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

Eric S. Secrist

Thomas Jefferson University

Kevin B. Freedman

Thomas Jefferson University

Michael G. Ciccotti


Thomas Jefferson University

Donald W. Mazur

Thomas Jefferson University

Sommer Hammoud

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

3 **Abstract**

4 **Background:**

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

7 **Purpose:**

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

10 **Study Design:**

11 Systematic review. Level 1 and 2.

12 **Methods:**

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

16 **Results:**

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

20 Single injection femoral nerves block provided superior analgesia to placebo for up to 24 hours
21 postoperatively, **however this also resulted in a quadriceps motor deficit**. Indwelling femoral catheters
22 utilized for 2 days postoperatively provided superior analgesia to a single injection femoral nerve block.

23 Local anesthetic injections at the surgical wound site or intraarticularly provided equivalent analgesia to

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

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

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

32 **Conclusion:**

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

39 **Clinical Relevance:**

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

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43

44

45 **Main Text**

46 **Introduction**

47 The anterior cruciate ligament (ACL) is the most commonly reconstructed ligament in the knee.⁷³ In 2006
48 129,836 ACL reconstructions were performed in the United States, and the annual rate is increasing.⁷⁴
49 Effective postoperative pain management is a critical component to recovery, effective rehabilitation and
50 patient satisfaction. Following ACL reconstruction, psychological factors are predictive of outcomes,³⁶
51 and pain levels are inversely associated with function¹⁹ and quality of life assessments.⁴⁰

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

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

62 **Methods**

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

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

88 Results

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

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

102 **Regional Nerve Blocks (Table 2):**

103 Femoral nerve block:

104 When compared to a saline injection, a single injection femoral nerve block (FNB) significantly decreased
105 VAS scores up to 60 minutes postoperatively⁹³ in one trial, up to the night of surgery in another,⁴⁴ and up
106 to 24 hours in a third.⁴⁸ A single injection FNB also significantly decreased postoperative morphine
107 consumption compared to saline injection.^{44,93} In a group of patients blinded to receiving a saline or
108 bupivacaine FNB injection, a supplemental bupivacaine FNB injection was offered with a reported VAS
109 score greater than 4. Significantly more patients in the saline group elected to receive the supplemental
110 FNB, with 50% of patients in the saline group doing so within 40 minutes of the completion of surgery.⁸⁷
111 Because the femoral nerve innervates the quadriceps, femoral nerve block resulted in a motor deficit in
112 all of these studies,^{44,48,93} which persisted for the same amount of time as the analgesic effect.⁸⁷

113 Other regional nerve blocks:

114 The addition of a sciatic nerve block to a FNB yielded significantly decreased analgesic consumption and
115 NRS scores at first analgesia request compared to FNB alone.⁵⁸ As compared to a standard FNB there
116 were no significant differences in pain scores or postoperative narcotic consumption between groups
117 receiving a fascia iliaca nerve block³⁸ or a subsartorial saphenous nerve block.¹⁸ The percentage of
118 patients requiring intraoperative analgesic supplementation was significantly lower when a posterior
119 psoas compartment block was used as compared to an anterior 3-in-1 FNB (femoral, obturator and lateral
120 femoral cutaneous nerves).¹⁷

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

129 Stimulating catheters for nerve block placement:

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

133 Dosages of nerve blocks:

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

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

139 Additions of other drugs to nerve blocks:

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

142 **Intraarticular Injections (Table 3):**

143 Intraarticular bupivacaine:

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

154 Intraarticular Morphine injections:

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

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

162 Combination bupivacaine-morphine intraarticular injections:

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

170 Other intraarticular injections

171 There were no significant differences in any measure between IA methadone and IA saline.^{4, 106} IA
172 tenoxicam (a non-steroidal anti-inflammatory drug (NSAID) indicated for the short-term treatment of
173 musculoskeletal injury) significantly decreased VAS scores and supplementation of pethidine (an opioid
174 analgesic marketed under the generic name demerol which the American Pain Society does not
175 recommend for use as an analgesic¹) compared to IA saline injections.⁴⁷ IA tenoxicam resulted in
176 significantly fewer patients requiring pethidine than IA morphine.⁴⁷ The addition of IA sufentanil (a
177 fentanyl analog) to an IA ropivacaine/clonidine injection significantly decreased rescue analgesia
178 requirement during the first postoperative hour compared to IA ropivacaine/clonidine alone but did not
179 significantly decrease VAS scores at any timepoint.³ The injection of a multidrug cocktail consisting of
180 ropivacaine, morphine, ketorolac and cefuroxime either periarticularly, or both intraarticularly and

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

183 **Intravenous or intramuscular Injections (Table 4)**

184 Rescue medication protocols:

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

189 Various drugs injected intravenously/intramuscularly:

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

196 **Comparative analgesic regimens (Table 5):**

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

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

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

218 Oral Medications (Table 6)

219 The administration of 800 mg ibuprofen or a combination of 800 mg ibuprofen and 1 g acetaminophen 1
220 hour prior to surgery, and at 6 and 12 hours post-surgery resulted in significantly lower VAS scores and
221 ketobemidone (an opioid analgesic indicated for the treatment of severe pain) consumption as compared
222 to 1 g acetaminophen alone. The addition of 1 g acetaminophen to 800 mg ibuprofen was no better than
223 800 mg ibuprofen alone.²⁶ Patients receiving 30 mg ketorolac had significantly better total pain relief at 3
224 hours as compared to patients receiving 20 mg hydrocodone combined with 2 g acetaminophen.⁵

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

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

237 Cryotherapy/Compression (Table 7)

238 Nine RCTs have analyzed the effects of noncompressive cryotherapy in ACL reconstruction, with 5
239 reporting decreased pain symptoms and 4 reporting no significant differences as compared to controls.
240 Postoperative cryotherapy consisting of a continuous flow cryotherapy device or a CryoCuff device
241 significantly decreased VAS scores and analgesic consumption when compared to no cryotherapy or a
242 single ice pack in the recovery room.^{6, 13} In another trial a continuous flow device significantly reduced
243 analgesic consumption as compared to no cryotherapy.²² Preoperative use of cryotherapy significantly
244 decreased percocet use on the day of surgery and VAS scores up to the morning of the first postoperative
245 day.⁶⁵ In 4 trials there were no significant differences in analgesic consumption or VAS scores between
246 cryocuff devices, ice packs, or continuous flow cooling pads with cold water or room temperature water.
247^{27, 30, 35, 64} In the only study measuring IA temperatures, a cryotherapy device that maintained IA

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

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

255 Mobilization Strategies (Table 8)

256 Immobilization with a plaster cast for 5 weeks postoperatively did not significantly decrease the
257 proportion of patients reporting pain on the Lysholm score as compared to a hinged brace with range of
258 motion exercises beginning on postoperative day 7. ⁴⁹ There were no significant differences in VAS scores
259 between an unhinged immobilizing brace for two weeks postoperatively and no immobilization. ⁵⁰

260 Immediate postoperative weightbearing significantly decreased the proportion of patients reporting pain
261 symptoms two weeks postoperatively as compared to delaying weightbearing for two weeks
262 postoperatively, and did not lead to an increase in joint laxity. ¹¹⁵

263 Continuous passive motion (CPM) device usage for 16 hours per day immediately following surgery
264 significantly decreased analgesic consumption but not VAS scores compared to controls not using CPM. ^{79,}

265 ¹²³ A continuous active motion (CAM) device, in which the patient used their contralateral leg to pedal
266 the injured leg, significantly improved proprioception but did not decrease VAS scores as compared to a
267 CPM device. ⁴³ There were no significant differences in analgesic consumption between patients using
268 physical therapy, CPM devices or both within the first month postoperatively. ¹⁰⁰

269 Surgical Technique (Table 8)

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

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

282 Quality Analysis

283 In many cases the nature of the interventions being studied limited the feasibility of blinding, however 52
284 of the trials used some form of blinding. Of these, 44 had blinded patients, 42 were double blinded, and 8
285 were triple blinded. An additional 8 trials did not have blinded patients but did have blinded assessors.

286 Graft type can influence initial post-operative pain symptoms because of harvest site pain. ⁴² There were
287 37 trials which used BPTB autografts exclusively and 19 which used hamstring autografts. Ten trials did
288 not list the graft type used during reconstruction, and 11 used multiple grafts within the same trial. Eight
289 of the trials which used more than one graft type included patients who received cadaveric allografts.

290 Allograft reconstructions do not involve graft harvest morbidity and pain and typically result in less initial
291 postoperative pain than autografts. ⁶⁶ This represents a significant possible source of bias in these trials.

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

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

309 Discussion

310 ACL reconstruction is now almost solely performed on an outpatient basis. While this has been beneficial
311 in terms of patient satisfaction⁶⁹ and costs,⁶⁰ it has also complicated postoperative pain management.
312 Effective pain management in outpatient ACL reconstruction is essential because pain levels are closely
313 linked to both functional recovery¹⁹ and quality of life assessments.⁴⁰ Currently there is no consensus

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

316 Previous systematic reviews have analyzed the efficacy of 4 of the interventions discussed here for pain
317 management following outpatient ACL reconstruction. A meta-analysis of RCTs analyzing cryotherapy use
318 found that it decreased pain ($P = .02$) but did not improve knee range of motion.⁹⁵ A systematic review of
319 CPM concluded that it was unclear whether or not it provided any benefit.¹⁰⁵ A systematic review of
320 postoperative rehabilitation methods concluded that immobilization provided no benefit and there were
321 no detrimental effects of accelerated rehabilitation.⁶⁸ A systematic review of FNB reported that single
322 injection FNB resulted in statistically significantly reduced pain in 5/13 trials, but the authors questioned
323 whether or not these decreases were clinically significant. They concluded that single injection FNB did
324 not decrease pain.⁷⁵ This systematic review, however, included studies where IA bupivacaine injections
325 were given to both the treatment group receiving FNB and the control group receiving no FNB.

326 Combining IA bupivacaine injection and FNB does not provide a synergistic analgesic effect.^{77, 89, 102} FNB
327 performed in the absence of IA bupivacaine injection, however, reduces pain symptoms for up to 24
328 hours.^{44, 48, 87, 93} The authors of the previous systematic review emphasized that FNB did not decrease
329 pain beyond 24 hours, but pain scores are highest immediately following surgery and decrease with time.
330⁵⁷ This makes the day of surgery a crucial period for effective pain relief. We believe this justifies the
331 inclusion of FNB as a component of a multimodal approach to postoperative analgesia in this setting,
332 particularly if no IA injection is used.

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

338 block provided equivalent analgesia without blocking motor output.¹⁸ This may provide a feasible
339 alternative to the traditional FNB, and we are currently investigating this. Rarer complications associated
340 with FNB include vascular puncture,⁷¹ femoral neuritis,¹⁰⁴ and persistent paresthesia.⁷¹ Stimulating
341 catheters improve the accuracy of injections at the femoral nerve²⁹ and reduce the risk of these
342 complications. Continuous infusion bupivacaine pumps prolong the effect of regional nerve blocks.¹¹⁹
343 This prolongs the quadriceps strength deficit, necessitating effective patient education and fall prevention
344 protocols.

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

352 Continuous infusion bupivacaine pumps prolong the effect of IA injections.^{2, 51, 92} However, Noyes et al.
353 reported a case series of 21 patients with disabling knee symptoms due to severe postoperative
354 chondrolysis secondary to IA bupivacaine pumps⁸⁸ and in vitro analysis revealed that 95 % of human
355 articular chondrocytes undergo apoptosis after 30 minutes of exposure to 0.5% bupivacaine.²¹ We do not
356 use continuous IA bupivacaine infusions in our practice because of this risk. Only continuous infusions of
357 IA ropivacaine or bupivacaine have been shown to lead to chondrolysis in vivo,¹¹⁸ however, and
358 ropivacaine is less chondrotoxic than bupivacaine in vitro.⁵⁴ This is why some physicians in our practice
359 utilize single IA ropivacaine injections.

360 In our practice we utilize either a preoperative single-injection FNB provided through a stimulating
361 catheter or an IA ropivacaine-fentanyl injection. We do not use both FNB and IA injections, because
362 combining IA bupivacaine injection and FNB does not result in a synergistic effect on pain symptoms.^{77, 89,}
363¹⁰² We do not commonly use continuous infusion FNB because of the associated fall risk,¹⁰⁴ but are
364 exploring the use of subsartorial saphenous nerve continuous infusion blocks, because saphenous nerve
365 blocks do not block quadriceps motor output¹⁸ and continuous infusion nerve blocks can provide longer
366 postoperative analgesia as compared with single injection regional blocks.¹¹⁹

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

379 We encourage our patients to begin moving their knees early after surgery and to engage in early,
380 aggressive physical therapy because immediate weightbearing decreases pain without affecting stability.
381¹¹⁵ Immobilization does not decrease pain symptoms and can lead to muscular atrophy, impeding the
382 recovery of function.^{49, 50} CPM device usage may have some benefits,^{79, 123} however early aggressive
383 physical therapy provided equivalent results¹⁰⁰ and it cost one group \$22,200 annually to rent 10 of these

384 devices in 2014.¹⁰ The combination of high costs and lack of strong evidence demonstrating decreased
385 pain symptoms with their use make it difficult to recommend CPM devices in this setting. We do not
386 utilize them in our practice for these reasons.

387 One of the main goals of pain control in the outpatient setting is to minimize the nausea, vomiting,
388 sedation, respiratory depression and pruritus associated with opioids⁹⁷ by providing safer alternatives.

389 NSAIDs provide a safer, lower risk alternative to opioids for pain medication, with oral ibuprofen providing
390 greater pain control than acetaminophen²⁶ and oral ketorolac providing greater pain control than a
391 combination of hydrocodone and acetaminophen.⁵ There is, however, evidence from animal and in vitro
392 studies linking NSAIDs to detrimental effects on bone, ligament and tendon healing.¹⁰⁷ One retrospective
393 analysis linked ketorolac to an increase in anterior-posterior knee laxity following BPTB autograft ACL
394 reconstruction.⁸³ Although the risk of impaired healing warrants further investigation, we view NSAIDs as
395 a safe, low cost alternative to oral opioids and prescribe them to our patients for the first 5 days
396 postoperatively. Gabapentin⁸⁴ and zolpidem¹¹² are additional oral medications that can be beneficial in
397 reducing opioid consumption postoperatively. Gabapentin, however, can cause drowsiness and dizziness,
398⁹⁹ and zolpidem can cause nightmares and hallucinations.¹¹³ The associated risk profiles of these
399 medications limit their use in our practice. The risk profiles and complications of these and other
400 interventions analyzed in this study can be found in table 9.

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

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

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

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

426 **Conclusions**

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

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

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770

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.

777 Table 2 – Significant results of RCTs analyzing pain outcomes for intraarticular injections in ACL
 778 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

779

780 Any intervention resulting in a statistically significant decrease in subjective pain scores or pain
 781 medication consumption is included in this table. Additional information regarding these trials can be
 782 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 etoricoxib 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.

813 Table 8 – Significant results of RCTs analyzing pain outcomes following differing intraoperative techniques
814 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

815

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

819

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
<i>Injectable</i>		
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 carpject	\$ 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
<i>PCA</i>		
Fentanyl 10 mcg/ml	55 ml syringe	\$ 12.20
Hydromorphone 0.2 mg/ml	50 ml syringe	\$ 11.90
<i>Oral</i>		
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
<i>Injections Ψ</i>		
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

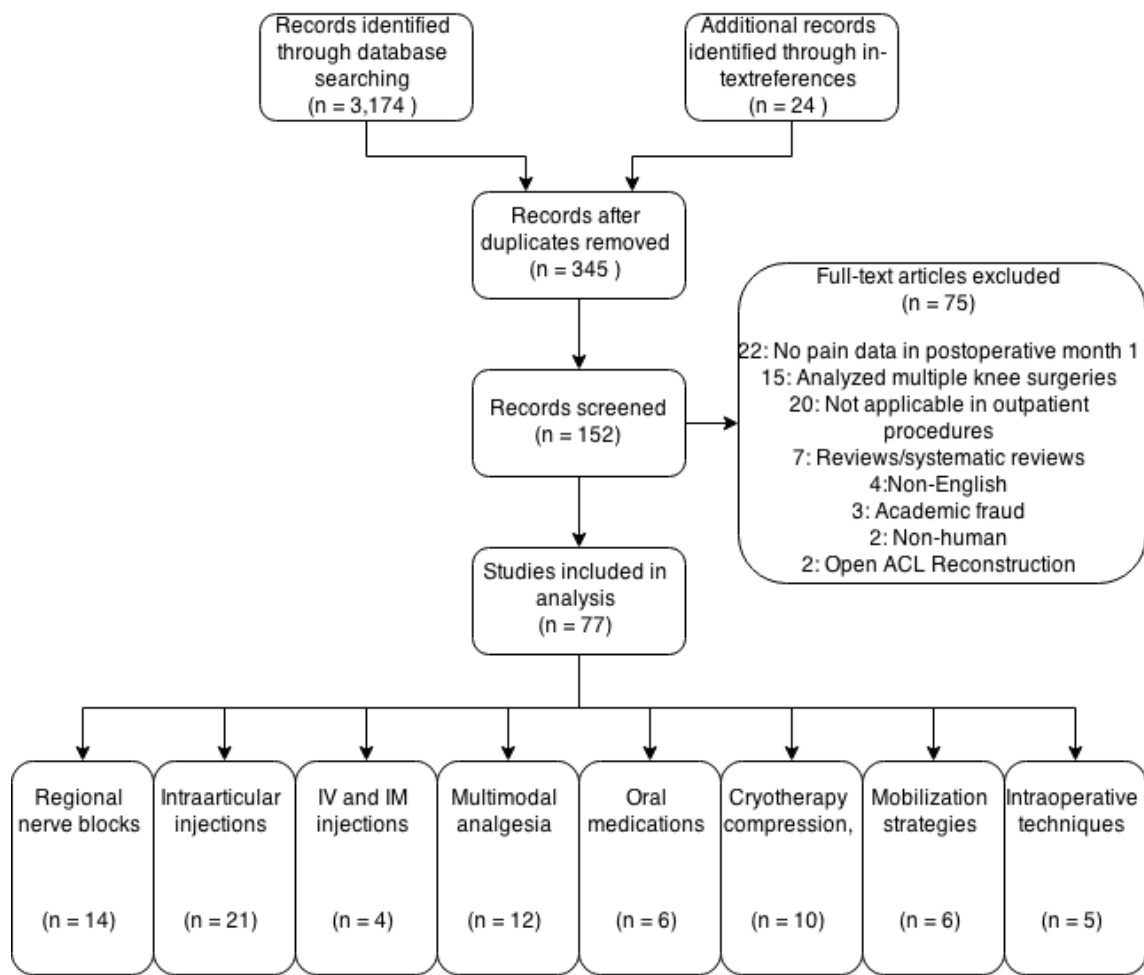
828 *Medication costs acquired from large tertiary care hospital pharmacy.

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

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833

834