maintaining quadriceps muscle strength (Bailey et al., 2019; Lynch et al., 2019). Furthermore, local infiltrative analgesia to the joint capsule provides adequate pain relief in the immediate post-operative period (Fauno et al., 2015; Koh et al., 2012; Kristensen et al., 2014; Kurosaka et al., 2018; Okoroha et al., 2016b). When periarticular anesthetics are targeted towards local neurological structures and are used in conjunction with nerve blockade, the efficacy of pain relief exceeds isolated nerve blocks (Fauno et al., 2015). It is imperative to understand the distribution and location of neurological structures in the knee joint in order to provide appropriate pain relief while minimizing the risk of chronic opioid usage.

Ethical statement

Due to the nature of this investigation as a review, there were no possible sources of ethical violations.

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