Pain Management After Outpatient Anterior Cruciate Ligament Reconstruction

CME

A Systematic Review of Randomized Controlled Trials

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Background: Effective pain management after anterior cruciate ligament (ACL) reconstruction improves patient satisfaction and function.

Purpose: To collect and evaluate the available evidence from randomized controlled trials (RCTs) on pain control after ACL reconstruction.

Study Design: Systematic review.

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

Results: A total of 77 RCTs met inclusion criteria: 14 on regional nerve blocks, 21 on intra-articular 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 nerve blocks 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 intra-articularly provided equivalent analgesia to regional nerve blocks. Continuous-infusion catheters of a local anesthetic provided 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 water at room temperature provided equivalent analgesic effects. Early weightbearing decreased pain compared to delayed weightbearing. Oral gabapentin given preoperatively and oral zolpidem given for the first week postoperatively each decreased opioid consumption as compared to placebo. Ibuprofen reduced pain compared to acetaminophen. Oral ketorolac reduced pain compared to hydrocodone-acetaminophen.

Conclusion: Regional nerve blocks and intra-articular injections are both effective forms of analgesia. Cryotherapy-compression appears to be beneficial, provided that intra-articular 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, 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 RCTs on pain control regimens after ACL reconstruction.

Keywords: anterior cruciate ligament; pain management; cryotherapy; intra-articular injections; regional nerve block

The anterior cruciate ligament (ACL) is the most commonly reconstructed ligament in the knee.[72] In 2006, a total of 129,836 ACL reconstructions were performed in the United States, and the annual rate is increasing.[73] Effective postoperative pain management is a critical component to recovery, effective rehabilitation, and patient satisfaction. After ACL reconstruction, psychological factors are predictive of outcomes,[35] and pain levels are inversely associated with function[18] and quality-of-life assessments.[39]

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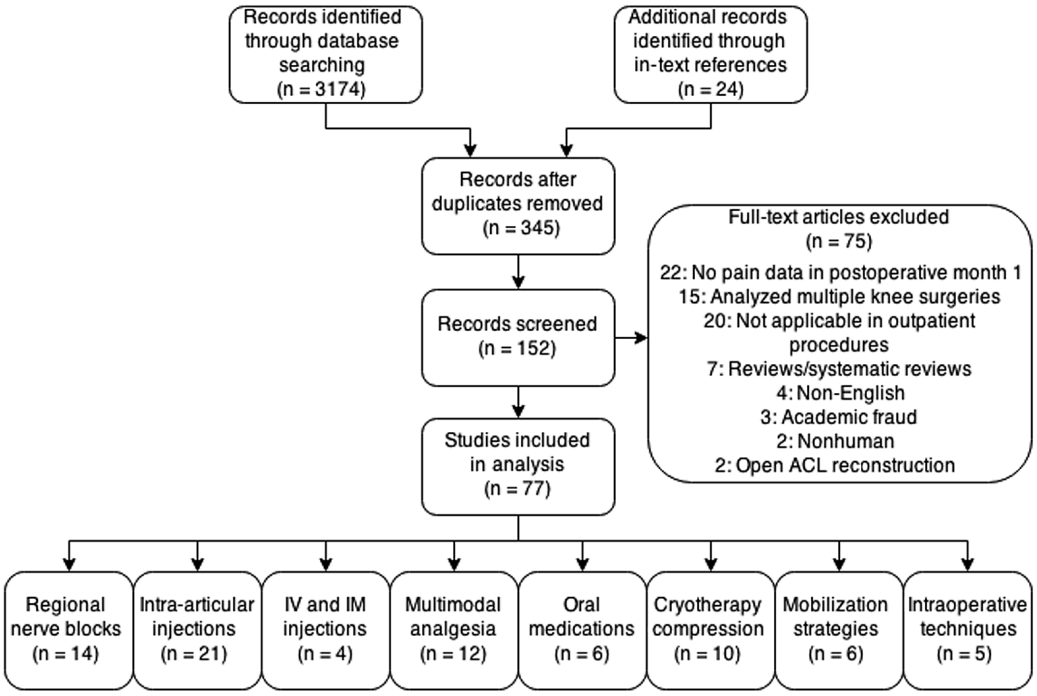

Figure 1. Literature review results according to PRISMA criteria.

The 2 main measures used to quantify patients' 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 numeric rating scale (NRS). Although these methods rely on patient reporting of subjective feelings, they are highly reproducible and reliable.[6,7]

There is an abundance of literature evaluating various pain management medications and modalities after ACL reconstruction. Individual systematic reviews have analyzed the efficacy of cryotherapy,[75] femoral nerve blocks (FNBs),[74] continuous passive motion (CPM),[105] and postoperative rehabilitation.[67] We performed a systematic review of all level 1 and 2 randomized controlled trials (RCTs) and present a comprehensive review of the evidence surrounding pain management after outpatient arthroscopic ACL reconstruction.

METHODS

A comprehensive literature review was performed to identify all RCTs on pain management after 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, CPM, immobilization, early weightbearing, cryotherapy, compression, intra-articular (IA) injections, nerve blocks, nonsteroidal anti-inflammatory drugs (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 RCTs, level 1 or 2, that compared any 2 or more pain management modalities to other modalities or placebo, utilizing objective measures to quantify postoperative pain within the first postoperative month. Only modalities that can be applied to 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 Appendix (available online at http://ajsm.sagepub.com/supplemental). All methods of arthroscopic reconstruction were included. Studies that 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 nonhuman articles, nonrandomized trials, studies that included patients undergoing other surgical interventions alongside patients undergoing ACL reconstruction, open ACL reconstruction, meta-analyses or systematic reviews of RCTs, retracted articles or articles published by first authors associated with multiple cases of academic fraud, and studies that did not measure pain symptoms. Data were collected including demographic information, pain outcomes, and complications for each included study. Wherever applicable, statistically significant results are reported. PRISMA (Preferred Reporting

TABLE 1
Significant Results of RCTs Analyzing Pain Outcomes for Regional Nerve Blocks After ACL Reconstruction[a]

Mulroy et al,[86] Harris et al,[47] Frost et al,[43] Peng et al[92]	FNB superior to saline injection or no injection
Jansen et al[57]	Femoral-sciatic nerve block superior to FNB
Cappelleri et al[16]	Posterior psoas approach to 3-in-1 FNB superior to anterior approach to 3-in-1 FNB
Williams et al[119]	Continuous-infusion FNB superior to single-injection FNB
Svediene et al[108]	Basal FNB bupivacaine infusion with on-demand boluses superior to on-demand boluses alone
Dauri et al[28]	FNB from stimulating catheter superior to FNB from nonstimulating catheter

[a]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 Appendix Table A1. ACL, anterior cruciate ligament; FNB, femoral nerve block; RCT, randomized controlled trial.

Items for Systematic Reviews and Meta-Analyses) criteria were followed throughout the study. Quality appraisal was also performed for each individual trial.

RESULTS

A total of 77 RCTs met the 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 IA injections, 4 were trials of intramuscular (IM) or IV injections, 12 were trials comparing differing analgesic regimens, 6 were trials of 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 2 separate phases, which are presented here as individual trials.[111] One trial analyzed 2 interventions in the same randomized cohort of patients, and these results are analyzed in both categories.[92] A concise summary of all interventions, which resulted in a statistically significant decrease in either reported pain symptoms or opioid consumption, can be found below. Additional information regarding each RCT including graft types, number of participants, dosages, pain metrics, rescue medications, *P* values, and pain and medication values for each comparison group can be found in Appendix Tables A1 to A8 (available online).

Regional Nerve Blocks (Table 1)

Femoral Nerve Blocks. When compared to a saline injection, a single-injection FNB significantly decreased VAS scores up to 60 minutes postoperatively[92] in one trial, up to the night of surgery in another trial,[43] and up to 24 hours in a third trial.[47] A single-injection FNB also significantly decreased postoperative morphine consumption compared to a saline injection.[43,92] In a group of patients blinded to receiving a saline or bupivacaine FNB injection, a supplemental bupivacaine FNB injection was provided 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.[86] Because the femoral nerve innervates the quadriceps, FNBs resulted in a motor deficit in all of these studies,[43,47,92] which persisted for the same amount of time as the analgesic effect.[86]

Other Regional Nerve Blocks. The addition of a sciatic nerve block to an FNB yielded significantly decreased analgesic consumption and NRS scores at the first request for analgesia compared to an FNB alone.[57] 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[37] or a subsartorial saphenous nerve block.[17] 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).[16]

Patients receiving a bupivacaine bolus followed by a continuous saline infusion through an FNB catheter had significantly reduced NRS scores and oxycodone consumption through postoperative day 1 as compared to patients receiving placebo (saline bolus, saline infusion). Moreover, patients receiving a bupivacaine bolus followed by a 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 an 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. An FNB provided through a stimulating catheter led to a significantly faster onset of anesthesia and significantly lower postoperative ketorolac consumption compared to an FNB performed using a nonstimulating catheter.[28]

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/h resulted in no significant differences in VAS scores or morphine consumption at any time point.[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]

Addition of Other Drugs to Nerve Blocks. The addition of clonidine to a femoral-sciatic nerve block did not

TABLE 2
Significant Results of RCTs Analyzing Pain Outcomes for IA Injections After ACL Reconstruction[a]

Karlsson et al[61]	IA bupivacaine injection superior to IA saline injection
Guler et al,[46] Arti and Mehdinasab,[3] Stewart et al,[106] Brandsson et al,[11] Joshi et al,[58] Yari et al,[122] Karlsson et al[61]	IA morphine injection superior to IA saline injection
Tetzlaff et al,[111] Yari et al[122]	IA injection of morphine and bupivacaine superior to IA bupivacaine injection
Arti and Mehdinasab,[3] Stewart et al[106]	IA morphine injection superior to IA methadone injection
Yari et al[122]	IA injection of bupivacaine and 15 mg morphine superior to IA injection of bupivacaine and 5 mg morphine
Vintar et al[116]	Patient-controlled analgesia device dispensing IA ropivacaine-morphine-ketorolac infusion superior to patient-controlled analgesia device dispensing IA saline infusion
Butterfield et al[15]	Preoperative and postoperative bupivacaine infiltrations and IA bupivacaine injection superior to IA bupivacaine injection
Parker et al,[91] Alford and Fadale[1]	Continuous IA bupivacaine infusion superior to no infusion in 1 of 2 trials
Parker et al,[91] Hoenecke et al,[50] Alford and Fadale[1]	Continuous IA bupivacaine infusion superior to continuous IA saline infusion in 2 of 3 trials
Guler et al[46]	IA tenoxicam injection superior to IA morphine injection
Armellin et al[2]	IA injection of ropivacaine, clonidine, and sufentanil superior to IA injection of ropivacaine and clonidine
Koh et al[62]	Periarticular or periarticular/IA injection of ropivacaine, morphine, ketorolac, and cefuroxime superior to IA injection of ropivacaine, morphine, ketorolac, and cefuroxime

[a]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 Appendix Table A2. ACL, anterior cruciate ligament; IA, intra-articular; RCT, randomized controlled trial.

significantly decrease VAS scores or analgesic consumption compared to a femoral-sciatic nerve block alone.[22]

IA Injections (Table 2)

IA Bupivacaine Injections. An IA bupivacaine injection significantly decreased VAS scores compared to an IA saline injection up to 4 hours postoperatively[61] but not on the night of surgery.[62] A preoperative local and IA infiltration of bupivacaine significantly decreased VAS scores on the night of surgery but did not significantly decrease piritramide (synthetic opioid analgesic available in certain European countries) consumption as compared to placebo (saline).[51] A continuous IA bupivacaine infusion significantly reduced median VAS scores[1] and narcotic consumption at 48 to 72 hours[91] as compared to no infusion. In 2 of 3 trials, a continuous IA bupivacaine infusion significantly reduced pain scores and rescue medication consumption compared to a continuous IA saline infusion.[1,50,91] The addition of preoperative and postoperative bupivacaine infiltrations at incision sites significantly decreased analgesic consumption as compared to a single postoperative IA bupivacaine injection.[15]

IA Morphine Injections. An IA morphine injection significantly decreased VAS scores and analgesic consumption compared to an IA saline injection[3,11,46,58,61,106,122] and IA methadone injection.[3,106] 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 an 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 a 3-in-1 FNB alone.[79]

Combination Bupivacaine-Morphine IA Injections. An IA bupivacaine-morphine injection significantly decreased VAS scores and analgesic consumption as compared to IA saline,[44,111] 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.[44] IA morphine-bupivacaine injections 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 time points.[45]

Other IA Injections. There were no significant differences in any measure between IA methadone and IA saline.[3,106] IA tenoxicam (an NSAID indicated for the short-term treatment of musculoskeletal injuries) significantly decreased VAS scores and the supplementation of pethidine (an opioid analgesic marketed under the trade name Demerol, which the American Pain Society does not recommend for use as an analgesic[94]) compared to IA saline injections.[46] IA tenoxicam resulted in significantly fewer patients requiring pethidine than IA morphine.[46] The addition of IA sufentanil (a fentanyl analog) to an IA ropivacaine/clonidine injection significantly decreased the requirement of rescue analgesics during the first postoperative hour compared to IA ropivacaine/clonidine alone but

TABLE 3
Significant Results of RCTs Analyzing Pain Outcomes for Intramuscular/IV Injections After ACL Reconstruction[a]

Menigaux et al[84]	IV ketamine superior to IV saline
Peng et al[92]	IV ketorolac superior to IV saline
Lenz et al[71]	Postoperative 3.0 μg/kg IV fentanyl injection superior to 1.5 μg/kg IV fentanyl injection both preoperatively and postoperatively

[a]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 Appendix Table A3. ACL, anterior cruciate ligament; IV, intravenous; RCT, randomized controlled trial.

TABLE 4
Significant Results of RCTs Analyzing Pain Outcomes for Differing Analgesic Regimens After ACL Reconstruction[a]

Mehdi et al,[81] Iskandar et al[55]	Single-injection FNB superior to single IA bupivacaine injection in 1 of 2 trials
Dauri et al[27]	Continuous-infusion FNB superior to continuous IA and wound-site bupivacaine infiltration
Tran et al[114]	Femoral-sciatic nerve block superior to IA injection of bupivacaine and 5 mg morphine
Mayr et al[77]	3-in-1 FNB superior to postoperative IA fentanyl-bupivacaine injection
Woods[120]	Continuous-infusion FNB superior to IA injection of bupivacaine and 10 mg morphine with available oxycodone tablets
Bushnell et al[14]	FNB with bupivacaine infiltration at hamstring autograft donor site superior to FNB alone
Rosaeg et al[98]	Preoperative intravenous ketorolac, IA ropivacaine-morphine injection, and FNB superior to the same multimodal regimen employed postoperatively

[a]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 Appendix Table A4. ACL, anterior cruciate ligament; FNB, femoral nerve block; IA, intra-articular; RCT, randomized controlled trial.

did not significantly decrease VAS scores at any time point.[2] The injection of a multidrug cocktail consisting of ropivacaine, morphine, ketorolac, and cefuroxime, either periarticularly or both intra-articularly and periarticularly, significantly decreased VAS scores in the first 24 hours compared to patients receiving no injection, an IA ropivacaine injection, or an IA injection of the same multidrug cocktail.[62]

IV or IM Injections (Table 3)

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 an IM ketorolac injection supplemented by oral oxycodone. The morphine group had a significantly higher incidence of postoperative nausea and vomiting as well as urinary retention.[93]

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 after surgery compared to patients receiving 1.5 μg/kg IV fentanyl both preoperatively and postoperatively.[71] The intraoperative use of IV ketamine infusions significantly decreased morphine consumption but not VAS scores as compared to an IV saline infusion.[84] An IV ketorolac injection significantly decreased both VAS scores and morphine consumption during the first postoperative hour compared to an IV saline injection.[92]

Comparative Analgesic Regimens (Table 4)

A single-injection bupivacaine FNB did not significantly decrease VAS scores compared to a single IA bupivacaine injection.[81] A single-injection ropivacaine FNB significantly decreased VAS scores and total morphine consumption compared to an IA ropivacaine injection.[55] A single-injection preoperative FNB did not significantly decrease VAS scores or analgesic consumption as compared to postoperative wound site infiltration.[66] 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.[77] 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 an IA injection (10 mg morphine, ropivacaine, and epinephrine).[120]

A continuous-infusion femoral-sciatic nerve block significantly decreased VAS scores and the administration of morphine/ketorolac boluses as compared to a continuous IA bupivacaine and patellar tendon wound site infusion.[27] The addition of either a single-injection or continuous FNB to an IA bupivacaine injection provided no significant decreases in pain scores or analgesic consumption compared to an IA bupivacaine injection alone.[76,90,102] The addition of local bupivacaine infiltration at the hamstring donor site to a single-injection FNB resulted in

TABLE 5
Significant Results of RCTs Analyzing Pain Outcomes for Oral Medications After ACL Reconstruction[a]

Dahl et al[24]	Oral ibuprofen superior to oral acetaminophen
Barber and Gladu[4]	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[10]	Oral etoricoxib superior to oral celecoxib or placebo
Menigaux et al[83]	Oral gabapentin superior to oral placebo
Tompkins et al[112]	Oral zolpidem superior to oral placebo

[a]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 Appendix Table A5. ACL, anterior cruciate ligament; RCT, randomized controlled trial.

TABLE 6
Significant Results of RCTs Analyzing Pain Outcomes for Cryotherapy and Compression After ACL Reconstruction[a]

Barber et al,[5] Brandsson et al,[12] Cohn et al,[21] Daniel et al,[26] Dervin et al,[29] Edwards et al,[34] Konrath et al,[63] Koyonos et al[64]	Cryotherapy superior to no cryotherapy or water at room temperature in 4 of 8 trials
Waterman et al[117]	Cryotherapy and compression superior to cryotherapy alone
Ohkoshi et al[89]	10°C intra-articular decrease below body temperature superior to 5°C intra-articular decrease below body temperature or no cryotherapy

[a]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 Appendix Table A6. ACL, anterior cruciate ligament; RCT, randomized controlled trial.

significantly decreased VAS scores up to 8 hours postoperatively compared to an FNB alone.[14] A combination of IV ketorolac, IA ropivacaine-morphine, and FNB administered prior to a 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 5)

The administration of 800 mg ibuprofen or a combination of 800 mg ibuprofen and 1 g acetaminophen 1 hour before surgery and at 6 and 12 hours after 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.[24] 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.[4]

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 to patients receiving celecoxib or placebo. There were no significant differences in postoperative fentanyl consumption.[10]

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 time points measured up to 36 hours. No adverse events were reported.[83] The use of 10 mg zolpidem (a nonhypnotic 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 6)

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 Cryo/Cuff device significantly decreased VAS scores and analgesic consumption when compared to no cryotherapy or a single ice pack in the recovery room.[5,12] In another trial, a continuous flow device significantly reduced analgesic consumption as compared to no cryotherapy.[21] The preoperative use of cryotherapy significantly decreased Percocet consumption on the day of surgery and VAS scores up to the morning of the first postoperative day.[64] In 4 trials, there were no significant differences in analgesic consumption or VAS scores between Cryo/Cuff devices, ice packs, or continuous flow cooling pads with cold water or water at room temperature.[26,29,34,63] In the only study measuring IA temperatures, a cryotherapy device that maintained IA temperatures of 10°C below body

TABLE 7
Significant Results of RCTs Analyzing Pain Outcomes for Differing Mobilization Strategies After ACL Reconstruction[a]

Tyler et al[115]	Immediate postoperative weightbearing superior to delayed postoperative weightbearing
McCarthy et al,[78] Yates et al[123]	Use of CPM device superior to no CPM

[a]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 Appendix Table A7. ACL, anterior cruciate ligament; CPM, continuous passive motion; RCT, randomized controlled trial.

TABLE 8
Significant Results of RCTs Analyzing Pain Outcomes for Differing Intraoperative Techniques After ACL Reconstruction[a]

Dhawan et al,[30] Karahan et al,[60] McCormack et al[80]	Postoperative drain insertion superior to no drain in 1 of 3 trials
Fanton et al[36]	Arthroscopic irrigation solution containing experimental drug OMS103HP superior to standard irrigation solution

[a]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 Appendix Table A8. ACL, anterior cruciate ligament; RCT, randomized controlled trial.

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.[89] 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 7)

Immobilization with a plaster cast for 5 weeks postoperatively did not significantly decrease the proportion of patients reporting pain according to the Lysholm score as compared to a hinged brace with range of motion exercises beginning on postoperative day 7.[48] There were no significant differences in VAS scores between an unhinged immobilizing brace for 2 weeks postoperatively and no immobilization.[49] Immediate postoperative weightbearing significantly decreased the proportion of patients reporting pain symptoms 2 weeks postoperatively as compared to delaying weightbearing for 2 weeks postoperatively and did not lead to an increase in joint laxity.[115]

The use of a CPM device for 16 hours per day immediately after surgery significantly decreased analgesic consumption but not VAS scores compared to controls not using CPM.[78,123] A continuous active motion device, in which the patient used the contralateral leg to pedal the injured leg, significantly improved proprioception but did not decrease VAS scores as compared to a CPM device.[42] 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,[30] significantly lower VAS scores in another trial,[60] and no significant differences in VAS scores or analgesic consumption in a third trial[80] when compared to no drain. All 3 studies reported no complications associated with the use of drains.[30,60,80] Intraoperative tourniquet inflation did not significantly increase morphine consumption or VRS scores as compared to no tourniquet, although it did improve intraoperative visibility.[52]

The 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 those with a standard irrigation solution. There was no increase in the incidence of adverse events associated with the use of OMS103HP.[36]

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 postoperative pain symptoms because of pain at the harvest site.[41] There were 37 trials that used bone–patellar tendon–bone (BPTB) autografts exclusively and 19 that 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 that used more than 1 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 autograft reconstructions.[65] This represents a significant possible source of bias in these trials.

The pain scales used here (VAS, NRS, and 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 time points at which these pain scale scores were reported. There was also variability in the nature of these time points 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 request of analgesia, waking the morning after 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 an RCT on cancer-related breakthrough pain, a decrease of 2 points on a 0-to-10 VAS led patients to forego rescue opioids.[38] This provides objective data for the use of a 2-point decrease as a criterion 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[68] and costs,[59] 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[18] and quality-of-life assessments.[39] Currently, there is no consensus regarding the optimal management of pain in this setting. Therefore, we undertook this study to review the evidence regarding pain management after ACL reconstruction.

Previous systematic reviews have analyzed the efficacy of 4 of the interventions discussed here for pain management after outpatient ACL reconstruction. A meta-analysis of RCTs analyzing the use of cryotherapy 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 it provided any benefit.[105] A systematic review of postoperative rehabilitation methods concluded that immobilization provided no benefit and that there were no detrimental effects of accelerated rehabilitation.[67] A systematic review of FNBs reported that a single-injection FNB resulted in statistically significantly reduced pain in 5 of 13 trials, but the authors questioned whether these decreases were clinically significant. They concluded that a single-injection FNB did not decrease pain.[74] This systematic review, however, included studies in which IA bupivacaine injections were given to both the treatment group receiving FNBs and the control group receiving no FNBs. Combining an IA bupivacaine injection and an FNB did not provide a synergistic analgesic effect.[76,90,102] FNBs performed in the absence of IA bupivacaine injections, however, reduced pain symptoms for up to 24 hours.[43,47,86,92] The authors of a previous systematic review emphasized that FNBs did not decrease pain beyond 24 hours but that pain scores were highest immediately after surgery and decreased with time.[56] This makes the day of surgery a crucial period for effective pain relief. We believe that this justifies the inclusion of FNBs 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.[43,47,86,92] While this was not long enough to provide effective pain management for the duration of the acute recovery phase (typically 48-72 hours), pain scores were highest on the day of surgery.[51] The main risk of FNBs is falls, as all FNB dosages block motor output to the quadriceps.[110,121] In 1 study, 1.6% of patients who received FNBs suffered a fall[104]; however, a subsartorial saphenous nerve block provided equivalent analgesia without blocking motor output.[17] This may provide a feasible alternative to a traditional FNB, and we are currently investigating this. Rarer complications associated with FNBs include vascular puncture,[70] femoral neuritis,[104] and persistent paresthesia.[70] Stimulating catheters improved the accuracy of injections at the femoral nerve[28] and reduced the risk of these complications. Continuous-infusion bupivacaine pumps prolonged the effect of regional nerve blocks.[119] This in turn prolongs the quadriceps strength deficit, necessitating effective patient education and fall prevention protocols.

Anesthetic injections at either the surgical wound site or intra-articularly provided effective analgesia,[15,51] which was equivalent to FNBs.[81] When IA injections are utilized, we add fentanyl to the injections because IA opioid injections significantly reduce postoperative pain,[3,11,46,58,61,106,122] are less chondrotoxic than both bupivacaine and ropivacaine,[53] 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 the use of IA fentanyl in patients undergoing arthroscopic surgery.[85]

Continuous-infusion bupivacaine pumps prolonged the effect of IA injections.[1,50,91] However, Noyes et al[87] reported a case series of 21 patients with disabling knee symptoms due to severe postoperative chondrolysis secondary to IA bupivacaine pumps, and in vitro analysis revealed that 95% of human articular chondrocytes undergo apoptosis after 30 minutes of exposure to 0.5% bupivacaine.[20] We do not use continuous IA bupivacaine infusions in our practice because of this risk. Only continuous infusions of IA ropivacaine or bupivacaine have been shown to lead to chondrolysis in vivo,[118] and ropivacaine is less chondrotoxic than bupivacaine in vitro.[53] This is why some physicians in our practice utilize single IA ropivacaine injections.

TABLE 9
Possible Complications Associated With Interventions Used for Pain Control After ACL Reconstruction[a]

Intervention	Complications
Single-injection FNB	Decreased quadriceps motor function and fall risk,[97] vascular puncture,[70] persistent paresthesia[70]
Continuous-infusion FNB	Bacterial catheter colonization,[23] permanent nerve injury[54]
Continuous intra-articular bupivacaine infusion	Chondrolysis leading to articular cartilage degeneration[87]
Bupivacaine/ropivacaine	Cardiac arrest,[31] seizure[40]
Ketamine	Sedation, sleep pattern change, dizziness, depersonalization, hallucinations[19]
Opioids	Dependency, nausea, vomiting, sedation, respiratory depression, pruritus[97]
NSAIDs	Gastrointestinal bleeding[69]; decreased bone, ligament, and tendon healing[107]
COX-2 inhibitors	Thrombosis[8]
Acetaminophen	Hepatotoxicity[13]
Gabapentin	Drowsiness, dizziness, ataxia, confusion[99]
Zolpidem	Nightmares, hallucinations[113]
Cryotherapy	Nerve palsy[32]
Continuous passive motion device	Increased wound drainage and wound complications[88]
Intra-articular drain	Increased need for transfusion,[96] bacterial colonization[33]
Tourniquet	Venous thromboembolic events[109]

[a]Complications for each intervention are based on a literature review and do not reflect the results of the individual randomized controlled trials presented in this systematic review. ACL, anterior cruciate ligament; FNB, femoral nerve block; NSAID, nonsteroidal anti-inflammatory drug.

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 FNBs and IA injections because combining IA bupivacaine injections and FNBs does not result in a synergistic effect on pain symptoms.[76,90,102] We do not commonly use continuous-infusion FNBs because of the associated fall risk[104] but are exploring the use of continuous-infusion subsartorial saphenous nerve blocks because saphenous nerve blocks do not block quadriceps motor output[17] 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[5,12,21,64] in 4 trials, but in 4 trials, ice water provided no improvement in pain symptoms compared to water at room temperature.[26,29,34,63] In 1 study, a 10°C decrease below core body temperature provided an analgesic effect after ACL reconstruction, while a 5°C decrease below core body temperature did not.[89] As none of the other trials studying cryotherapy measured IA temperatures, the failure to achieve the required decrease in IA temperatures may provide an explanation for the conflicting results regarding the efficacy of cryotherapy in these studies. This makes it difficult to determine whether 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.[48,49] The use of a CPM device may have some benefits[78,123]; 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.[9] 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 provided a safer, lower risk alternative to opioids for pain medication, with oral ibuprofen providing greater pain control than acetaminophen[24] and oral ketorolac providing greater pain control than a combination of hydrocodone and acetaminophen.[4] 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 after ACL reconstruction with a BPTB autograft.[82] 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[83] 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.

TABLE 10
Costs Associated With Medications Used for Pain Control in ACL Reconstruction[a]

Medication[b]	Unit Dose	Cost/Fee, US$
Injectable		
Bupivacaine PF 0.5%	10-mL vial	1.21
Bupivacaine 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 1/100,000	1-mL ampule	1.27
Fentanyl 50 μg/mL	2-mL vial	1.00
Ketamine 50 mg/mL	10-mL vial	2.70
Dexamethasone 4 mg	1-mL vial	0.68
Patient-controlled analgesia		
Fentanyl 10 μg/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[c]		
Single sciatic nerve injection		139.15
Continuous sciatic nerve infusion		78.59
Single femoral nerve injection		121.46
Continuous femoral nerve infusion		70.43

[a]ACL, anterior cruciate ligament.
[b]Medication costs acquired from a pharmacy of a large tertiary care hospital.
[c]Nonfacility fees acquired from the 2013 Medicare physician fee schedule (national average).

Cost analyses are extremely challenging with respect to 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 nonfacility 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 pain control after ACL reconstruction. Only level 1 and 2 RCTs 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 the heterogeneity of regimens used. We restricted our study to RCTs to limit any effects of bias and confounding. Many of the studies discussed here were based on small patient pools and therefore could be subject to type II 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 the evidence reviewed in this systematic review, our current multimodal approach to pain control involves a preoperative single-injection FNB or IA ropivacaine/fentanyl injection, intraoperative tourniquet use, NSAIDs for the first 5 days postoperatively, cryotherapy/compression (optional because of the 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.

CONCLUSION

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