Systematic Review

Perioperative Gabapentin May Reduce Opioid Requirement for Early Postoperative Pain in Patients Undergoing Anterior Cruciate Ligament Reconstruction: A Systematic Review of Randomized Controlled Trials

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Purpose: To evaluate the efficacy of perioperative gabapentin or pregabalin treatment on postoperative pain and opioid requirement reduction in patients undergoing anterior cruciate ligament reconstruction (ACLR). **Methods:** A systematic review of randomized control trials was conducted evaluating the effect of gabapentin or pregabalin on postoperative pain and opioid requirement for patients undergoing ACLR. The primary outcomes assessed were postoperative pain scores and opioid requirements. Secondary outcomes were complications, side effects, dosage, and timing of intervention. **Results:** The initial search query identified 151 studies and 6 studies were included after full-text articles were reviewed. Three studies investigated the use of gabapentin and three studies investigated pregabalin. All three gabapentin studies reported significantly decreased or equivalent pain scores while also significantly reducing or removing total opioid consumption compared to control groups. Pregabalin demonstrated inconsistent efficacy for pain control and opioid consumption parameters across three studies. One study (pregabalin, $n = 1$) reported significantly increased incidence of dizziness with pregabalin compared to placebo. **Conclusion:** There is moderate evidence demonstrating that preoperative gabapentin may be safe and effective in reducing postoperative pain and opioid consumption after ACLR. Gabapentin may be considered when employed as part of a multimodal analgesia regimen; however, the optimal protocol has yet to be determined. Currently, there is limited evidence demonstrating the efficacy of pregabalin on pain and opioid consumption in the setting of ACLR. **Level of Evidence:** Systematic Review of Level I Studies

Introduction

Anterior cruciate ligament reconstruction (ACLR) is one of the most common arthroscopic surgeries performed in the United States[1,2] and is associated with moderate to severe pain in the postoperative period.[3–5] Optimizing postoperative pain control is associated with a decreased length of stay, lower rates of readmissions, faster mobilization and rehabilitation, and improved patient satisfaction.[1,5–7] Opioids have historically been a standard for postoperative pain control including in ACLR.[8] Today, there remains no gold standard in post-ACLR pain management protocols; however, multimodal analgesia is broadly accepted as a means to reduce narcotic consumption in the setting of an opioid epidemic in America and effectively decrease pain.[9] Multimodal analgesia combines agents that target

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different modulators of the pain pathways to effectively control pain through their synergistic or additive effects.[9,10]

One component of multimodal pain management is preemptive analgesia.[11] This involves administering pre-operative medications to prevent central sensitization of pain, thereby dampening the perception of postoperative pain.[11] In an effort to optimize preemptive multimodal analgesia protocols, gabapentinoids have been suggested as a potentially effective adjunct therapeutic. Gabapentinoids, including gabapentin and pregabalin which differ in mainly in their bioavailability, work by binding α2-δ subunit of voltage-gated calcium channels and inhibiting the release of excitatory neurotransmitters that modulate the pain pathway.[12,13] A recent systematic review and meta-analysis by Hannon et al. reported on 13 studies using gabapentinoids as an adjunct analgesic in total joint arthroplasty (TJA) and found moderate evidence supporting the use of pregabalin, but not gabapentin, to reduce postoperative pain and opioid burden following TJA.[13] Furthermore, gabapentin has been utilized across other specialties in orthopedics; more specifically, in a meta-analysis of randomized controlled trials, Han et al found that gabapentin had dual benefits of decreasing postoperative narcotic use along with decreasing incidence of pruritis.[14]

Despite the potential evidence of gabapentinoids for joint arthroplasty and the increasing popularity of gabapentinoids in arthroscopic knee procedures[15,16] including ACLR[5], there have been limited review studies that critically evaluate the literature describing gabapentinoids for pain management in ACLR. Therefore, the purpose of this systematic review was to evaluate the efficacy of perioperative gabapentin or pregabalin treatment on postoperative pain and opioid requirement reduction in patients undergoing anterior cruciate ligament reconstruction (ACLR). It was hypothesized that gabapentinoids would significantly reduce postoperative pain and opioid consumption in ACLR patients.

Methods

Article Identification and Selection

A systematic review of the literature reporting the effect of gabapentin or pregabalin on postoperative pain and opioid requirement for patients undergoing ACL reconstruction or repair was performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines.[17] The search query was performed in January 2022 using the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (1980-2022), MEDLINE (1980-2022), and Embase (1980-2022) using the search terms ["gabapentin" AND "ACL"], ["pregabalin" AND "ACL"], ["gabapentin" AND "knee"], ["pregabalin" AND "knee"].

The inclusion criteria were randomized controlled trials published between 2000-2022 reporting on the effect of perioperative gabapentin or pregabalin on postoperative pain and opioid consumption following ACLR. Exclusion criteria were insufficient reporting of treatment protocols, non-ACLR knee arthroscopy, animal or preclinical studies, non-English full-text, unpublished clinical trials, and nonrandomized studies. Following implementation of search criteria, two investigators (*OKB, ZSA*) independently reviewed titles, abstracts, and full-text articles of identified articles for inclusion and exclusion criteria. Discrepancies in final included articles between investigators were further reviewed by the senior author (*TJD*) for final decision. To minimize the possibility of not identifying all potential studies meeting the inclusion criteria, the references of each included study were also reviewed and assessed.

Data Collection and Statistical Analysis

The primary outcomes assessed were pain scores as reported by the numeric rating scale (NRS) for pain, visual analog scale (VAS) for pain, maximum verbal rating scale (VRS), and opioid requirements as reported by total opioid consumption, timeline of first request for opioid medication, or frequency of intravenous patient controlled analgesia (IV-PCA) utilization. The reported incidence of gabapentin or pregabalin side effects and complications were recorded as secondary outcomes. For all studies, patient demographics and treatment protocols including general anesthesia, use of a nerve block (if applicable), intraoperative and postoperative analgesics, discharge medications, and follow-up time were recorded. Primary and secondary outcomes were analyzed with descriptive statistics.

Quality Assessment and Critical Appraisal

All included studies were reviewed by one author (*OKB*) independently to evaluate for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment methodology.[18] The risk of bias was assessed in the following domains: randomization, allocation concealment, blinding, completeness of outcome data, and selective reporting (Table 2).[18] Further, the JADAD score, a tool often used to assess the methodological quality of controlled trials, was calculated for each of the included studies (Table 3).[19] A JADAD score of 3 or higher classifies the study as high-quality using this system.[19] All included studies scored a 3 or higher.

Table 1. Study Design, Demographics, and Characteristics of Studies Evaluating Perioperative Gabapentinoids in Patients Undergoing ACL Surgery

Author	LOE	Surgery	Study Groups	Sample Size	Age (mean, range/ SD)	Sex (M:F)	BMI	Follow Up
Moutzouros 2021	RCT; I	ACLR (BTB auto; n=39, HS auto; n=23)	Group 1: Gabapentin (Multimodal nonopioid analgesia protocol)	MMNOA; n=34	MMNOA; 27.2 6 13.1	MMNOA; 19:15	MMNOA; 27.7 6 4.2	10 days, recorded pain levels 3 times per day
			Group 2; Standard Opioid Regimen (hydrocodone-acetaminophen)	Opioid, n=28	Opioid; 27.4 6 12.4	Opioid; 15:13	Opioid; 27.3 6 5.2	
Ménigaux 2005	RCT; I	ACLR (HS auto, n=40)	Group 1; Gabapentin	Gabapentin N=20	Gabapentin 31 SD 8	Gabapentin 14:6	NR	48 hrs
			Group 2; Placebo (Control)	Control N=20	Control 31(SD 8)	Control 13:7		
Cho 2019	RCT; I	ACLR (HS auto, n=94)	Group 1; Pregabalin	Pregabalin N=46	Pregabalin 32 (10)	Pregabalin 40:6	Pregabalin 24.8 (4.4)	12 hrs, 24 hrs, 36 hrs and 2 weeks
			Group 2; Placebo (Control)	Control N=47	Control 30 (10)	Control 37:10	Control 25.1 (3.3)	
Mardani-Kivi 2013	RCT; I	ACLR (HS auto, n=114)	Group 1; gabapentin	Gabapentin N=57	Gabapentin 32.2 (9.3)	Gabapentin 49:8	Gabapentin 24.2 (2.2)	6 hrs and 24 hrs
			Group 2; Placebo	Placebo N=57	Placebo 30.5 (10.2)	Placebo 51:6	Placebo 23.5 (2.8)	
Akelma 2020	RCT; I	ACLR (BTB auto, n=51)	Group P; pregabalin Group A; adductor canal block + placebo	Pregabalin N=16	Pregabalin 29.5 (9.49)	Pregabalin 14:2	Pregabalin 27.59 (3.90)	1, 4,8,12, and 24 hrs
				ACB N=17	ACB 28.76 (8.26)	ACB 14:3	ACB 26.09 (2.89)	
			Group C; placebo only (no block or pregabalin) (control)	Control; N=18	Control; 33.27 (14.06)	Control; 15:3	Control; 27.45 (5.69)	
Nimmaanrat 2012	RCT; I	ACLR (n= 56)	Group 1; Pregabalin	Pregabalin N=27	Pregabalin 29.3 (NR)	Pregabalin 24:3	Pregabalin 23.4 (NR)	Baseline (pre-op), 4, 8, 12, 16, 20, 24 hrs
			Group 2; Placebo (control)	Control N=29	Control 33.8 (NR)	Control 26:3	Control 23.7 (NR)	

ACLR, anterior cruciate ligament reconstruction; MMNOA, multimodal nonopioids analgesia; RCT, randomized control trial; NR, not reported; BTB, bone-tendon-bone patellar graft; HS, hamstring tendon; Hrs, hours.

Results

Study Characteristics

The initial search query identified 151 studies and 6 studies were included after applying exclusion criteria (Fig 1). Three studies investigated the use of gabapentin and 3 studies investigated pregabalin. Study characteristics and demographics are summarized in Table 1. The quality of evidence was appraised with a GRADE assessment demonstrating all 6 included studies were high quality (Table 2).[18]

Lea et al. defined three phases of the post-operative period: early recovery (in-hospital; within the first 24 hours after surgery), intermediate recovery (in-hospital; beyond 24 hours) and late recovery (after hospital discharge).[20] All seven studies reported follow-up in the

Table 2. Investigation Study Inclusions and Quality Assessment

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome data	Selective Reporting	Other Bias	Inclusion	Strength
Moutzouros 2021	Y	Y	n*	Y**	n	n	Include	High quality
Ménigaux 2005	y	y	y	Y**	n	n	Include	High quality
Cho 2019	y	y	y	n	n	n	Include	High quality
Mardani-Kivi 2013	y	y	y	n	n	n	Include	High quality
Akelma 2020	y	y	y	Y**	n	n	Include	High quality
Nimmaanrat 2012	y	y	y	n	n	n	Include	High quality

*Observers blinded, patients not blinded as the control group was opioids requiring education and monitoring of adverse effects ** Reported if there was a significant difference between study and controls group VAS, NRS, or VRS score but did not report the mean numeric outcome or only reported it with visual graphics Y, yes; N, no.

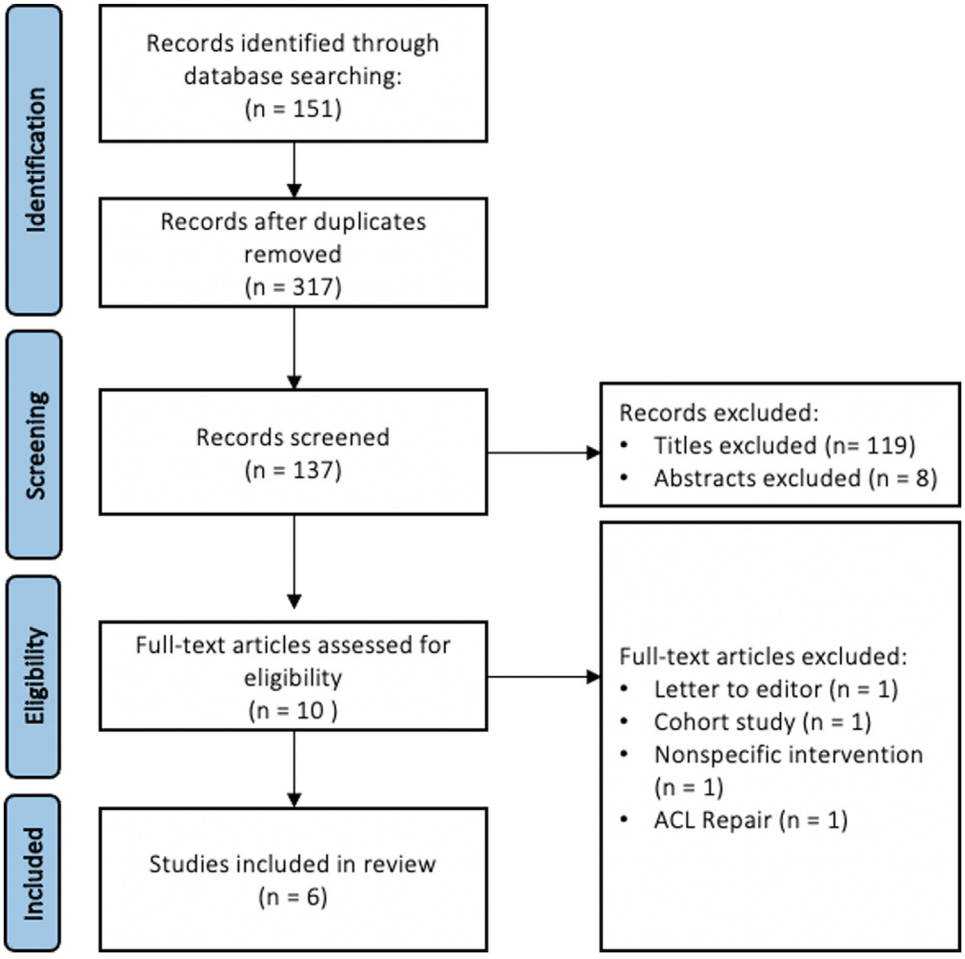

Fig 1. PRISMA flowchart demonstrating selection criteria applied to studies identified with search strategy.

early postoperative period; four studies reported follow-up in the intermediate recovery period and three studies reported follow-up in the late recovery period.

There were no major differences in reported surgical methods, comorbidities, accompanied pathologies, or complications between included studies.

Gabapentin vs. Control

Pain Scores

Two studies compared gabapentin to a placebo control group[5,21] and one study compared a multimodal nonopioid analgesia (MMNOA) regiment including gabapentin to a standard opioid regimen (hydrocodone-acetaminophen) control group.[8] VAS scores were evaluated for postoperative pain for all three studies (100%). Ménigaux et al. reported that patients treated with gabapentin had significantly less pain at only one hour postoperatively compared to the placebo group ($p<0.05$), while Mardani-Kivi et al reported that the gabapentin group had significantly less pain at both 6 hours and 24 hours postoperatively (both $p<0.001$).[5,21] Moutzouros et al reported that patients treated with multimodal nonopioid analgesia with gabapentin had significantly decreased mean daily pain scores compared to the control group over ten days after ACL compared to patients treated with a standard postoperative opioid protocol (mean VAS difference, 1.56 (unadjusted) and 1.71 (adjusted), both $p<0.001$).[8] However, there was no significant difference in pain levels when averaged over time (interaction $P = .5844$ (unadjusted), interaction $P = .5708$ (adjusted).[8] Reported pain values for studies investigating gabapentin are detailed in Table 4.

Opioid Consumption

Two of three (67%) studies investigating gabapentin reported on opioid consumption. In one study, Moutzouros et al did not prescribe opioid analgesics to patients in the MMNOA with gabapentin group. Both studies comparing gabapentin to placebo demonstrated that gabapentin significantly decreased opioid consumption compared to a placebo at all postoperative time points. [21] Ménigaux et al. reported that patients treated with gabapentin had significantly prolonged time to first morphine request (16 min. vs. 1 min, $p=0.001$), and significantly less mean morphine

Table 3. JADAD Score Calculation for Clinical Trial Quality

Item	Score	Cho 2019	Akelma 2020	Nimmaanrat 2012	Moutzouros 2021	Ménigaux 2005	Mardani-Kivi 2013
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1	1	1	1	1	1	1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1	1	1	1	1	1	1
Was the study described as double blind?	0/1	1	1	0	0	1	1
Was the method of double blinding described and appropriate (identical plcebo, active placebo, dummy, etc)?	0/1	1	1	0	0	1	1
Was there a description of withdrawals and dropouts?	0/1	1	1	1*	1*	1*	1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1	0	0	0	0	0	0
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1	9	0	0	0	0	0
Total Score	Max 5	5	5	3	3	5	5

*There were no dropouts or withdrawals requiring explanation in this study.

consumption at both 24 hours (21 mg vs. 48 mg, p<0.001) and 48 hours (29 mg vs. 69 mg, p<0.001) compared to the placebo group[21]. Mardani-Kivi et al also reported significantly less mean pethidine consumption at both 6 hours (20 mg vs. 34 mg, p<0.001) and 24 hours (25 mg vs. 37 mg, p=0.032) compared to the placebo group[5]. The effect of gabapentin and opioid consumption is summarized in Table 5.

Side Effects

All studies investigating gabapentin reported side effects, although no studies demonstrated an increased incidence of adverse effects with gabapentin when compared to controls ($p>0.05$). Across studies, the reported side effects were heterogenous and are detailed in Table 6.

Dosing & Timing

Two of three gabapentin studies exclusively examined the role of preoperative gabapentin dosed 1-2 hours prior to surgery,[5,21] and one (33%) gabapentin study examined the impact of both preoperative (within 2 hours prior to surgery) and postoperative gabapentin administration.[8] Further, all three gabapentin studies administered different doses of gabapentin ranging from 300-1200 mg. The two studies that demonstrated a significant reduction in postoperative pain and decreased opioid consumption utilized higher doses of gabapentin (600 and 1200 mg).[5,21] Moutzouros et al. was the only study that examined the effect of preoperative gabapentin (300mg) with continued postoperative gabapentin as part of a MMNOA regiment for nine days after ACLR.[8] This lower dose offered

Table 4. Summary of Reported Pain Scores in Patients Receiving Perioperative Gabapentin for Anterior Cruciate Ligament Reconstruction (ACLR)

Study	Time Points	Gabapentin Group	Control Group	*P*
Moutzouros 2021*	Days 1-10	1.56 (95% CI, 1.35 to 1.78) (unadjusted)		**P<0.001**
	Avg. Daily Diff. VAS score	1.71 (95% CI, 1.49 to 1.93) (adjusted)		**P<0.001**
	Over Time	NR (unadjusted)		P=0.5844
		NR (adjusted)		P=0.5708
Ménigaux 2005*	At Rest	NR	NR	
	1 h			**p<0.05**
	4 h − 48 h			p>0.05
	After ROM			
	24 h			p>0.05
	48 h			p>0.05
Mardani-Kivi 2013	6 hours	4.8 (4.3-5.4, 95% CI)	6.9 (6.5-7.5, 95% CI)	**p<0.001**
	24 hours	4.4 (3.9-4.9, 95% CI)	NR (NR, 95% CI)	**p<0.001**

*Refer to figure in article depicting NRS scores, no objective numerical data for VAS scores reported. P values less than 0.05 indicate significantly decreased pain levels in Gabapentin groups. CI, confidence interval; NR, not reported; ROM, range of motion; H, hours; VAS, visual analogue scale.

Table 5. Summary of Reported Opioid Consumption in Patients Receiving Perioperative Gabapentin for Anterior Cruciate Ligament Reconstruction (ACLR)

Study	Time Point	Gabapentin Group (Mean Opioid Consumption)	Control Group (Mean Opioid Consumption)	*P*
Moutzouros 2021	POD 1	0	13.1 ± 8 MME	**n/a***
	POD 2	0	15.2 ± 11.3 MME	**-**
	POD 9	0	4.3 ± 4.7 MME	**-**
	POD 10	0	6.7 ± 7.5 MME	**-**
Ménigaux 2005	24 h	21 ± 12 mg	48 ± 19 mg	**p< 0.001**
	48 h	29 ± 22 mg	69 ± 40 mg	**p<0.001**
Mardani-Kivi 2013	6 h	20 mg (18.9-31.3, 95% CI)	34 mg (28.5-39.8, 95% CI)	**p<0.001**
	24 h	25 mg (14-26.6, 95% CI)	37 mg (30.4-44, 95% CI)	**p=0.032**

CI, confidence interval; NR, not reported; ROM, range of motion; H, hours; mg, milligrams; MME, morphine milliequivalents.

equivalent pain control compared to traditional opioid analgesics when used in tandem with other nonopioid analgesics. Perioperative analgesic and anesthesia treatment protocols in studies administering gabapentin are detailed in Table 7.

Pregabalin Versus Control

Pain Scores

All 3 studies investigating pregabalin were compared to a placebo control group. A numerical grading scale system was utilized to report postoperative pain in all studies (100%). Two of three studies investigating pregabalin treatment reported significant differences in pain levels. Cho et al reported that patients treated with pregabalin had significantly less pain with range of motion at 24 and 36 hours (p=0.043 and p=0.042, respectively) and at rest at 2 weeks (p<0.001) when compared to the placebo group.[9] Akelma reported significantly decreased pain at 8 hours postoperatively in the pregabalin group compared to placebo (p=0.04)[1]. Nimmaanrat et al did not demonstrate significant differences in pain within the first 24 hours postoperatively (all p>0.05).[15] Reported objective pain scores for studies investigating pregabalin are detailed in Table 8.

Opioid Consumption

All three pregabalin studies evaluated postoperative opioid consumption compared to placebo. Only one of three studies demonstrated a significantly decreased need for postoperative opioids.[9,12] Akelma et al reported significantly decreased tramadol consumption over 24 hours compared to the placebo group (178.75 ± 65.4 mg vs. 318.61 ± 127.89 mg, p<0.001), although there were no significant differences in PCA demand (mean 27 vs. 51, p=0.220), total rescue analgesic consumption (mean 0 vs. 25, p=0.174), or number of rescue analgesics (mean 6 vs. 9, p=0.469). Cho et al found no differences in number of patients receiving rescue opioids, dose of rescue per patient, or cumulative IV-PCA consumption at any time point. Only one study compared pregabalin to an adductor canal block for ACLR.[1] Akelma et al. demonstrated that preoperative pregabalin was as effective as a postoperative adductor canal block in

Table 6. Summary of Reported Side Effects in Patients Receiving Perioperative Gabapentin for Anterior Cruciate Ligament Reconstruction (ACLR)

Study	Side Effect	Gabapentin Group	Control Group	*P*
Moutzouros 2021	Constipation	n=12 (55%)	N= 13 (65%)	p>0.05
	Nausea	n=9 (43%)	N=10 (56%)	p>0.05
	Diarrhea	n=2 (11%)	N= 2 (15%)	p>0.05
	Upset Stomach	n=17 (89%)	N= 8 (50%)	p>0.05
	Drowsy	n=18 (72%)	N=12 (67%)	p>0.05
	Loopy	n=12 (55%)	N= 4 (29%)	p>0.05
Ménigaux 2005	Nausea	n=3	n=3	p>0.05
	Sedation Score >2	n=0	n=0	p>0.05
Mardani-Kivi 2013	At 6 h.			
	Nausea/Vomiting	N= 5 (9%);	N= 7 (13%)	p>0.05
	Dizziness	N= 7 (13%),	N= 4 (7.5%)	p>0.05
	2nd or 3rd degree sedation	n= 6 (11%)	n=3 (6%)	p>0.05
	At 24 h.			
	Nausea/Vomiting	n= 3 (7.5%),	n= 4 (7.5%)	p>0.05
	Dizziness	N= 3 (5.5%)	n= 6 (11%)	p>0.05
	2nd or 3rd degree sedation	N=2 (4%)	n= 3 (6%)	p>0.05

H, hours.

Table 7. Summary of Perioperative Anesthesia and Analgesic Treatment Protocols in Studies Investigating Gbapentin

Author	Gabapentin/ Pregabalin Protocol	Anesthesia	Local Infiltration Anesthesia	Nerve Block	Intraoperative Analgesia Protocol	Postoperative Analgesia Protocol
Moutzouros et al.[8] 2021	Preoperative: 300 mg oral gabapentin within 2 hours preoperatively Postoperative: Days 1-5 300 mg oral, tid Days 6-7 400 mg oral, bid Days 8-9 400 mg oral, qd	NR	150 mg (30 mL) of 0.50% ropivacaine, 30 mg (1 mL) of ketorolac, and 1 mg (1 mL) of epinephrine	Femoral Nerve (n=1) Adductor Canal (n=33)	400 mg oral celecoxib, 975 mg oral acetaminophen, 8 mg IV dexamethasone, 50 mg oral tramadol	Days 1-5 Ketorolac 10mg oral, qid, Diazepam 5 mg oral, qid, Acetaminophen 1000 mg tid Days 6-14 Meloxicam 7.5 mg oral bid, Diazepam 5 mg oral tid, Acetaminophen 1000 mg tid
Ménigaux et al.[21] 2005	1x dose 1-2 hours prior to surgery 1200 mg oral gabapentin	Continuous propofol target 2-6 µg/mL, remifentanil target 2 ng/ml, 50% N2O oxygen	No LIA	No nerve block	0.1 mg/kg bolus IV morphine 30-minutes prior to end of surgery	PACU − morphine titrated in 3 mg every 5 min until VAS pain < 30 PCA device 1-mg bolus every 5 minutes for 48 hours Ketoprofen, 150 mg oral bid
Mardani-Kivi et al.[5] 2013	1 dose of 600 mg oral gabapentin two hours prior to surgery	fentanyl 2µg/kg and thiopental (4mg/ kg) and maintained with 0.8-1.5% Isoflurane and N2O and O2 in a ratio of 50%. Atracurium (0.5/mg/ kg)	No LIA	None	None	Pethidine 0.5 mg/kg injection as needed for first 24 hours

LIA, Local infiltration analgesia; QID, four times a day; TID, three times a day; BID, twice a day; QD, daily; PCA, patient-controlled analgesia; PACU, post-anesthesia care unit; VAS, visual analogue scale; µg, micrograms; Mg, milligrams; mL, milliliters; Kg, kilograms; IV, intravenous; N2O, nitrous oxide; O2, oxygen; NR, not reported.

reducing postoperative opioid consumption.[1] Reported objective opioid consumption data for studies investigating pregabalin are detailed in Table 9.

Side Effects

All three(100%) pregabalin studies reported side effects compared to a placebo group and are detailed in Table 10. One of three studies reported significantly higher incidence in postoperative dizziness in the pregabalin group compared to placebo (11 vs. 3, p=0.018).[9,12] No other significant differences were identified for adverse effects between pregabalin and placebo groups. Reported side effects are detailed in table 10.

Dosing & Timing

One of three pregabalin studies investigated the use of one dose of 75 mg oral pregabalin 1 hour prior to surgery and another dose 12 hours postoperatively.[15] The other two pregabalin studies investigated the use of 150 mg oral preoperative pregabalin.[1,9] Both studies that administered 150 mg reported significantly reduced postoperative pain compared to placebo (p<0.001 and p=0.04),[1,9] while the study that administered 75 mg did not appreciate any significance in pain scores (p>0.05).[12,15] The same relationship was not true for opioid consumption. Akelma et al. administered a single dose of 150 mg oral pregabalin 1 hour prior to surgery and reported significantly decreased tramadol consumption (p<0.05) but no significant difference in total opioid consumption (p>0.05).[1] The other two studies investigating 75 mg or 150 mg did not see a difference in any opioid consumption parameters (p>0.05). Perioperative analgesic and anesthesia treatment protocols in studies administering pregabalin are summarized in Table 11.

Table 8. Summary of Reported Pain Scores in Patients Receiving Perioperative Pregabalin for Anterior Cruciate Ligament Reconstruction (ACLR)

Author	Time Point	Pregabalin Group (mean VAS or NRS score)	Control Group (mean VAS)	*P*
Cho 2019	At rest			
	12 h	5(4-7)	6 (4-7)	P=0.238
	24 h	4 (3-5)	4 (3-6)	P=0.194
	36 h	3 (2-3)	3 (2-5)	P=0.138
	2 weeks	0 (0-1)	1 (0-2)	**P<0.001**
	With ROM			
	12 h	8 (6−10)	8 (7−9)	p = 0.195
	24 h	7 (4−8)	8 (6−9)	**p = 0.043**
	36 h	4 (3−7)	5 (4−9)	**p = 0.042**
	2 weeks	2 (1−4)	3 (1−5)	p = 0.127
Akelma 2020*	1 h	NR	NR	p>0.05
	4 h	-	-	p>0.05
	8 h	-	-	**p=0.04**
	12 h	-	-	p>0.05
	24 h	-	-	p>0.05
Nimmaanrat 2012	4 h	1.1	0.97	p>0.05
	8 h	5.4	5.5	p>0.05
	12 h	4.9	5.6	p>0.05
	16 h	4.3	5.2	p>0.05
	20 h	4.4	4.6	p>0.05
	24 h	4.6	4.6	p>0.05

*Refer to figure in article depicting NRS scores, no objective numerical data for VAS scores reported. P values less than 0.05 indicate significantly decreased pain levels in Gabapentin groups. CI, confidence interval; NR, not reported; ROM, range of motion; H, hours; VAS, visual analogue scale.

Postoperative Analgesia

All studies reported on other agents used as part of their postoperative analgesia protocols and are detailed in Tables 7 and 11. The postoperative pain protocols consisted of opioid and nonopioid agents and were not standardized across studies.

Discussion

The most important finding of this study was that the use of preoperative gabapentin as an adjunct to a multimodal analgesic regiment may safely reduce postoperative pain and opioid consumption after ACLR. In all three randomized control trials investigating gabapentin adjunct therapy compared to placebo, gabapentin demonstrated significantly reduced or equivalent pain scores while simultaneously reducing opioid consumption. This includes the single study comparing gabapentin adjunct therapy with MMNOA to a standard opioid regimen showed at least equivalent pain control. Furthermore, there were no significant differences in side effects between gabapentin and control groups. These findings suggest that preemptive treatment with gabapentin may be efficacious in safely reducing postoperative opioid consumption with favorable short-term analgesia as compared to standard opioid management. However, there is limited and conflicting evidence demonstrating the same efficacy for pregabalin studies.

In this systematic review, all studies investigating gabapentin demonstrated favorable postoperative pain and opioid consumption profiles when used as an adjunctive therapy to standard opioid regimens. Although pregabalin also demonstrated favorable analgesic profiles in 66% of included studies, there were discrepancies across studies regarding its effects on pain and opioid consumption. Only one study investigating pregabalin demonstrated significantly reduced total opioid consumption with equivalent pain scores on postoperative day 1. In contrast, Nimmaanrat et al did not demonstrate any significant differences in opioid consumption or pain scores. Cho et al reported that pregabalin demonstrated reduced pain levels with active range of motion within the first two days and decreased pain at rest at 2 weeks, although there were no differences in opioid consumption metrics. Therefore, the use of pregabalin in the setting of ACLR can not be recommended at this time and further studies are warranted.

The findings of this systematic review are in contrast to a recent systematic review of gabapentinoids for total joint arthroplasty, which demonstrated that pregabalin alone was associated with a significant reduction in postoperative pain and opioid consumption, while gabapentin demonstrated minimal efficacy.[13] A recent randomized controlled trial comparing a single dose of either pregabalin (300 mg), gabapentin (1200 mg), or

Table 9. Summary of Reported Opioid Consumption in Patients Receiving Perioperative Pregabalin for Anterior Cruciate Ligament Reconstruction (ACLR)

Author	Time Point	Pregabalin Group (mean opioid consumption)	Control Group (mean opioid consumption)	*P*
Cho 2019	0-6 h	32.9 ± 5.1 ml	34.9 ± 5.6 ml	P=0.089
	12-24 h	66.5 ± 11.5 ml	70.1 ± 12.2 ml	P=0.150
	24-36 h	125.0 ± 28.8 ml	134.1 ± 27.3	P=0.134
Akelma 2020	Total over 24 h	178.75 ± 65.4 mg	318.61 ± 127.89 mg	**P <0.001**
Nimmaanrat	4 h	0.96	0.8	p>0.05
2012	8 h	7.6	6.8	p>0.05
	12 h	13.9	12.8	p>0.05
	16 h	18.8	16.7	p>0.05
	20 h	22.3	21.3	p>0.05
	24 h	26.3	24.1	p>0.05

CI, confidence interva; NR, not reported; H, hours; mg, milligrams; MME, morphine milliequivalents; Ml, milliliters.

placebo found that pregabalin was superior to both groups in prolonging the postoperative pain free period and reducing rescue analgesics.[22] However, both groups reported superior results compared to placebo which was consistent with the findings of the current study.[22] The effects of pregabalin were also highlighted in another randomized control trial comparing a one-time preoperative oral dose of 300 mg pregabalin or 900 mg gabapentin in patients undergoing lower abdominal and limb surgery, wherein pregabalin demonstrated significant reduction in postoperative analgesia consumption compared to gabapentin.[23] Therefore, it is possible that the inconsistencies in the current literature regarding pregabalin or gabapentin efficacy may be secondary to differences in dosage, treatment protocols, and the use of spinal anesthesia for lower limb surgery.

Dosing and frequency protocols were heterogenous across both gabapentin and pregabalin studies. Oral gabapentin dosage ranged from 300-1200 mg and was administered once 1-2 hours prior to surgery in all studies, with one study continuing a tapered treatment regimen for 9 days postoperatively. In contrast, there were no consistent pregabalin protocols in the three included studies, with dosages ranging between 75-150 mg, which is considerably lower than the dosages utilized in previous orthopedic investigations.[13,22,23] This is highlighted in the two studies that were not associated with reduced postoperative pain, where the lowest dosage of gabapentinoid was administered among the studies evaluated (75mg of pregabalin).[12,15] Therefore, it is postulated that higher doses of pregabalin may produce superior outcomes in pain control and opioid burden reduction. Further randomized control trials are recommended to determine the optimal dosage of pregabalin in patients undergoing ACLR, as well as direct comparisons between pregabalin and gabapentin administration.

The heterogeneity in multimodal pain regiments inherent to this study posed further challenges to drawing conclusions about optimal gabapentinoid adjuncts. This finding is consistent with literature highlighting a lack of consensus on an optimal multimodal analgesia protocol for ALCR.[2] Recent studies seeking to clarify optimal pain management protocols for ACLR highlighted that nerve blocks, regional anesthesia, and intra-articular bupivacaine injections are consistently reported to reduce postoperative pain and opioid use.[24–29] Accordingly, the authors have observed a shift away from IV-PCA as a modality for post-ACLR pain management. As such, evaluating postoperative IV-PCA opioid consumption may no longer be a relevant

Table 10. Summary of reported side effects in patients receiving perioperative pregabalin for anterior cruciate ligament reconstruction (ACLR).

Author	Side Effect	Pregabalin Group	Control Group	*P*
Cho 2019	Dizziness	N= 11 (23.9%)*	N=3 (6.4%)	**p=0.018**
	Headache	N= 5 (10.9%)	N=2 (4.3%)	p>0.05
	Nausea/Vomiting	N= 15 (32.9%)	N= 9 (19.1%)	p>0.05
Akelma 2020	Vomiting	n=2	n=2	p>0.05
	Drowsiness	n=1	N=0	p>0.05
	Urinary retention	n=1	n=1	p>0.05
Nimmaanrat	Nausea/vomiting	n= 10	n= 14	p>0.05
2012	Dizziness	n=7	n=14	p>0.05
	Headache	n=6	n=7	p>0.05
	Blurred vision	n=2	n=3	p>0.05

H, hours.

Table 11. Summary of Perioperative Anesthesia and Analgesic Treatment Protocols in Studies Investigating Pregabalin

Author	Gabapentin/Pregabalin Protocol	Anesthesia	Local Infiltration Anesthesia	Nerve Block	Intraoperative Analgesia Protocol	Postoperative Analgesia Protocol
Cho et al.[9] 2019	1 dose of 150 mg oral pregabalin 1 hr prior to surgery and 1 dose 12 hr post-surgery	No general anesthesia	No LIA	Spinal Block with 0.5% bupivacaine (14 mg for males; 12 mg for females) .	1-5 mg IV Midazolam	IV- PCA of 1000 microg and 0.3 mg ramosetron at 4 ml/hr background and 2 ml every 20 min as needed for 24 hr If pain verbal numeric rating scale >5 given 0.5 mg/kg meperidine Naproxen/esmeprazole 500/20 mg twice a day starting postop day 1 until postop 2 weeks
Akelma et al.[1] 2020	1 dose 150 mg oral pregabalin 1 hr prior to surgery	NR	No LIA	Spinal Block with 2.5 mL of 0.5% hyperbaric bupivacaine	NR	dexketoprofen trometamol 50 mg every 12 hr, tramadol IV PCA 10 mg bolus as needed 10 min lock for 24 hrs Patients with pain numeric rating scale > given 50 mg tramadol
Nimmaanrat et al.[15] 2012	2 doses 75 mg pregabalin 1 dose 1 hr prior to surgery, 1 dose 12 hr later	NR	No LIA	Spinal Block with 0.5% hyperbaric bupivacaine	NR	PCA morphine: no continuous infusion, bolus 1 mg, lockout interval 5-min and 4-hr limit of 40 mg

NR, Not reported; LIA, Local Infiltration analgesia; IV, intravenous; PCA, patient-controlled analgesia; μg, micrograms; Mg, milligrams; mL, milliliters; Hr, hour.

way to measure postoperative opioid burden. Future studies investigating gabapentinoids should aim to incorporate evidence-based nonopioid analgesics and limit heterogeneity in intraoperative and postoperative management protocols for further optimization.

It should be acknowledged that previous literature has indicated 300 mg as the highest safe dose of pregabalin when used preoperatively, and it is possible that further randomized control trials evaluating higher dosages of pregabalin may report improved efficacy, but should be balanced with the possible known side effects of light headedness and dizziness postoperatively. Additional investigation into the optimal post-ACLR analgesia protocol and potential favorable interactions between gabapentinoids and other agents are also needed to recommend an ideal postoperative pain management protocol.

Limitations

We recognize some limitations in this systematic review. First, the assessment of quality of the included studies was performed by a single author which introduces a risk of bias. In attempt to reduce such bias, objective scoring mechanisms were used. Further, there was no uniform outcome reporting across studies. Pain was scored using different metrics and at different time points postoperatively, while opioid consumption metrics were also variable. The few numbers of studies with homogenous outcomes measures and pain protocols limited the ability to perform a meta analysis and draw definitive conclusions across study results. Furthermore, there was heterogeneity of patient population, non-standardized controls, and lack of numerical reporting that limits the strength of the included studies. Due to the scoping review design heterogeneity was not analyzed. None of the included studies performed direct comparisons between gabapentin and pregabalin, and all studies differed in the broader anesthetic and analgesic protocols within which a gabapentinoid was included. This lack of direct comparison and variability posed a challenge in reporting the best overall protocol for pain management

Conclusion

There is moderate evidence demonstrating that preoperative gabapentin may be safe and effective in reducing postoperative pain and opioid consumption after ACLR. Gabapentin may be considered when employed as part of a multimodal analgesia regimen; however, the optimal protocol has yet to be determined. Currently, there is limited evidence demonstrating the efficacy of pregabalin on pain and opioid consumption in the setting of ACLR.

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