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Pain Management After Outpatient Anterior Cruciate Ligament Reconstruction: A Systematic Review of Randomized Controlled Trials.

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Postoperative Pain Management Following Outpatient Anterior Cruciate Ligament Reconstruction – A Systematic Review of Randomized Controlled Trials

Abstract

Background:

Effective pain management following anterior cruciate ligament reconstruction improves patient satisfaction and function.

Purpose:

We collected and evaluated the available evidence from randomized controlled trials on postoperative pain control following anterior cruciate ligament reconstruction.

Study Design:

Systematic review. Level 1 and 2.

Methods:

A systematic literature review was performed using PubMed, Medline, Google Scholar, UpToDate, CINAHL and Scopus following PRISMA guidelines (July 2014). Only randomized control trials comparing a method of postoperative pain control to another method or placebo were included.

Results:

Seventy seven randomized controlled trials met inclusion criteria, 14 on regional nerve blocks, 21 on intraarticular injections, 4 on intramuscular/intravenous injections, 12 on multimodal regimens, 6 on oral medications, 10 on cryotherapy/compression, 6 on mobilization and 5 on intraoperative techniques.

Single injection femoral nerves block provided superior analgesia to placebo for up to 24 hours postoperatively, however this also resulted in a quadriceps motor deficit. Indwelling femoral catheters utilized for 2 days postoperatively provided superior analgesia to a single injection femoral nerve block. Local anesthetic injections at the surgical wound site or intraarticularly provided equivalent analgesia to

regional nerve block. Continuous infusion catheters of local anesthetic provide adequate pain relief, but have been shown to cause chondrolysis.

Cryotherapy improved analgesia compared to no cryotherapy in 4 trials, while in 4 trials ice water and room temperature water provided equivalent analgesic effects. Early weightbearing decreased pain compared to delayed weightbearing.

Preoperative gabapentin and zolpidem for the first week postoperatively each decreased opioid consumption compared to placebo. Ibuprofen reduced pain compared to acetaminophen. Oral ketorolac reduced pain compared to hydrocodone-acetaminophen.

Conclusion:

Regional nerve blocks and intraarticular injections are both effective forms of analgesia. Cryotherapy-compression appears beneficial provided IA temperatures are sufficiently decreased. Early mobilization reduces pain symptoms. Gabapentin, zolpidem, ketorolac and ibuprofen decrease opioid consumption. Despite the vast amount of high quality evidence on this topic, however, further research is needed to determine the optimal multimodal approach that can maximize recovery while minimizing pain and opioid consumption.

Clinical Relevance:

These results provide the best available evidence from randomized controlled trials on pain control regimens for anterior cruciate ligament reconstruction.

Main Text

Introduction

The anterior cruciate ligament (ACL) is the most commonly reconstructed ligament in the knee. [73] In 2006 129,836 ACL reconstructions were performed in the United States, and the annual rate is increasing. [74] Effective postoperative pain management is a critical component to recovery, effective rehabilitation and patient satisfaction. Following ACL reconstruction, psychological factors are predictive of outcomes, [36] and pain levels are inversely associated with function [19] and quality of life assessments. [40]

The two main measures used to quantify patient pain symptoms are postoperative opioid medication consumption and pain scales. Commonly used pain scales include the visual analog scale (VAS), verbal rating scale (VRS) and the numeric rating scale (NRS). Although these methods rely on patient reporting of subjective feelings, they are highly reproducible and reliable. [7, 8]

There is an abundance of literature evaluating various postoperative pain management medications and modalities following ACL reconstruction. Individual systematic reviews have analyzed the efficacy of cryotherapy, [76] femoral nerve blocks (FNB), [75] continuous passive motion (CPM), [105] and postoperative rehabilitation. [68] We performed a systematic review of all level I and level II randomized controlled trials and present a comprehensive review of the evidence surrounding postoperative pain management for outpatient arthroscopic ACL reconstruction.

Methods

A comprehensive literature review was performed to identify all randomized controlled trials (RCTs) on postoperative pain management following ACL reconstruction. Searches for the terms “anterior cruciate ligament” and “postoperative pain” were performed using the search engines PubMed, Medline, Google Scholar, UpToDate, Cochrane Reviews, CINAHL and Scopus (from inception to July 2014). Additional

searches for multimodal analgesia, continuous passive motion, immobilization, early weightbearing, cryotherapy, compression, intraarticular injection, nerve block, NSAIDs, hydrocodone, acetaminophen, and opiates were also conducted in the same databases along with the term “anterior cruciate ligament.” Reference sections of relevant articles were reviewed in an attempt to identify further relevant trials. Inclusion criteria were studies that were randomized control trials, level I or II, that compared any two or more pain management modalities to other modalities or placebo, utilizing objective measures to quantify post-operative pain within the first postoperative month. Only modalities that can be applied to postoperative pain management after ACL reconstruction in the *outpatient* setting were included. Notation was made of the surgical methodology used in each study and this can be found in the supplemental tables. All methods of arthroscopic reconstruction were included. Studies which performed co-procedures such as meniscus or articular cartilage surgery alongside ACL reconstruction were included. Intravenous (IV) morphine was considered valid as a pain metric but not as a treatment because of our desire to evaluate “outpatient” treatment approaches. Exclusion criteria were as follows: non English language or non-human articles, nonrandomized trials, studies which included patients undergoing other surgical interventions alongside patients undergoing ACL reconstruction, open ACL reconstruction, meta-analyses or systematic reviews of randomized controlled trials, retracted papers or papers published by first authors associated with multiple cases of academic fraud, and studies which did not measure pain symptoms. Data was collected including demographic information, pain outcomes and complications for each included study. Wherever applicable, statistically significant results are reported. PRISMA criteria were followed throughout the study. Quality appraisal was also performed for each individual trial.

Results

A total of 77 RCTs met inclusion criteria for this systematic review. A PRISMA flow diagram of the literature search and included studies can be found in Figure 1. Of the 77 included studies, 14 were trials

of regional nerve blocks, 21 were trials of intraarticular (IA) injections, 4 were trials of intramuscular (IM) or intravenous (IV) injections, 12 compared differing analgesic regimens, 6 were trials on oral medications, 10 were trials of cryotherapy or compression, 6 were trials of differing postoperative mobilization strategies and 5 were trials of intraoperative techniques. One trial consisted of two separate phases, which are presented here as individual trials. A concise summary of all interventions, which resulted in a statistically significant decrease in either reported pain symptoms or opioid consumption, can be found in tables 1-8. Additional information regarding each RCT including graft types, number of subjects, dosages, pain metrics, rescue medications, p-values, as well as pain and medication values for each comparison group can be found in tables 1-8 of the supplemental section. Complications reported in association with each intervention analyzed in this systematic review are included in table 9. The costs of each medication and the Medicare fee schedule for preoperative injections are included in table 10.

Regional Nerve Blocks (Table 2):

Femoral nerve block:

When compared to a saline injection, a single injection femoral nerve block (FNB) significantly decreased VAS scores up to 60 minutes postoperatively [93] in one trial, up to the night of surgery in another, [44] and up to 24 hours in a third. [48] A single injection FNB also significantly decreased postoperative morphine consumption compared to saline injection. [44, 93] In a group of patients blinded to receiving a saline or bupivacaine FNB injection, a supplemental bupivacaine FNB injection was offered with a reported VAS score greater than 4. Significantly more patients in the saline group elected to receive the supplemental FNB, with 50% of patients in the saline group doing so within 40 minutes of the completion of surgery. [87] Because the femoral nerve innervates the quadriceps, femoral nerve block resulted in a motor deficit in all of these studies, [44, 48, 93] which persisted for the same amount of time as the analgesic effect. [87]

Other regional nerve blocks:

The addition of a sciatic nerve block to a FNB yielded significantly decreased analgesic consumption and NRS scores at first analgesia request compared to FNB alone. [58] As compared to a standard FNB there were no significant differences in pain scores or postoperative narcotic consumption between groups receiving a fascia iliaca nerve block [38] or a subsartorial saphenous nerve block. [18] The percentage of patients requiring intraoperative analgesic supplementation was significantly lower when a posterior psoas compartment block was used as compared to an anterior 3-in-1 FNB (femoral, obturator and lateral femoral cutaneous nerves). [17]

Patients receiving a bupivacaine bolus followed by a continuous saline infusion through a FNB catheter had significantly reduced NRS pain scores and oxycodone consumption through postoperative day one as compared to patients receiving placebo (saline bolus, saline infusion). Moreover, patients receiving a bupivacaine bolus followed by continuous bupivacaine infusion had significantly lower NRS scores on postoperative days 1, 2 and 4 and significantly lower oxycodone consumption on day 2 as compared to placebo. [119] The addition of a continuous infusion of bupivacaine provided through a FNB catheter to a patient controlled analgesia (PCA) device that dispensed bupivacaine boluses resulted in significantly lower NRS scores compared to PCA boluses alone. [108]

Stimulating catheters for nerve block placement:

FNB provided through a stimulating catheter led to significantly faster onset of anesthesia and significantly lower postoperative ketorolac consumption compared to FNB performed using a nonstimulating catheter. [29]

Dosages of nerve blocks:

A comparison of 0.0625 % bupivacaine, 0.125% bupivacaine, and 0.25 % bupivacaine for a continuous infusion FNB at 0.12 mg/kg/hour, resulted in no significant differences in VAS scores or morphine consumption at any timepoint. [110] No significant differences were found in VAS scores up to 24 hours

when comparing a single injection FNB using 0.25 % bupivacaine, 0.20 % ropivacaine, or 0.75 % ropivacaine. [121]

Additions of other drugs to nerve blocks:

The addition of clonidine to a femoral-sciatic nerve block did not significantly decrease VAS scores or analgesic consumption compared to femoral-sciatic nerve block alone. [23]

Intraarticular Injections (Table 3):

Intraarticular bupivacaine:

An IA bupivacaine injection significantly decreased VAS scores compared to an IA saline injection up to 4 hours postoperatively [62] but not on the night of surgery. [63] A preoperative local and IA infiltration of bupivacaine significantly decreased VAS scores on the night of surgery but did not significantly decrease piritramid (synthetic opiod analgesic available in certain European countries) consumption as compared to placebo (saline). [52] Continuous IA bupivacaine infusion significantly reduced median VAS scores [2] and narcotic consumption at 48-72 hours [92] as compared to no infusion. In two of three trials continuous IA bupivacaine infusion significantly reduced pain scores and rescue medication consumption compared to continuous IA saline infusion. [2, 51, 92] The addition of preoperative and postoperative bupivacaine infiltrations at incision sites significantly decreased analgesic consumption as compared to a single postoperative IA bupivacaine injection. [16]

Intraarticular Morphine injections:

IA morphine significantly decreased VAS scores and analgesic consumption compared to IA saline injection [4, 12, 47, 59, 62, 106, 122] and IA methadone injection. [4, 106] A dose-dependent response was reported when IA injections of 5 mg, 10 mg, and 15 mg of morphine were compared, [122] but not when 1 mg and 3 mg were compared. [111] A continuous 48 hour IA infusion of morphine and ropivacaine did not

significantly decrease VAS scores compared to IA saline infusion. [116] The addition of an IA morphine injection to a 3 in 1 FNB did not significantly decrease morphine consumption or VAS scores compared to the 3 in 1 FNB alone. [80]

Combination bupivacaine-morphine intraarticular injections:

An IA bupivacaine-morphine injection significantly decreased VAS scores and analgesic consumption as compared to IA saline, [45, 111] IA morphine alone, [111] and IA bupivacaine alone. [103, 111] One study showed no significant difference in VAS scores and analgesic consumption between IA bupivacaine-morphine and IA bupivacaine injections. [45] IA morphine-bupivacaine injections provided after tourniquet release significantly decreased VAS scores 30 minutes after tourniquet release and analgesic consumption in the first 30 minutes postoperatively compared to the same injection before tourniquet release but there were no significant differences beyond these timepoints. [46]

Other intraarticular injections

There were no significant differences in any measure between IA methadone and IA saline. [4, 106] IA tenoxicam (a non-steroidal anti-inflammatory drug (NSAID) indicated for the short-term treatment of musculoskeletal injury) significantly decreased VAS scores and supplementation of pethidine (an opioid analgesic marketed under the generic name demerol which the American Pain Society does not recommend for use as an analgesic [1]) compared to IA saline injections. [47] IA tenoxicam resulted in significantly fewer patients requiring pethidine than IA morphine. [47] The addition of IA sufentanil (a fentanyl analog) to an IA ropivacaine/clonidine injection significantly decreased rescue analgesia requirement during the first postoperative hour compared to IA ropivacaine/clonidine alone but did not significantly decrease VAS scores at any timepoint. [3] The injection of a multidrug cocktail consisting of ropivacaine, morphine, ketorolac and cefuroxime either periarticularly, or both intraarticularly and

periarticularly significantly decreased VAS scores in the first 24 hours compared to patients receiving no injection, IA ropivacaine injection, or IA injection of the same multidrug cocktail. [63]

Intravenous or intramuscular Injections (Table 4)

Rescue medication protocols:

There were no significant differences in VAS scores between patients receiving a standard inpatient rescue medication protocol of IV morphine provided through a PCA device and patients receiving IM ketorolac injection supplemented by oral (PO) oxycodone. The morphine group had a significantly higher incidence of postoperative nausea and vomiting as well as urinary retention. [94]

Various drugs injected intravenously/intramuscularly:

Patients receiving a postoperative 3.0 μg/kg IV fentanyl injection had significantly lower VRS scores between 4 and 24 hours following surgery compared to patients receiving 1.5 μg/kg IV fentanyl both preoperatively and postoperatively. [72] Intraoperative use of IV ketamine infusions significantly decreased morphine consumption, but not VAS scores, as compared to an IV saline infusion. [85] IV ketorolac injection significantly decreased both VAS scores and morphine consumption during the first postoperative hour compared to IV saline injection. [93]

Comparative analgesic regimens (Table 5):

A single-injection bupivacaine FNB did not significantly decrease VAS scores compared to a single IA bupivacaine injection. [82] A single injection ropivacaine FNB significantly decreased VAS scores and total morphine consumption compared to an IA ropivacaine injection. [56] A single injection preoperative FNB did not significantly decrease VAS scores or analgesic consumption as compared to postoperative wound site infiltration. [67] There was no significant difference in VAS scores between a preoperative IA fentanyl/bupivacaine injection and a 3 in 1 FNB, however a 3 in 1 FNB significantly decreased VAS scores

as compared to the same IA injection administered postoperatively. [78] A femoral-sciatic nerve block resulted in significantly lower VAS scores and morphine consumption as compared to an IA injection (5 mg morphine, clonidine and bupivacaine). [114] A continuous infusion FNB resulted in no significant difference in pain scores but significantly less breakthrough pain as compared to patients receiving an IA injection (10 mg morphine, ropivacaine, epinephrine). [120]

A continuous infusion femoral-sciatic nerve block significantly decreased VAS scores and morphine/ketorolac bolus administration as compared to a continuous bupivacaine IA and patellar tendon wound site infusion. [28] The addition of either single-injection or continuous FNB to an IA bupivacaine injection provided no significant decreases in pain scores or analgesic consumption compared to IA bupivacaine injection alone. [77, 89, 102] The addition of a local bupivacaine infiltration at the hamstring donor site to single injection FNB resulted in significantly decreased VAS scores up to 8 hours postoperatively compared to FNB alone. [15] A combination of ketorolac IV, IA ropivacaine-morphine and FNB administered prior to skin incision resulted in significantly lower VRS scores for the first 2 hours postoperatively and decreased IV PCA morphine consumption as compared to the same regimen administered after skin closure. [98]

Oral Medications (Table 6)

The administration of 800 mg ibuprofen or a combination of 800 mg ibuprofen and 1 g acetaminophen 1 hour prior to surgery, and at 6 and 12 hours post-surgery resulted in significantly lower VAS scores and ketobemidone (an opioid analgesic indicated for the treatment of severe pain) consumption as compared to 1 g acetaminophen alone. The addition of 1 g acetaminophen to 800 mg ibuprofen was no better than 800 mg ibuprofen alone. [26] Patients receiving 30 mg ketorolac had significantly better total pain relief at 3 hours as compared to patients receiving 20 mg hydrocodone combined with 2 g acetaminophen. [5]

Patients receiving dexamethasone and parecoxib/etoricoxib/valdecoxib (selective COX-2 inhibitor NSAIDs) had significantly lower VAS scores during rest at 24 hours and consumed less morphine compared to patients receiving only parecoxib/etoricoxib/valdecoxib or only dexamethasone. [25] Patients receiving etoricoxib reported significantly lower VAS scores up to 8 hours postoperatively compared patients receiving celecoxib or placebo. There were no significant differences in postoperative fentanyl consumption. [11]

The use of 1200 mg gabapentin preoperatively resulted in significantly lower VAS scores during the first postoperative hour compared to placebo and less morphine consumption at all timepoints measured up to 36 hours. No adverse events were reported. [84] The use of 10 mg zolpidem (a non-hypnotic sleep aid) for the first 7 nights postoperatively resulted in significantly lower Vicodin consumption as compared to placebo, however there was no difference in VAS scores. No adverse events were reported. [112] The costs of these medications can be found in table 10.

Cryotherapy/Compression (Table 7)

Nine RCTs have analyzed the effects of noncompressive cryotherapy in ACL reconstruction, with 5 reporting decreased pain symptoms and 4 reporting no significant differences as compared to controls. Postoperative cryotherapy consisting of a continuous flow cryotherapy device or a CryoCuff device significantly decreased VAS scores and analgesic consumption when compared to no cryotherapy or a single ice pack in the recovery room. [6, 13] In another trial a continuous flow device significantly reduced analgesic consumption as compared to no cryotherapy. [22] Preoperative use of cryotherapy significantly decreased percocet use on the day of surgery and VAS scores up to the morning of the first postoperative day. [65] In 4 trials there were no significant differences in analgesic consumption or VAS scores between cryocuff devices, ice packs, or continuous flow cooling pads with cold water or room temperature water. [27, 30, 35, 64] In the only study measuring IA temperatures, a cryotherapy device that maintained IA

temperatures 10 ° C below body temperature resulted in lower VAS scores than no cryotherapy or a 5 ° C decrease. A 10 ° C decrease in IA temperatures also decreased diclofenac consumption as compared to controls. No significant differences were observed between a 5 ° C decrease in IA temperatures and controls. [91] No study reported any adverse events associated with the use of cryotherapy.

A combined cryotherapy-compression device resulted in a significantly higher percentage of patients discontinuing narcotics 6 weeks postoperatively and a significantly greater decrease in VAS scores from preoperative levels at 2 and 6 weeks postoperatively compared to ice packs alone. [117]

Mobilization Strategies (Table 8)

Immobilization with a plaster cast for 5 weeks postoperatively did not significantly decrease the proportion of patients reporting pain on the Lysholm score as compared to a hinged brace with range of motion exercises beginning on postoperative day 7. [49] There were no significant differences in VAS scores between an unhinged immobilizing brace for two weeks postoperatively and no immobilization. [50] Immediate postoperative weightbearing significantly decreased the proportion of patients reporting pain symptoms two weeks postoperatively as compared to delaying weightbearing for two weeks postoperatively, and did not lead to an increase in joint laxity. [115]

Continuous passive motion (CPM) device usage for 16 hours per day immediately following surgery significantly decreased analgesic consumption but not VAS scores compared to controls not using CPM. [79, 123] A continuous active motion (CAM) device, in which the patient used their contralateral leg to pedal the injured leg, significantly improved proprioception but did not decrease VAS scores as compared to a CPM device. [43] There were no significant differences in analgesic consumption between patients using physical therapy, CPM devices or both within the first month postoperatively. [100]

Surgical Technique (Table 8)

Patients receiving a postoperative drain reported significantly higher VAS scores in one trial, [31] significantly lower VAS scores in another, [61] and no significant differences in VAS scores or analgesic consumption in a third [81] when compared to no drain. All 3 studies reported no complications associated with the use of the drains. [31, 61, 81] Intraoperative tourniquet inflation did not significantly increase morphine consumption or VRS scores as compared to no tourniquet, although it did improve intraoperative visibility. [53]

Intraoperative use of OMS103HP (an investigational drug product consisting of 13.75 mg ketoprofen, 4.52 mg amitriptyline, and 4.28 mg oxymetazoline added to a 3 L bag of irrigation solution which is used for arthroscopic irrigation) significantly increased the percentage of patients with satisfactory pain control (defined as VAS scores less than 20/100 and consuming a maximum of 2 hydrocodone/acetaminophen tablets per day within the first postoperative week) as compared to standard irrigation solution. There was no increase in the incidence of adverse events associated with OMS103HP use. [37]

Quality Analysis

In many cases the nature of the interventions being studied limited the feasibility of blinding, however 52 of the trials used some form of blinding. Of these, 44 had blinded patients, 42 were double blinded, and 8 were triple blinded. An additional 8 trials did not have blinded patients but did have blinded assessors. Graft type can influence initial post-operative pain symptoms because of harvest site pain. [42] There were 37 trials which used BPTB autografts exclusively and 19 which used hamstring autografts. Ten trials did not list the graft type used during reconstruction, and 11 used multiple grafts within the same trial. Eight of the trials which used more than one graft type included patients who received cadaveric allografts. Allograft reconstructions do not involve graft harvest morbidity and pain and typically result in less initial postoperative pain than autografts. [66] This represents a significant possible source of bias in these trials.

The pain scales used here (VAS, NRS, VRS) differed only in whether patients were asked to rate their pain by marking on a continuous scale or selecting a number out of a given range. There was, however, significant heterogeneity in the number of timepoints that these pain scale scores were reported. There was also variability in the nature of these timepoints as some studies reported pain scores based on the number of hours since the conclusion of surgery while others reported pain scores at milestones such as entry into the recovery room, first analgesia request, waking the morning following surgery or discharge. The time of day that surgery is conducted (morning/afternoon/evening) means that the amount of elapsed time when these milestones occur will differ greatly, introducing possible bias in these studies. In a RCT on cancer-related breakthrough pain a decrease of 2 points on a 0-10 VAS scale led patients to forego rescue opioids. [39] This provides objective data for the use of a 2-point decrease as criteria for a clinically significant result, however the definition of clinical relevance varied significantly between these trials.

Sixty-three trials reported postoperative medication consumption using 18 different medications. In 11 trials it was unclear what medication was used. Morphine was the most common drug used (27 trials) however this represents only 42 % of the trials measuring postoperative medication consumption. This introduces variability into these results and makes comparison of rescue medication consumption between studies difficult.

Discussion

ACL reconstruction is now almost solely performed on an outpatient basis. While this has been beneficial in terms of patient satisfaction [69] and costs, [60] it has also complicated postoperative pain management. Effective pain management in outpatient ACL reconstruction is essential because pain levels are closely linked to both functional recovery [19] and quality of life assessments. [40] Currently there is no consensus

regarding the optimal management of pain in this setting. Therefore we undertook this study to review the evidence regarding postoperative pain management following ACL reconstruction.

Previous systematic reviews have analyzed the efficacy of 4 of the interventions discussed here for pain management following outpatient ACL reconstruction. A meta-analysis of RCTs analyzing cryotherapy use found that it decreased pain (P = .02) but did not improve knee range of motion. [95] A systematic review of CPM concluded that it was unclear whether or not it provided any benefit. [105] A systematic review of postoperative rehabilitation methods concluded that immobilization provided no benefit and there were no detrimental effects of accelerated rehabilitation. [68] A systematic review of FNB reported that single injection FNB resulted in statistically significantly reduced pain in 5/13 trials, but the authors questioned whether or not these decreases were clinically significant. They concluded that single injection FNB did not decrease pain. [75] This systematic review, however, included studies where IA bupivacaine injections were given to both the treatment group receiving FNB and the control group receiving no FNB. Combining IA bupivacaine injection and FNB does not provide a synergistic analgesic effect. [77, 89, 102] FNB performed in the absence of IA bupivacaine injection, however, reduces pain symptoms for up to 24 hours. [44, 48, 87, 93] The authors of the previous systematic review emphasized that FNB did not decrease pain beyond 24 hours, but pain scores are highest immediately following surgery and decrease with time. [57] This makes the day of surgery a crucial period for effective pain relief. We believe this justifies the inclusion of FNB as a component of a multimodal approach to postoperative analgesia in this setting, particularly if no IA injection is used.

Single injection nerve blocks have consistently been shown to provide superior analgesia to placebo for up to 24 hours. [44, 48, 87, 93] While this is not long enough to provide effective pain management for the duration of the acute recovery phase (typically 48-72 hours), pain scores are highest on the day of surgery. [52] The main risk of FNB is falls, as all FNB dosages block motor output to the quadriceps. [110, 121] In one study, 1.6 % of patients who received FNB suffered a fall, [104] however, subsartorial saphenous nerve

block provided equivalent analgesia without blocking motor output. [18] This may provide a feasible alternative to the traditional FNB, and we are currently investigating this. Rarer complications associated with FNB include vascular puncture, [71] femoral neuritis, [104] and persistent paresthesia. [71] Stimulating catheters improve the accuracy of injections at the femoral nerve [29] and reduce the risk of these complications. Continuous infusion bupivacaine pumps prolong the effect of regional nerve blocks. [119] This prolongs the quadriceps strength deficit, necessitating effective patient education and fall prevention protocols.

Anesthetic injections provided at either the surgical wound site or intraarticularly provide effective analgesia [16, 52] which is equivalent to FNB. [82] When IA injections are utilized, we add fentanyl to the injections because IA opioid injections significantly reduce postoperative pain, [4, 12, 47, 59, 62, 106, 122] are less chondrotoxic than both bupivacaine and ropivacaine, [54] and are not associated with significantly increased side effects as compared to placebo. [124] While much of the evidence presented here analyzed the use of IA morphine, we use fentanyl because our decision to incorporate IA opioids into our practice was based on an RCT analyzing IA fentanyl use in arthroscopy patients. [86]

Continuous infusion bupivacaine pumps prolong the effect of IA injections. [2, 51, 92] However, Noyes et al. reported a case series of 21 patients with disabling knee symptoms due to severe postoperative chondrolysis secondary to IA bupivacaine pumps [88] and in vitro analysis revealed that 95 % of human articular chondrocytes undergo apoptosis after 30 minutes of exposure to 0.5% bupivacaine. [21] We do not use continuous IA bupivacaine infusions in our practice because of this risk. Only continuous infusions of IA ropivicaine or bupivacaine have been shown to lead to chondrolysis in vivo, [118] however, and ropivacaine is less chondrotoxic than bupivacaine in vitro. [54] This is why some physicians in our practice utilize single IA ropivacaine injections.

In our practice we utilize either a preoperative single-injection FNB provided through a stimulating catheter or an IA ropivacaine-fentanyl injection. We do not use both FNB and IA injections, because combining IA bupivacaine injection and FNB does not result in a synergistic effect on pain symptoms. [77, 89, 102] We do not commonly use continuous infusion FNB because of the associated fall risk, [104] but are exploring the use of subsartorial saphenous nerve continuous infusion blocks, because saphenous nerve blocks do not block quadriceps motor output [18] and continuous infusion nerve blocks can provide longer postoperative analgesia as compared with single injection regional blocks. [119]

Cryotherapy provided effective analgesia compared to controls receiving no cryotherapy [6, 13, 22, 65] in 4 trials, but in 3 trials ice water provided no improvement in pain symptoms compared to room temperature water. [27, 35, 64] In one study, a 10 ° C decrease below core body temperature provides an analgesic effect following ACL reconstruction, while a 5 ° C decrease below core body temperature does not. [91] As none of the other trials studying cryotherapy measured IA temperature, the failure to achieve the required decrease in IA temperature may provide an explanation for the conflicting results regarding the efficacy of cryotherapy in these studies. This makes it difficult to determine whether or not this intervention is beneficial in ACL reconstruction. Combined compression-cryotherapy devices provided superior analgesia [101, 117] as compared to ice packs alone. We offer cryotherapy-compression devices to our patients, however insurance does not cover the cost of these devices, leading to a $150 out of pocket cost to patients who choose to utilize them. This limits the wide applicability of this treatment in our practice.

We encourage our patients to begin moving their knees early after surgery and to engage in early, aggressive physical therapy because immediate weightbearing decreases pain without affecting stability. [115] Immobilization does not decrease pain symptoms and can lead to muscular atrophy, impeding the recovery of function. [49, 50] CPM device usage may have some benefits, [79, 123] however early aggressive physical therapy provided equivalent results [100] and it cost one group $22,200 annually to rent 10 of these

devices in 2014. [10] The combination of high costs and lack of strong evidence demonstrating decreased pain symptoms with their use make it difficult to recommend CPM devices in this setting. We do not utilize them in our practice for these reasons.

One of the main goals of pain control in the outpatient setting is to minimize the nausea, vomiting, sedation, respiratory depression and pruritus associated with opioids [97] by providing safer alternatives. NSAIDs provide a safer, lower risk alternative to opioids for pain medication, with oral ibuprofen providing greater pain control than acetaminophen [26] and oral ketorolac providing greater pain control than a combination of hydrocodone and acetaminophen. [5] There is, however, evidence from animal and in vitro studies linking NSAIDs to detrimental effects on bone, ligament and tendon healing. [107] One retrospective analysis linked ketorolac to an increase in anterior-posterior knee laxity following BPTB autograft ACL reconstruction. [83] Although the risk of impaired healing warrants further investigation, we view NSAIDs as a safe, low cost alternative to oral opioids and prescribe them to our patients for the first 5 days postoperatively. Gabapentin [84] and zolpidem [112] are additional oral medications that can be beneficial in reducing opioid consumption postoperatively. Gabapentin, however, can cause drowsiness and dizziness, [99] and zolpidem can cause nightmares and hallucinations. [113] The associated risk profiles of these medications limit their use in our practice. The risk profiles and complications of these and other interventions analyzed in this study can be found in table 9.

Cost analysis is extremely challenging with respect to postoperative pain management after ACL reconstruction and this study was not intended to provide a true cost analysis, however we have provided the costs of common medications used in table 10. The specific costs, dosages utilized and combinations vary from institution to institution. It should be noted that IA injections do not incur an anesthesiologist fee, while regional nerve blocks/catheters do. These non-facility fees, as determined from the 2013 Medicare physician fee schedule, are also listed in table 10.

This study has several strengths. It is the first comprehensive systematic review to evaluate all methods of post-operative pain control following ACL reconstruction. Only Level I and Level II randomized controlled trials were included, comprising the best available evidence on the topic. In addition, the results have been tabulated for the reader to compare different regimens available for outpatient ACL reconstruction.

This study is limited mainly by the quality of the studies included and heterogeneity of regimens used. We restricted our study to randomized control trials to limit any effects of bias and confounding. Many of the studies discussed here were based upon small patient pools, and therefore could be subject to type 2 errors. Additionally, wide variations in the timing of pain scale scores and postoperative rescue medications made comparisons of multiple results difficult. Because of the heterogeneity in measurement techniques and the wide breadth of interventions studied, a combination of data in the form of a meta-analysis was not attempted.

In accordance with this evidence reviewed in this systematic review, our current multimodal approach to pain control involves a preoperative single injection femoral nerve block or intraarticular ropivacaine/fentanyl injection, intraoperative tourniquet use, NSAIDs for the first 5 days postoperatively, cryotherapy/compression (optional due to associated cost), early weightbearing, early aggressive physical therapy, and oral percocet as needed. However, there is little evidence regarding the optimal utilization of evidence-supported modalities in this setting and additional research is needed to compare differing multimodal regimens.

Conclusions

This study presents and evaluates the currently available randomized, controlled studies on postoperative pain management after ACL surgery. Nerve blocks and intraarticular injections are both effective forms of analgesia. Cryotherapy appears to be beneficial provided IA temperatures are sufficiently decreased, and

is most effective when employed in conjunction with compression. Early mobilization reduces pain symptoms. Several oral medications, namely gabapentin, zolpidem, ketorolac and ibuprofen, provide effective, reliable alternatives to opioids. Despite the vast amount of high quality evidence on this topic, however, no consensus exists on the ideal regimen. Further research is needed to determine the optimal multimodal approach that can maximize recovery while minimizing pain and opioid consumption.

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771 Table 1: Significant results of RCTs analyzing pain outcomes following regional nerve block in ACL
772 reconstruction

Mulroy et al., Harris et al., Frost et al., Peng et al. [44, 48, 87, 93]	Femoral nerve block superior to saline injection or no injection
Jansen et al. [58]	Femoral-sciatic nerve block superior to femoral nerve block
Cappelleri et al. [17]	Posterior psoas approach to 3-in-1 femoral nerve block superior to anterior approach to 3-in-1 femoral nerve block
Williams et al. [119]	Continuous infusion femoral nerve block superior to single injection femoral nerve block
Svediene et al. [108]	Basal FNB bupivacaine infusion with on-demand boluses superior to on-demand boluses alone
Dauri et al. [29]	Femoral nerve block from stimulating catheter superior to femoral nerve block from nonstimulating catheter

773

774 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
775 medication consumption is included in this table. Additional information regarding these trials can be
776 found in table 1 of the supplemental section.

Table 2 – Significant results of RCTs analyzing pain outcomes for intraarticular injections in ACL reconstruction

Karlsson et al. [62]	Intraarticular bupivacaine injection superior to intraarticular saline injection
Guler et al., Arti et al., Stewart et al., Brandsson et al., Joshi et al., Yari et al., Karlsson et al. [4, 12, 47, 59, 62, 106, 122]	Intraarticular morphine injection superior to intraarticular saline injection
Tetzlaff et al., Yari et al. [111, 122]	Intraarticular injection of morphine and bupivacaine superior to intraarticular bupivacaine injection
Arti et al., Stewart et al. [4, 106]	Intraarticular morphine injection superior to intraarticular methadone injection
Yari et al. [122]	Intraarticular injection of bupivacaine and 15 mg morphine superior to intraarticular injection of bupivacaine and 5 mg morphine
Vintar et al. [116]	Patient controlled analgesia device dispensing intraarticular ropivacaine-morphine-ketorolac infusion superior to patient controlled analgesia device dispensing intraarticular saline infusion
Butterfield et al. [16]	Preoperative and postoperative bupivacaine infiltrations and intraarticular bupivacaine injection superior to intraarticular bupivacaine injection
Parker et al., Alford et al. [2, 92]	Continuous intraarticular bupivacaine infusion superior to no infusion in 1 of 2 trials
Parker et al., Hoenecke et al., Alford et al.[2, 51, 92]	Continuous intraarticular bupivacaine infusion superior to continuous intraarticular saline infusion in 2 of 3 trials
Guler et al. [47]	Intraarticular tenoxicam injection superior to intraarticular morphine injection
Armellin et al. [3]	Intraarticular injection of ropivacaine, clonidine and sufentanil superior to intraarticular injection of ropivacaine and clonidine
Koh et al. [63]	Periarticular or periarticular/intraarticular injection of ropivacaine, morphine, ketorolac and cerufoxime superior to intraarticular injection of ropivacaine, morphine, ketorolac and cerufoxime

Any intervention resulting in a statistically significant decrease in subjective pain scores or pain medication consumption is included in this table. Additional information regarding these trials can be found in table 2 of the supplemental section.

783 Table 3 – Significant results of RCTs analyzing pain outcomes following intramuscular/Intravenous
784 injections in ACL reconstruction

Menigaux et al. [85]	Intravenous ketamine superior to intravenous saline
Peng et al. [93]	Intravenous ketorolac superior to intravenous saline
Lenz et al. [72]	Postoperative 3.0 µg/kg intravenous fentanyl injection superior to 1.5 µg/kg intravenous fentanyl injection both preoperatively and postoperatively

785

786 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
787 medication consumption is included in this table. Additional information regarding these trials can be
788 found in table 3 of the supplemental section.

789 Table 4 – Significant results of RCTs analyzing pain outcomes of differing analgesia regimens in ACL
790 reconstruction

Mehdi et al., Iskandar et al. [56, 82]	Single injection femoral nerve block superior to single intraarticular bupivacaine injection in 1 of 2 trials
Dauri et al. [28]	Continuous infusion femoral nerve block superior to continuous intraarticular and wound site bupivacaine infiltration
Tran et al. [114]	Femoral-sciatic nerve block superior to intraarticular injection of bupivacaine + 5 mg morphine
Mayr et al. [78]	3-in-1 femoral nerve block superior to postoperative intraarticular fentanyl-bupivacaine injection
Woods et al. [120]	Continuous infusion FNB superior to intraarticular injection of bupivacaine and 10 mg morphine with available oxycodone tablets
Bushnell et al. [15]	Femoral nerve block with hamstring autograft donor site bupivacaine infiltration superior to femoral nerve block alone
Rosaeg et al. [98]	Preoperative intravenous ketorolac, intraarticular ropivacaine-morphine injection and femoral nerve block superior to the same multimodal regimen employed postoperatively

791

792 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
793 medication consumption is included in this table. Additional information regarding these trials can be
794 found in table 4 of the supplemental section.

795 Table 5 – Significant results of RCTs analyzing pain outcomes following oral medications for ACL
796 reconstruction

Dahl et al. [26]	Oral ibuprofen superior to oral acetaminophen
Barber et al. [5]	Oral ketorolac superior to oral hydrocodone and acetaminophen
Dahl et al. [25]	Oral dexamethasone and parecoxib/etoricoxib/valdecoxib superior to oral dexamethasone/parecoxib/etoricoxib/valdecoxib
Boonriong et al. [11]	Oral eteroicoxib superior to oral celecoxib or placebo
Menigaux et al. [84]	Oral gabapentin superior to oral placebo
Tompkins et al. [112]	Oral zolpidem superior to oral placebo

797

798 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
799 medication consumption is included in this table. Additional information regarding these trials can be
800 found in table 5 of the supplemental section.

801 Table 6 – Significant results of RCTs analyzing pain outcomes for cryotherapy and compression in ACL
802 reconstruction

Barber et al., Brandsson et al., Cohn et al., Daniel et al., Dervin et al., Edwards et al., Konrath et al., Koyonos et al. [6, 13, 22, 27, 30, 35, 64, 65]	Cryotherapy superior to no cryotherapy or room temperature water in 4 of 8 trials
Waterman et al. [117]	Cryotherapy and compression superior to cryotherapy alone
Ohkoshi et al. [91]	10 ° C intraarticular decrease below body temperature superior to 5 ° C intraarticular decrease below body temperature or no cryotherapy

803

804 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
805 medication consumption is included in this table. Additional information regarding these trials can be
806 found in table 6 of the supplemental section.

807 Table 7 – Significant results of RCTs analyzing pain outcomes with differing mobilization strategies for ACL
808 reconstruction

Tyler et al. [115]	Immediate postoperative weightbearing superior to delayed postoperative weightbearing
Mccarthy et al., Yates et al. [79, 123]	Continuous passive motion device use superior to no continuous passive motion

809

810 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
811 medication consumption is included in this table. Additional information regarding these trials can be
812 found in table 7 of the supplemental section.

Table 8 – Significant results of RCTs analyzing pain outcomes following differing intraoperative techniques for ACL reconstruction

Dhawan et al., Karahan et al., Mccormack et al. [31, 61, 81]	Postoperative drain insertion superior to no drain in 1 of 3 trials
Fanton et al. [37]	Arthroscopic irrigation solution containing experimental drug OMS103HP superior to standard irrigation solution

Any intervention resulting in a statistically significant decrease in subjective pain scores or pain medication consumption is included in this table. Additional information regarding these trials can be found in table 8 of the supplemental section.

820 Table 9 – Possible complications associated with interventions used for pain control following ACL
821 reconstruction

Intervention	Complications
Single injection femoral nerve block	Decreased quadriceps motor function and fall risk, [97] vascular puncture, [71] persistent paresthesia [71]
Continuous infusion femoral nerve block	Bacterial catheter colonization, [24] permanent nerve injury [55]
Continuous intraarticular bupivacaine infusion	Chondrolysis leading to articular cartilage degeneration [88]
Bupivacaine/Ropivacaine	Cardiac arrest, [32] seizure, [41]
Ketamine	Sedation, sleep pattern change, dizziness, depersonalization, hallucinations [20]
Opioids	Dependency, nausea, vomiting, sedation, respiratory depression, pruritus [97]
NSAIDs	Gastrointestinal bleeding, [70] decreased bone, ligament and tendon healing [107]
COX-2 Inhibitors	Thrombosis [9]
Acetaminophen	Hepatotoxicity [14]
Gabapentin	Drowsiness, dizziness, ataxia and confusion [99]
Zolpidem	Nightmares, hallucinations [113]
Cryotherapy	Nerve palsy [33]
CPM device	Increased wound drainage and wound complications [90]
Intraarticular drain	Increased need for transfusion, [96] bacterial colonization [34]
Tourniquet	Venous thromboembolic events [109]

822

823 Complications for each intervention are based on a literature review and do not reflect the results of the
824 individual randomized controlled trials presented in this systematic review.

825

826 Table 10 – Costs associated with medications used for pain control following ACL reconstruction

Medication*	Unit Dose	Cost/Fee
Injectable		
Bupivacaine pf 0.5%	10 ml vial	$ 1.21
Bupivacine pf 0.5%	30 ml vial	$ 1.30
Ropivacaine pf 0.5%	30 ml vial	$ 6.35
Morphine 2 mg	1 ml carpuject	$ 1.77
ketorolac 30 mg	1 ml vial	$ 1.79
Epinephrine 1/100000	1 ml ampule	$ 1.27
Fentanyl 50 mcg/ml	2 ml vial	$ 1.00
Ketamine 50 mg/ml	10 ml vial	$ 2.70
Dexamethasone 4mg	1 ml vial	$ 0.68
PCA		
Fentanyl 10 mcg/ml	55 ml syringe	$ 12.20
Hydromorphone 0.2 mg/ml	50 ml syringe	$ 11.90
Oral		
Hydrocodone	2 mg tablet	$ 0.16
Ibuprofen	200 mg tablet	$ 0.30
Acetaminophen	325 mg tablet	$ 0.02
Celecoxib	200 mg tablet	$ 1.95
Zolpidem	5 mg tablet	$ 0.04
Injections Ψ		
Single sciatic nerve injection		$139.15
Continuous sciatic nerve infusion		$78.59
Single femoral nerve injection		$121.46
Continuous femoral nerve infusion		$70.43

827

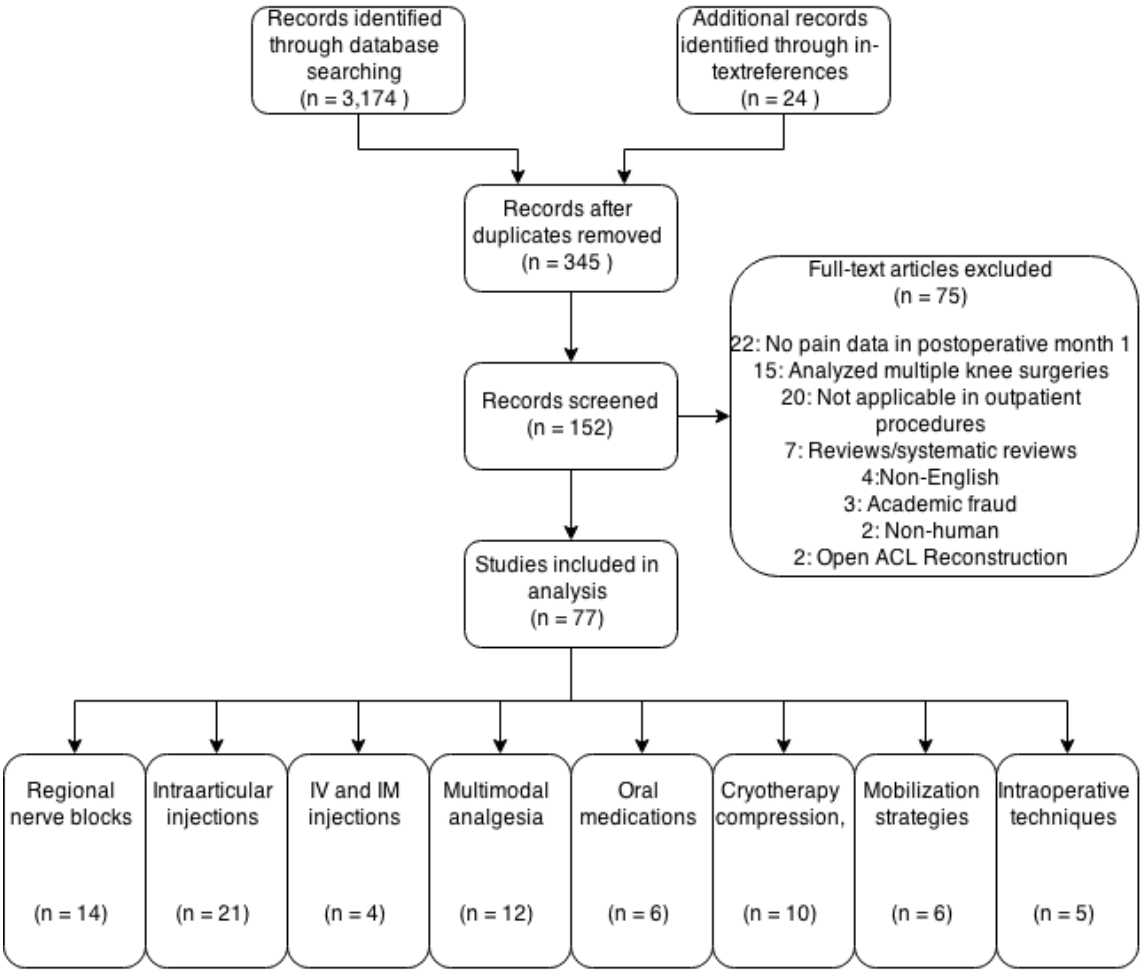
828 *Medication costs acquired from large tertiary care hospital pharmacy.

829 Ψ Non-facility fees acquired from 2013 Medicare physician fee schedule – national average.

830

831 Figure 1 – Literature review results according to PRISMA criteria

832



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