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Reviews

Liposomal Bupivacaine Decreases Post-Operative Opioid Use after Anterior Cruciate Ligament Reconstruction: A Review of Level I Evidence

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Introduction

Anterior Cruciate Ligament tears are common after a non-contact injury and several thousand reconstructions (ACLR) occur yearly in the United States. Multimodal pain management has evolved greatly to include nerve blocks to minimize physical therapy losses post-operatively, pericapsular and wound injections, and other adjunctive measures. However, there is a surprisingly high use of opioid use after ACLR.

Objective

The purpose of present investigation is to summarize the current state of knowledge regarding opioid use after ACLR and to synthesize the literature regarding the use of liposomal bupivacaine and its potential to reduce post-operative opioid use in ACLR patients.

Methods

The literature search was performed in Mendeley. Search fields were varied until redundant. All articles were screened by title and abstract and a preliminary decision to include an article was made. A full-text screening was performed on the selected articles. Any question regarding the inclusion of an article was discussed by three authors until an agreement was reached.

Results

Eighteen articles summarized the literature around the opioid epidemic in ACL surgery and the current context of multimodal pain strategies in ACLR. Five primary articles directly studied the use of liposomal bupivacaine as compared to reasonable control options. There remains to be over prescription of opioids within orthopedic surgery. Patient and prescriber education are effective methods at decreasing opioid prescriptions. Many opioid pills prescribed for ACLR are not used for the correct purpose. Several risk factors have been identified for opioid overuse in ACLR: American Society of Anesthesiologists score, concurrent meniscal/cartilage injury, preoperative opioid use, age < 50, COPD, and substance abuse disorder. Liposomal bupivacaine is effective in decreasing post-operative opioid use and reducing post-operative pain scores as compared to traditional bupivacaine. LB may also be effective as a nerve block, though the data on this is more limited and the effects on post-operative therapy need to be

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weighed against the potential therapeutic benefit. LB is associated with significantly greater costs than traditional bupivacaine.

Discussion

The role for opioid medications in ACLR should continue to decrease over time. Liposomal bupivacaine is a powerful tool that can reduce post-operative opioid consumption in ACLR.

I. INTRODUCTION

Anterior Cruciate Ligament (ACL) injuries are common with nearly 400,000 reconstructions occurring yearly in the United States. They are more common in females and generally occur following non-contact pivoting injury.

The literature on postoperative pain management after ACL reconstruction has evolved greatly and has resulted in the development of several multimodal pain management strategies to reduce pain scores and also improve functional outcomes. Intraoperative peripheral nerve blocks (PNB) serve as the backbone of these strategies in ACL surgeries.[1] Wound injections with local anesthetics are also commonly performed. There has also been significant conversation around intraarticular injections, with liposomal bupivacaine showing some recent promising results considering its long-activating and slowly dissolving form.

Several studies have pointed to opioid overuse in orthopedic surgery and specifically in ACL reconstructions. However, preoperative measures that can reduce opioid dependence in the post-operative period have been well demonstrated.[2] It has been demonstrated that decreasing the strength of opioids given after surgery does not increase pain scores or subsequent opioid consumption.[3] Thus, further study is needed in determining what, if any, role opioids play in the ideal multimodal pain management strategy after ACL reconstruction surgery.

Liposomal Bupivacaine serves as a promising adjunct to existing multimodal pain management therapies that can reduce dependency on opioids. The purpose of the present investigation, therefore, is to summarize the current state of opioid use after ACLR and to highlight the potential of LB to reduce postoperative opioid use in ACLR.

2. MATERIALS AND METHODS

2.1. GENERAL

This was an IRB-exempt scoping review. The scoping review checklist available at the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews Checklist (RPSIMA-ScR) was followed strictly. The international prospective register of systematic reviews (PROSPERO) was contacted regarding our intention for this article and advised that scoping views do not require registration with PROSPERO.

2.2. SEARCH STRATEGY

The literature search was performed using Medical Search Headings (MeSH) in Mendeley version 1.19.8. Articles published between January 1975 to December 2021 were Search fields were varied until no new articles were collected at which point the search was considered exhaustive.

Table 1. Inclusion and exclusion criteria as applied during the title/abstract screening to define 'Tier 1' articles.

Inclusion Criteria	Exclusion Criteria
• Publication between 1975 - 2022 • A primary study with a direct comparison of patients undergoing ACLR with LB as an adjunctive to a comparable group not receiving LB • Level I evidence only	• Absence of study of liposomal bupivacaine in the context of ACLR • Retrospective studies, cohort studies, Case series, case reports, expert opinion, or other Level II, III, IV, or V evidence

2.3. STUDY SCREENING

All articles were screened by title and abstract. An initial decision to include a given article was made based on the relevance of the information within the abstract as determined by our inclusion/exclusion criteria (**Table 1**). This constructed a list of preliminarily included articles. These preliminarily included articles underwent classification as 'Tier 1', 'Tier 2', or 'Tier 3' articles. Tier 1 articles were defined as primary studies of level I clinical evidence that directly compared the use of liposomal bupivacaine in ACLR to a reasonable control with adherence to the remaining inclusion/exclusion criteria. Tier 2 articles were relevant articles that summarized the current state of pain control ACLR, the opioid epidemic ACLR, or the current standard of care regarding regional anesthesia in ACLR. Tier 3 articles were those that included relevant search terms but did not meet the above two criteria.

2.4. STUDY SELECTION

Articles from Tier 1 and Tier 2 then underwent a full-text screening process. This resulted in the elimination of many articles until 5 articles in Tier 1 and 18 articles in Tier 2. The results of the articles from Tier 2 are described qualitatively in **Sections 3.1-3.4** and **Section 3.6**. The results of the Tier 1 articles are discussed in **Section 3.5**. Any question regarding the inclusion of an article was discussed by all authors until an agreement was reached. The bibliographies of these articles were also hand-searched to identify any missing articles.

3. RESULTS

3.1. PATHOPHYSIOLOGY OF POST-SURGICAL PAIN IN ACL RECONSTRUCTIONS

It is normal for patients to experience moderate pain after an ACLR. The current standard of care regarding postoperative pain control has evolved to include multimodal pain strategies that maximize pain control without affecting quadriceps function and rehabilitation.[4] In this section, the pathophysiology of post-surgical pain in ACLR is described. This section provides the necessary basic science to understand the integration of liposomal bupivacaine into current multimodal pain strategies for ACLRs.

There is extensive innervation variation among patients with regard to the neurovascular anatomy of the knee joint. In general, the infrapatellar branch of the saphenous nerve originates at the knee joint and provides sensory innervation to the skin surrounding the patella and medial to the knee. Branching of the femoral nerve distal to the vastus medialis exits the adductor canal and supplies the knee with both motor and sensory innervation. Together, these nerves form a plexus that gives rise to the anterior and posterior genicular nerves.[4]

The types of nerves within the knee joint have been studied extensively and research in animal models has shown that up to eighty percent of afferent fibers in the knee are nociceptive.[4] These free nerve endings mediate pain via many mechanisms such as neuropeptides activating sensory receptors on the nerve fibers, ion channel activation, and mechanoreceptor activation.[4]

Neuropeptides are released and elevated during injury and inflammation, and cause nociceptor sensitization which is perceived as a painful stimulus. Prominent neuropeptide and pain mediators released during ACLR are prostaglandins, glycosamines, chondroitin sulfate, immunocytes, substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide.[4]

Ion channels, such as voltage-gated sodium channels, can also mediate pain as they can exist on nociceptors. Activation of ion channels via chronic inflammation gene upregulation or shear stress can lead to increased pain propagation.[4] Mechanoreceptors can also play a role in pain sensation. Many myelinated mechanoreceptors located on the ACL are activated during both injury and surgery via postural changes, deformations of the ligament, and tension.[4] The degree of initial joint inflammation is also implicated in long-term outcomes regarding pain with ACLR.[5] Injury leads to local blood vessel dilation with increased vascular endothelial permeability to plasma proteins. This leads to an increased fluid flow to the interstitium, causing increased articular pressure that can affect the afferent nerve fibers mediating pain.[4] The nerve anatomy and pathophysiology of post-surgical pain in ACLR are important when discussing the appropriate analgesic care.

3.2. THE OPIOID EPIDEMIC

3.2.1. OPIOID EPIDEMIC IN ORTHOPEDIC SURGERY

In the 1990s, pain became classified as the "fifth patient vital sign," and the reduction of pain became a staple of inpatient care. This resulted in a significant rise in the prescription of opioids.[6] Due to the concern for litigation for undertreatment of pain and the expansion of the indications for the use of opioids to non-cancer-related pain, physicians across all specialties began prescribing opioids by more than 200%. Currently, the pharmaceutical industry in the United States has far outpaced many other nations in opioid prescription. This has had disastrous consequences on both the economy[6] and drug addiction[7] in the nation.

A 2006 study conducted by the National Survey on Drug Use and Health found that of those abusing opioids more than 90% came from a legitimate physician's prescription. However, opioid overprescription is not isolated to any one subspecialty. Orthopedic surgeons prescribe nearly 7.7% of all opioid prescriptions,[8] which is arguable a disproportionately small fraction considering the intimate relationship of pain management with the field. Part of the issue stems from the fact that only a minority of patients are counseled regarding the safe disposal of unused opioid medications.[8] Patient education programs have been associated with lower rates of opioid use at 6 weeks post-operatively, and prescriber education is a useful tool for persuading physicians to prescribe dosages that are more in line with patients' needs.[8]

3.2.2. OPIOID EPIDEMIC IN ACL SURGERY

ACL reconstruction is an example of a common operation with great potential to reduce the number of opioid prescriptions in orthopedic surgery. An estimated 48% of the opioid pills that are prescribed to ACL reconstruction patients are utilized for pain directly related to the procedure. It is reasonable to conclude that more than half of the prescribed could be reduced.[9] It has also been shown that the strength of oxycodone (from 7.5 mg to 5.0 mg Percocet) did not increase pain scores or opioid consumption in patients undergoing ACLR.[3] Two other studies that utilized a multimodal analgesia approach after ACL reconstruction found that they have the potential to reduce opioid prescriptions.[2,10]

An interesting case study around this conversation is that of the Ohio government. In August 2017, the government of Ohio imposed a limitation that reduced opioid prescription following ACL reconstruction surgery by more than 34%. A retrospective cohort study, comparing a group of patients undergoing ACLR before and after the limitations, demonstrated that there was no significant difference in pain-related complications, opioid demand, office calls, emergency department visits, unplanned readmissions, or subsequent surgery between the two groups.[7] Thus, there may have been significant overprescribing of narcotic pain medication before the 2017 limitations. This study reasonably advocates that there is room for growth regarding cutting back on opioids in the postoperative period for ACLRs.

Patient Risk Factors	Medical Risk Factors
ASA Score[11]	COPD[11]
Meniscal, cartilage injury[11]	Substance abuse disorder[11]
Preoperative opioid use[12]	
Age < 50[12,13]	

Figure 1. A summary of the identified risk factors for higher opioid use after ACLR in the literature.

ASA: American Society of Anesthesiologists
COPD: Chronic Obstructive Pulmonary Disease

These numbers are important for orthopedic surgeons and anesthesiologists alike to consider as we develop further multimodal pain strategies for ligament reconstruction surgeries.

3.3. RISK FACTORS FOR POST-OPERATIVE OPIOID OVERUSE IN ACL RECONSTRUCTION SURGERIES

Several risk factors have been highlighted regarding increased postoperative opioid usage after ACLR (**Figure 1**) including preoperative opioid use, increasing age, American Society of Anesthesiology (ASA) score of 3 or more, other activity at the time of injury, repaired meniscal injury, cartilage repair, chronic pulmonary disease, and substance abuse.[11] A 2017 cohort study found that up to 35% of patients undergoing ACLR are filling opioid pain prescriptions pre-operatively. The same study also found that preoperative opioid use was a strong predictor of postoperative opioid demand.[12] Preoperative opioid use for more than one month also leads to a longer hospital stay and lower patient-reported outcomes.[12] Anthony et al. found that individuals filling preoperative opioid prescriptions were 7.54 and 6.42 times more likely to be filling ACLR postoperative opioid prescriptions at 9 and 12 months, respectively.[12] Patients under the age of 25 and older than the age of 50 have also been shown to be at an increased risk of filling opioid prescriptions postoperatively.[12,13] Studies have shown women to be more likely than men to fill prescriptions, and that race is an unimportant factor in predicting future opioid use.

3.4. CURRENT STANDARD OF CARE FOR PAIN CONTROL IN ACL SURGERIES

3.4.1. PERIPHERAL NERVE BLOCKS

Though the femoral nerve block (FNB) was priorly popular in ACLR, the effects that femoral nerve blocks have on ACL considering denervation of the quadriceps muscle have become well known to the orthopedic community. Thus, there has been a dramatic shift towards the ACB in recent years. Multiple studies suggest that between the ACB and the FNB, there is no statistically significant difference in postoperative pain.[14,15] Further patients receiving an ACB have a significantly shorter time to straight leg raise and a reported greater satisfaction with pain control.

Though the saphenous nerve (adductor canal) nerve block is the most utilized, considering the recent literature does shed light on other nerve block options. These are discussed below.

A recent systematic review highlights the efficacy of the femoral-sciatic nerve block.[16] They found multiple studies that demonstrated that a femoral nerve block significantly decreases postoperative VAS scores as compared to a saline injection, and the addition of a sciatic nerve block to an FNB (femoral nerve block) lowered both NRS scores and analgesic consumption.[16] Though the sciatic nerve block is not widely prevalent in ACLR, it does represent a potential addition to the realm of multimodal pain control in ACLRs.[17]

The obturator nerve has also been described as an alternative. It has been shown that the FOS (femoral-obturator-sciatic) block has a higher success rate than the PLPS (posterior lumbar plexus-sciatic) block, less postoperative pain scores, and decreased opioid consumption in patients undergoing ACLR.[18]

A study evaluating the pain management of pediatric (ages 12-17) ACL reconstruction patients compared the FNB, combined femoral + sciatic block, and IA injection of bupivacaine. Patients in the combined femoral and sciatic block group had significantly better pain scores than the other two groups, significantly fewer opioid prescriptions filled and significantly fewer morphine equivalents among those who did receive opioids.[19] This study not only highlights that postoperative pain control in the pediatric patient may be significantly different and require unique multimodal pain strategies, but also that standard bupivacaine may have its limitations.

3.4.2. LOCAL ANESTHESIA

A recent randomized control trial demonstrates the potential that local anesthesia alone can have in post-operative pain control and opioid use. Kurosaka et al. 2018 demonstrated that a group receiving a periarticular 44 mL solution of 7.5 mg/mL ropivacaine, 10 mg/mL of morphine hydrochloride hydrate, 40 mg of methylprednisolone, 20 mg/mL of ketoprofen, and 1 mg/mL of epinephrine to a group receiving an FNB. They demonstrated that the periarticular injection group demonstrated significantly lower VAS scores and opioid consumption with no difference in the complication rate as compared to the FNB group. Though it may be overzealous to interpret these results as evidence to abandon nerve blocks altogether, they certainly highlight the potential that local, periarticular analgesia has in ACLR.

Intraarticular injections of anesthetic certainly make the orthopedic community nervous considering the well-known chondrotoxic effects of local anesthetics within the joint. However, the recent systematic review does find several studies that utilize limited, low-concentration bupivacaine intraarticularly. Many studies in their review do clearly specify low-concentration and low-volume use and

Secrist et al. did find that continuous infusion catheters do indeed cause chondrotoxicity.

Morphine and bupivacaine have been shown to significantly decrease VAS scores and analgesic consumption as compared to isolated bupivacaine, morphine, or saline (saline was also inferior to both bupivacaine alone and morphine alone). Intraarticular morphine injection has been shown to be superior to intraarticular methadone injection (significantly decreased VAS scores and analgesic consumption) but inferior to tenoxicam injection (more patients requiring pethidine in the morphine group). Regarding means of administering analgesic: preoperative and postoperative bupivacaine infiltrations and IA injection were demonstrated to be superior to IA bupivacaine injection; and periarticular or periarticular/IA injection of a "cocktail of drugs" (ropivacaine, morphine, ketorolac, and cefuroxime) proved to be superior to IA injection of the same drugs (significantly decreased VAS scores in the first 24 hours).[16] The studies studying the role of liposomal bupivacaine in ACLRs have not been summarized to date and this is done so in **Section 3.5**.

3.5. USE OF LIPOSOMAL BUPIVACAINE IN ACL SURGERIES

Liposomal bupivacaine (LB) has demonstrated great potential in the recent literature in reducing post-operative pain scores in orthopedic surgery and sports medicine. Our literature search revealed four articles articles of level I clinical evidence that studied the role of liposomal bupivacaine in decreasing postoperative opioid use in ACLR (see **Table 2**). Liposomal bupivacaine combines bupivacaine with a multivesicular-based lipid delivery platform, specifically designed to provide a slow release of the anesthetic agent.[20] As a long-acting non-opioid analgesic, it has many properties that make it ideal in arthroscopic surgery. Periarticular injection of liposomal bupivacaine following ACL reconstruction remains an exciting area of research: one randomized control trial demonstrated that though patients had increased pain in the acute postoperative period when treated with liposomal bupivacaine after this period was over, the same patients had adequate pain control, better sleep quality, and fewer numbers of calls to the physician related to rebound pain when compared to FNB.[20] Another randomized control trial found that a group treated with liposomal bupivacaine reported diffusely better pain management and lower opioid consumption.[21] A final randomized control trial showed that the number of opioid pills prescribed postoperatively was significantly lower in a group receiving liposomal bupivacaine as a local analgesic than in the control group.[22]

3.6. OTHER MEASURES

In addition to a nerve block, non-opioid adjuvant medication preoperatively shows some promise for potential integration into multimodal pain strategies. Though pre-operative gabapentin has demonstrated decreased pain scores and opioid use post-operatively following ACLRs,[23] there is mixed evidence regarding its use with concurrent nerve blocks.[24] However, a recent systematic review of randomized controlled trials did find that oral gabapentin did reduce opioid consumption. Postoperative zolpidem was also found to decrease opioid consumption.[16]

Pregabalin, a γ-aminobutyric acid analog, is another analgesic that has been considered an addition to post-operative pain analgesia. Though pregabalin has been proven efficacious for pain management in various types of surgeries, its role in ACL reconstruction has only recently been studied. One randomized control study determined that in patients undergoing ACL reconstruction, perioperative pregabalin administration was shown to greatly reduce post-operative pain without additional use of postoperative opioids and IV-PCA.[25] Another study compared the use of pregabalin to an adductor nerve block, finding that preoperative pregabalin reduced postoperative opioid consumption to the same degree as the adductor nerve block.[26] A final study determined that prolonged administration of pregabalin 7 days before and after ACL reconstruction decreased the need for supplemental analgesics.[27] Thus, pregabalin may also represent a potential addition to future multimodal pain strategies in ACLRs.

4. CONCLUSIONS

Opioids may be overprescribed after ACLR in the United States. It is unclear whether or not opioid use significantly lowers pain scores or improves function after ACLR. The role of opioid medications in ACLR should continue to decrease over time. The existing clinical evidence in favor of liposomal bupivacaine is strong; however, significant barriers exist particularly the high cost. Liposomal bupivacaine is a powerful tool that can reduce post-operative opioid consumption in ACLR. As more evidence emerges for the use of periarticular liposomal bupivacaine, multimodal pain strategies that utilize its use liposomal bupivacaine may emerge carving the way for decreased opioid prescription after ACLR. However, further work including further comparisons to similar periarticular concoctions and efforts to decrease the costs of liposomal bupivacaine are required.

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We have no disclosures or potential conflicts of interest.

Table 2. A summary of the level I clinical evidence regarding liposomal bupivacaine after ACLRs.

Lead Author	Year	Journal	Institution	Study Type	Level of Evidence	Number of Patients	Liposomal Bupivacaine Dose Given	Concurrent Nerve Block (Y/N + Nerve Block Type)	Comparison Group	Outcome Measured	1-2 Sentence Conclusion
Okoroha, K	2016	Arthroscopy - Journal of Arthroscopic and Related Surgery	Henry Ford Hospital, Detroit, Michigan	Randomized control trial	I	85	20 mL of LB (266 mg) mixed with 10 mL of saline	No	Received a single shot of 40 mL of 0.5% ropivacaine	Daily pain difference	The patients treated with LB had increased pain levels in the initial postoperative hours when compared with FNB. After the acute postoperative period, LB provided similar pain control compared with FNB.
Premkumar, A	2016	American Journal of Sports Medicine	Emory Orthopaedics and Spine Center	Randomized control trial	I	32	20 mL Exparel (1 vial of bupivacaine liposome injectable suspension). Injections were at the hamstring graft sites and port sites (not periarticular).	No	Received 20 mL 0.5% bupivacaine HCl and 20 mL 0.9% injectable saline	Efficacy of liposomal bupivacaine compared to bupivacaine HCL.	There were comparable outcomes with 0.25% bupivacaine HCl at a 200-fold lower cost than liposomal bupivacaine.
Stryder, B	2021	Orthopedics	Med-Star Washington Hospital Center	Randomized control trial	I	67	20 mL of LB (266 mg)	No	Received Catheter-based peripheral nerve block	Quantity of opioids prescribed to patients who received LB	Patients who received liposomal bupivacaine as part of multimodal pain management had significantly fewer opioid prescriptions.
Keller, R	2018	Knee surgery, sports traumatology, arthroscopy	Ascension Crittenton Hospital	Randomized control trial	I	42	20 mL of LB	No	Received femoral nerve block	Postoperative pain levels and opioid consumption	Injecting the posterior capsule of the knee with LB significantly reduced pain in the early postoperative period as well as the total number of opiate medications taken by patients recovering from ACLR.

FURTHER INFORMATION

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REFERENCES

1. Adams AJ, Muhly WT, Gurnaney HG, Kerr JC, Aoyama JT, Wells L. POSTOPERATIVE AND POST-DISCHARGE PAIN OUTCOMES AND OPIOID REQUIREMENTS IN PEDIATRIC ARTHROSCOPIC ACL RECONSTRUCTION AND/OR MENISCUS PROCEDURES MANAGED WITH PERIPHERAL NERVE BLOCKADE. *Orthop J Sport Med*. 2019;7(3_suppl). doi:10.1177/2325967119s00041

2. Malige A, Bram JT, Maguire KJ, McNeely LW, Ganley TJ, Williams BA. Decreased Prescribing of Postoperative Opioids in Pediatric ACL Reconstruction: Treatment Trends at a Single Center. *Orthop J Sport Med*. 2021;9(2). doi:10.1177/2325967120979993

3. Nazzal E. Characterizing the Effect of Opioid Tablet Strength on Post-Operative Opioid Consumption Following ACL Reconstruction. *Orthop J Sport Med*. 2020;8(7_suppl6). doi:10.1177/2325967120s00503

4. Hong AJ, Agarwalla A, Liu JN, et al. Neurological structures and mediators of pain sensation in anterior cruciate ligament reconstruction. *Ann Anat*. 2019;225:28-32. doi:10.1016/j.aanat.2019.05.010

5. Urban H, Blaker C, Shu C, Clarke E, Little CB. Synovial inflammation in anterior cruciate ligament injury knees in mice: surgical vs non-surgical models. *Osteoarthr Cartil*. 2020;28:S213-S214. doi:10.1016/j.joca.2020.02.349

6. Morris BJ, Mir HR. The opioid epidemic: Impact on orthopaedic surgery. *J Am Acad Orthop Surg*. 2015;23(5):267-271. doi:10.5435/jaaos-d-14-00163

7. Kamaci S, Ozdemir E, Utz C, Colosimo A. Mandatory Prescription Limits and Opioid Use After Anterior Cruciate Ligament Reconstruction. *Orthop J Sport Med*. 2021;9(9). doi:10.1177/23259671211027546

8. Soffin EM, Waldman SA, Stack RJ, Liguori GA. An Evidence-Based Approach to the Prescription Opioid Epidemic in Orthopedic Surgery. *Anesth Analg*. 2017;125(5):1704-1713. doi:10.1213/ane.0000000000002433

9. Thompson MM, Popp L, Foster MJ, Malik H, Henn RFI. Opioid Prescribing Habits for Common Arthroscopic Procedures in Opioid Naïve Patients. *Orthop J Sport Med*. 2021;9(5). doi:10.1177/2325967121100926 3

10. Hajewski CJ, Westermann RW, Holte A, Shamrock A, Bollier M, Wolf BR. Impact of a Standardized Multimodal Analgesia Protocol on Opioid Prescriptions After Common Arthroscopic Procedures. *Orthop J Sport Med*. 2019;7(9). doi:10.1177/2325967119870753

11. Rao AG, Prentice HA, Chan PH, Paxton LW, Funahashi TT, Maletis GB. Risk Factors for Opioid Use Following Anterior Cruciate Ligament Reconstruction (ACLR) in a Cohort of 21,202 ACLR. *Orthop J Sport Med*. 2019;7(7_suppl5). doi:10.1177/2325967119s00257

12. Anthony C, Westermann RW, Bedard N, et al. Opioid Demand after Anterior Cruciate Ligament Reconstruction. *Orthop J Sport Med*. 2017;5(7_suppl6). doi:10.1177/2325967117s00278

13. Anderson AB, Balazs GC, Brooks DI, Potter BK, Forsberg JA, Dickens JF. Prescription Patterns and Risk Factors for Prolonged Opioid Dependence in Elective Anterior Cruciate Ligament Reconstruction in a Military Population. *Orthop J Sport Med*. 2020;8(6). doi:10.1177/2325967120926489

14. Lynch JR, Okoroha KR, Lizzio V, Yu CC, Jildeh TR, Moutzouros V. Adductor Canal Block Versus Femoral Nerve Block for Pain Control After Anterior Cruciate Ligament Reconstruction: A Prospective Randomized Trial. *Am J Sports Med*. 2019;47(2):355-363. doi:10.1177/0363546518815874

15. Xerogeanes JW, Premkumar A, Godfrey W, et al. Adductor Canal vs. Femoral Nerve Block in Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Orthop J Sport Med*. 2017;5(7_suppl6). doi:10.1177/2325967117s00277

16. Secrist ES, Freedman KB, Ciccotti MG, Mazur DW, Hammoud S. Pain Management After Outpatient Anterior Cruciate Ligament Reconstruction. *Am J Sports Med*. 2016;44(9):2435-2447. doi:10.1177/0363546515617737

17. Faunø P, Lund B, Christiansen SE, Gjøderum O, Lind M. Analgesic effect of hamstring block after anterior cruciate ligament reconstruction compared with placebo: A prospective randomized trial. *Arthrosc - J Arthrosc Relat Surg*. 2015;31(1):63-68. doi:10.1016/j.arthro.2014.07.024

18. Bareka M, Hantes M, Arnaoutoglou E, Vretzakis G. Superior perioperative analgesia with combined femoral–obturator–sciatic nerve block in comparison with posterior lumbar plexus and sciatic nerve block for ACL reconstructive surgery. *Knee Surg Sports Traumatol Arthrosc*. 2018;26(2):478-484. doi:10.1007/s00167-017-4525-7

19. Lovejoy JF III, Santana L, Atanda A Jr, Mandel D, Day J, Kiebzak GM. COMPARISON OF POSTOPERATIVE PAIN SCORES AND MEDICATION USAGE BETWEEN THREE PAIN CONTROL STRATEGIES FOR PEDIATRIC ANTERIOR CRUCIATE LIGAMENT (ACL) SURGERY. *Orthop J Sport Med*. 2019;7(3_suppl). doi:10.1177/2325967119s00185

20. Okoroha KR, Keller RA, Marshall NE, et al. Liposomal Bupivacaine Versus Femoral Nerve Block for Pain Control After Anterior Cruciate Ligament Reconstruction: A Prospective Randomized Trial. *Arthrosc - J Arthrosc Relat Surg*. 2016;32(9):1838-1845. doi:10.1016/j.arthro.2016.05.033

21. Kurosaka K, Tsukada S, Nakayama H, et al. Periarticular Injection Versus Femoral Nerve Block for Pain Relief After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Arthrosc - J Arthrosc Relat Surg*. 2018;34(1):182-188. doi:10.1016/j.arthro.2017.08.307

22. Stryder BT, Szakiel PM, Kelly M, et al. Reduced opioid use among patients who received liposomal bupivacaine for ACL reconstruction. *Orthopedics*. 2021;44(2). doi:10.3928/01477447-20210104-03

23. Mrdani Kivi M, Karimi Mobarakeh M, Keyhani S, Hashemi Motlagh K, sahab Ekhtiari K. Is gabapentin effective on pain management after arthroscopic anterior cruciate ligament reconstruction? A triple blinded randomized controlled trial. *Arch Bone Jt Surg*. 2013;1(1). doi:10.22038/abjs.2013.1735

24. Ahearn B, Kumar A, Premkumar A, et al. Effect of Preoperative Gabapentin With a Concomitant Adductor Canal Block on Pain and Opioid Usage After Anterior Cruciate Ligament Reconstruction. *Orthop J Sport Med*. 2019;7(3). doi:10.1177/2325967119828357

25. Cho EA, Kim N, Lee B, Song J, Choi YS. The Effect of perioperative pregabalin on pain after arthroscopic anterior cruciate ligament reconstruction: A randomized controlled trial. *J Clin Med*. 2019;8(9):1426. doi:10.3390/jcm8091426

26. Kavak Akelma F, Baran Akkuş İ, Altinsoy S, Özkan D, Ergil J. The effects of pregabalin and adductor canal block on postoperative pain in arthroscopic anterior cruciate ligament reconstruction. *Turkish J Med Sci*. Published online 2020. doi:10.3906/sag-1906-66

27. Tobias AF, Moura ECR, Honda CADO, et al. Evaluation of the Efficacy of Prolonged Pregabalin Administration before and after Surgery in Patients Undergoing Arthroscopic Anterior Cruciate Ligament Repair: A Prospective, Randomized, Double-blind Study. *Clin J Pain*. 2020;36(8):584-588. doi:10.1097/ajp.0000000000000841