Original Article

Tramadol Provides Similar Pain Relief and a Better Side Effect Profile than Oxycodone (or Hydrocodone) Alone or in Combination With Tramadol After Anterior Cruciate Ligament Reconstruction or Arthroscopic Knee Debridement

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Purpose: To evaluate whether tramadol provides similar postoperative pain relief after anterior cruciate ligament (ACL) reconstruction surgery or arthroscopic debridement surgery compared to oxycodone (or hydrocodone) or a combination of tramadol and oxycodone. **Methods:** Patients over the age of 14 undergoing ACL surgery or arthroscopic debridement surgery performed by the same surgeon were provided a postoperative pain diary over the first 10 postoperative days. Patients were either provided tramadol, oxycodone (or hydrocodone), or a combination of tramadol in addition to oxycodone (or hydrocodone). Pain scores were measured on visual analog scale (VAS), including average pain, maximum pain, and minimum pain throughout the day. Additionally, side effects and number of over-the-counter analgesics were recorded. **Results:** 121 patient surveys were reviewed. Tramadol alone for ACL with autograft provided lower average pain scores on postoperative day 1-3 (VAS 3.3 vs oxycodone 6.1 and hybrid of 5.1) with lowest maximum pain on postoperative day 1 (VAS 5.3 vs oxycodone 6.6 and hybrid 5.1) and the lowest number of average nights awakened by knee pain (3.6 vs oxycodone 6.0 and hybrid 8.5). Tramadol alone provided the lowest number of days of constipation (3 vs oxycodone 4.68 and hybrid 4.08), nausea (0.42 vs oxycodone 1.48 and hybrid 1.72), and dizziness (0.68 vs oxycodone 0.84 vs hybrid 1.28). Individual medication group breakdown of ACL surgery with allograft, as well as arthrosopic knee debridements did not have a large enough quantity to have three separate comparison groups. **Conclusions:** Tramadol provides similar, and in most cases better, pain relief for ACL reconstruction and arthroscopic knee debridements compared to oxycodone (or hydrocodone) alone or a combination of tramadol with oxycodone (or hydrocodone), while providing a lower side-effect profile. **Clinical Relevance:** Alternative analgesic therapies outside of traditional opioids (like oxycodone and hydrocodone) are lacking in popularity or reputation. This retrospective comparative study cohort evaluation can help provide clinicians an alternative analgesic therapy for various knee surgeries that have comparable pain relief with less addictive properties and less side effects.

Introduction

Anterior cruciate ligament (ACL) reconstruction is a common surgery that is known to be associated with substantial pain in the acute postoperative period. Arthroscopic knee debridements, such as partial meniscectomy and chondroplasty, are also frequently performed; however, patients typically experience less pain compared to an ACL reconstruction. Medications are often used to help alleviate postoperative pain. Opioid-based medication is commonplace and often is a first-line postoperative medication class that have been recently reevaluated, as more information of their

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potential side effects, abuse, and addictive potential have been noted.[1] Two out of three drug overdose deaths in 2018 involved an opioid and of those, 32% involved prescription opioids.[1] Anthony et al.[2] reported that at 12 months after ACL reconstruction, up to 4.7% of patients were still being prescribed and filling their opioid prescription. With this surgical procedure increasing over the years up to over 100,000 procedures performed annually in the United States, 2006,[3,4] there is additional interest in improving postoperative analgesia for this procedure and less invasive procedures like arthroscopic partial meniscectomy or chondroplasty while weighing this against the risks of the opioid epidemic.

Tramadol is a synthetic minimally opioid-based narcotic that is metabolized by the kidneys with a mean half-life of 6 hours.[5] It is a mixed-mechanism medication in that it works by binding to mu receptors (lower affinity compared to other narcotics like oxycodone), as well as blocking the reuptake of monoamines like serotonin and norepinephrine. Tramadol has been shown to have a lower addiction rate compared to traditional codone-based opioids like oxycodone and hyrodcodone[6,7] in procedures such as total knee arthroplasty,[8] while providing adequate acute postoperative pain relief in patients undergoing total knee arthroplasty (TKA) in lieu of opioids.[9] Additionally, because of the monoaminergic effects, tramadol may provide an anxiolytic and/or antidepressant effect that may help with pain management.[10]

Our purpose was to evaluate whether tramadol provides similar postoperative pain relief after anterior cruciate ligament (ACL) reconstruction surgery or arthroscopic debridement surgery compared to oxycodone (or hydrocodone) or a combination of tramadol and oxycodone. Our hypothesis is that tramadol would provide similar pain relief with a better side-effect profile.

Methods

After approval by the institutional review board, patients scheduled to undergo either ipsilateral primary anterior cruciate ligament reconstruction or arthroscopic meniscectomy, chondroplasty, or debridement were identified. Exclusion criteria included pediatric patients (14 years of age or younger), non-English speaking, allergy to proposed medications, revision procedure, contralateral graft harvest, neurologic disorder affecting movement, or back injury limiting normal movement in the past 3 months. Partial meniscectomy, chondroplasty, and debridement were all grouped into one patient category that we called Debridement. Investigators would identify qualifying individuals preoperatively and obtain informed consent. All ACL reconstructions were performed under general anesthesia with a single-shot adductor canal block, and all arthroscopic debridement procedures were performed under general anesthesia with 20 mL of local 0.50% bupivicaine injected around the portals and in the knee joint. All ACL reconstructions (either bone-tendon-bone autograft or bone-tendon-bone allograft) were performed with anteromedial portal flexible reamer technique with absorbable interference screw fixation on both the femur and tibia. All surgeries were performed by a single surgeon (P.D.A.). Surgeries were performed between 2017 and 2019. Postoperative physical therapy and pain medication regimens remained unchanged throughout this time period. Postoperative medication options were reviewed with patients prior to surgery, and the general practices of the surgeon were reviewed on the basis of the upcoming procedure. This standard practice did not vary if the patient was not in the study. ACL reconstruction patients received either a prescription of oxycodone 5 mg, 1 tablet by mouth, every 3-4 h, tramadol 50 mg, 1 tablet by mouth, every 4-6 h, hydrocodone 5 mg/acetaminophen 325 mg (Norco), 1 by mouth, every 4-6 h, or a combination of oxycodone and tramadol. ACL autografts were the only group to get the hybrid, as this procedure was felt to be the most painful postoperatively. The ACL allograft group would get either tramadol or Norco but not both. These were all written "as needed for pain". Selection of which patient received which medication was not formally randomized and was left to decision of the provider. If the patient had an allergy or sensitivity to a specific medication, an alternative analgesic medication plan was prescribed. If the medication they received placed them into one of our testing categories, their responses would be recorded. If the patient was taking a serotonin reuptake inhibitor (SSRI) medication, they did not receive tramadol. All patients received aspirin EC 325 mg, 1 tablet by mouth every 24 h for anticoagulation. The oxycodone and Norco groups were combined to form an "opioid" group for comparison.

A total of 124 patients enrolled; 121 patients (97.6%) were included in the final analysis. None of the enrolled patients were taking preoperative opioids or narcotics. The first questionnaire was to be filled out on postoperative day 1 in the evening (over 24 hours from surgery finishing), and subsequent questionnaires were

Table 1. Characteristics of Study Sample

Total	121	
Age, years, means ± SD (range)	37.6 ± 15.6 (15-74)	
BMI, kg/m^2, means ± SD (range)	25.3 ± 4.0 (18.6-43.9)	
Sex		
Male	50	41%
Female	71	59%
Ethnicity		
Hispanic	1	1%
Not Hispanic	49	40%
Not Reported	71	59%
Surgery		
ACL with BTB Autograft	56	46.3%
ACL with Allograft	37	30.6%
Arthroscopy	28	23.1%

Data are expressed as n with the percentage of the total cohort.

Table 2. Average Quantity of Medications Taken Daily by Surgery Type

Average Medications Taken Daily			
Female	ACL Allograft	ACL with BTB Autograft	Arthroscopy
Tramadol	5.7	6.1	5.4
Opioids	4.4	4.3	3.3
Combo	1.8	3.6	7.7
Male	ACL Allograft	ACL with BTB Autograft	Arthroscopy
Tramadol	5.6	4.5	3.3
Opioids	2.3	4.0	4.0
Combo		4.1	2.3

ACL, anterior cruciate ligament; BTB, bone-tendon-bone; OTC, over the counter.

filled out at the same time daily. The questions ask patients to report pain at various time points throughout the day, total medication intake each day, if pain was not controlled on their regimen, and if they experienced any side effects. Over-the-counter (OTC) medication usage was also recorded with patients able to select ibuprofen, naproxen, or acetaminophen, and the total OTC was recorded.

One-way analysis of variance was conducted to analyze differences in pain scores between pain medication groups at different time points after surgery, including type of surgery, medication, and sex. Post hoc pairwise comparisons between groups were performed using Tukey's test. All statistical analyses were conducted using R Statistical Software.

Results

A total of 124 forms were submitted, and 121 patients (97.6%) were included in the final analysis. Three ACL surgeries were excluded as 1 was a contralateral autograft and the other 2 were revision procedures. Five knee arthroscopic debridements were eventually excluded, as their respective groupings (no prescribed medications or combination of a narcotic and tramadol) were too few (3 debridements from one group and 2 from another) to provide meaningful results. Of the 121 remaining forms, 93 (76.9% of cohort) underwent ACL reconstruction and 28 (23.1% of cohort) with knee arthroscopy. Of the ACL reconstructions, 60.2% ($n = 56$) of those were bone-tendon-bone patella tendon autograft (BTB) and the remaining 39.8% ($n = 37$) was BTB allograft. Table 1 identifies the characteristics of the study sample.

Tables 2 and 3 display patient totals between procedures, including average amount of medications taken, average pain, and greatest pain levels.

For ACL reconstruction using BTB autograft, there were 3 groups observed: Oxycodone only ($n = 9$), tramadol only ($n = 11$), and a combination group of tramadol and oxycodone ($n = 31$). A comprehensive breakdown can be found in Table 4 and Figure 1. The tramadol group had the lowest incidence of calling the office to request a stronger medication (0 times vs 0.3 times/10 days on average for the opioid and combination group) and the lowest incidence of times being awoken at night due to pain (3.6 times per week vs 6.0 in the oxycodone group and 8.5 with the combination group).

The tramadol group consumed an average of 17.7 pills, the opioid group consumed an average of 9.3 pills, and the combination group consumed 25.4 pills of tramadol with 7.5 pills of opioids. The combination group consumed the fewest number of over-the-counter pills, such as ibuprofen, naproxen, or acetaminophen (38.2 compared to 40.1 in the tramadol group and 48.2 in the opioid group). The opioid group and tramadol groups consumed near identical total number of pills consumed (prescription + over-the-counter) (57.4 and 57.8) that were both less than the total number of pills consumed in the combination group (71.0).

Patients were asked to record visual analog scale pain scores at the end of each day for the first 10 days. Postoperative day 1 would be recorded at least 24 hours after completion of their surgery. For the ACL autograft group (Table 5), the tramadol-only group had the lowest average pain postoperative day 1 (1.9 vs 4.2 with opioid and 3.6 with combo; $P = .004$), lowest maximum pain at day 1 (5.3 vs 8.8 with opioid and 7.2 with combo; $P = .003$), and lowest minimum pain at day 1 (1.9 vs 4.2 for opioid and 3.6 with combo; $P = .112$). Postoperative ranges were also stratified between postoperative days 1-3, 4-6, and 7-10. The tramadol only group had lower maximum pain (days 1-3; $P = .002$), minimum pain, and average daily pain (days 1-3; $P = .003$, days 4-6; $P = .041$) at all 3 time ranges compared to the opioid and combination group. Further breakdown can be found in Table 5 and Figure 1.

Table 3. Average VAS Pain Scores by Surgery

Average Overall Pain Scores by Surgery			
	ACL Allograft	ACL with BTB Autograft	Arthroscopy
Days 1-3 maximum pain	5.5	7.2	6.0
Days 4-6 maximum pain	4.0	5.8	3.8
Days 7-10 maximum pain	3.2	4.1	3.6
Days 1-3 minimum pain	2.5	3.5	3.5
Days 4-6 minimum pain	1.9	2.7	2.4
Days 7-10 minimum pain	1.3	2.0	2.0
Days 1-3 average pain	3.8	5.0	4.5
Days 4-6 average pain	2.6	3.8	3.1
Days 7-10 Average Pain	1.9	2.6	2.5
Minimum pain - day 1	2.5	3.4	3.2
Maximum pain - day 1	5.6	7.2	5.8
Average pain - day 1	4.0	5.1	4.2

Table 4. ACL Autograft Pill Consumption by Prescription Group (Averages Over First 10 days From Surgery)

	ACL Auto Opiods Only ($n = 9$)	ACL Auto Tramadol Only ($n = 11$)	ACL Auto Combined Meds ($n = 31$)
Times called office to change medications	0.3	0.0	0.3
Times woken up at night due to pain	6.0	3.6	8.5
Total tramadol consumed		17.7	25.4
Total oxycodone consumed	9.3		7.5
Total OTCs consumed	48.2	40.1	38.2
Total pills consumed	57.4	57.8	71.0
Tramadol days 1-3: pills		12.0	14.3
Tramadol days 4-6: pills		4.4	8.1
Tramadol days 7-10: pills		1.3	2.9
Oxycodone days 1-3: pills	7.3		5.5
Oxycodone days 4-6: pills	1.9		1.5
Oxycodone days 7-10; pills	0.1		0.4
OTC quantity days 1-3: pills	16.5	15.0	13.6
OTC quantity days 4-6: pills	14.7	13.1	11.5
OTC quantity days 7-10: pills	17.0	12.0	26.3

Patients were also asked about varying symptoms after surgery commonly associated with side effects of varying pain medications, including dizziness, disorientation, headache, gastrointestinal (GI) upset, nausea, vomiting, and constipation. Incidence in number of days of effects occurring is outlined in Table 6. Tramadol only had the lowest incidence of dizziness ($P = .14$), headache ($P = .010$), nausea ($P = .002$), and constipation ($P = .016$). Opioids had the lowest rate of disorientation ($P = .468$) and GI upset ($P = .12$). The opioid group and the tramadol group tied for lowest incidence of vomiting ($P = .078$). The combination group of tramadol with opioid did not have the lowest side effect group of any of the 7 inquired categories. Further breakdown can be seen in Figure 2.

Discussion

Tramadol provided adequate postoperative analgesia in the setting of ACL reconstruction and arthroscopic debridement's of the knee compared to opioids and a combination of tramadol with an opioid in this cohort. The side effect profile, as well as sleep disturbance, was more favorable in the tramadol group compared to the opioids or the tramadol/opioid combination group.

These findings have several important implications for clinical practice. Having a substitute medication for a commonly painful procedure like ACL reconstruction is helpful in providing clinicians with another alternative to traditional opioids like oxycodone or hydrocodone. The choice for postoperative analgesic therapy is multifactorial, including past reactions to varying medication therapies, concomitant procedures performed at the time of surgery, familiarity/reputation of a medication by patient (and provider), among others. In some cases, it may be what the clinician has always used since their training or simple habit. There has been an investigation on regional trends for opioid distribution for ACL reconstruction. In a study of more than 90,000 ACL reconstructions from 2010 to 2017, there was an increase in opioid prescriptions with the highest incidence in the Western United States, and the lowest incidence in the Northeast.[11] As various analgesic

Table 5. Average VAS Pain Scores for ACL Autograft by Prescription Group

	ACL Auto Opioids Only ($n = 9$)	ACL Auto Tramadol Only ($n = 11$)	ACL Auto Combined Meds ($n = 31$)	ANOVA P Value
Days 1-3 maximum pain	8.2	5.6	7.3	.002
Days 4-6 maximum pain	6.2	4.5	6.1	.057
Days 7-10 maximum pain	4.0	3.2	4.4	.296
Days 1-3 minimum pain	3.6	2.1	3.8	.229
Days 4-6 minimum pain	2.4	1.8	3.1	.181
Days 7-10 minimum pain	1.6	1.0	2.3	.124
Days 1-3 average pain	6.1	3.3	5.1	.003
Days 4-6 average pain	3.1	2.8	4.3	.041
Days 7-10 average pain	2.3	1.7	2.9	.195
Minimum pain - day 1	4.2	1.9	3.6	.112
Maximum Pain - day 1	8.8	5.3	7.2	.003
Average Pain - day 1	6.6	3.2	5.1	.004

Table 6. Side Effects Reported (in Days Occurred) by Medication Group in First 10 Days After ACL Reconstruction

	Opioids Only ($n = 25$)	Tramadol Only ($n = 50$)	Combined Meds ($n = 39$)	ANOVA P Value
Dizziness	0.84	0.68	1.28	.14
Disorientation	0.24	0.40	0.51	.468
Headache	0.68	0.34	1.31	.010
GI Upset	0.12	0.2	0.36	.287
Nausea	1.48	0.42	1.72	.002
Vomiting	0.04	0.04	0.23	.078
Constipation	4.68	3.00	4.08	.116

ANOVA, analysis of variance; GI, gastrointestinal.

therapies has become more scrutinized, we have started to see various methods used to try to mitigate opioid use and distribution. A Danish study published in 2021 evaluated trends in use of tramadol and oxycodone once media attention rose in 2017 and actually showed that tramadol use decreased significantly, while opioid use remained fairly steady.[12] While the reasoning for this difference is unclear, these investigations show that there is an outside influence on prescription distribution.

Patient education is likely an important factor in postoperative pain management. Reassurance that various levels of discomfort (incisional pain, swelling, stiffness, limited range of motion, quad weakness, etc.) are important to educate patients prior to the procedure. Preoperative education on expectation of discomfort (even with medication use) may potentially decrease pain scores but can ease the "stress of the unknown" for the patient, which may reduce anxiety.[13] Educating patients that multimodal analgesic therapy can be helpful rather than exclusively relying on prescription medications. Using other options such as acetaminophen, ibuprofen, and heat and cryotherapy can also be effective.

The side effects of varying analgesic medications are well documented and represent an additional factor to be considered. Oxycodone has been shown to have a relatively high rate of constipation and nausea compared to other over-the-counter and central-acting pain relievers.[14] This current patient cohort shows that tramadol, in isolation, has a statistically significant lower chance of nausea and headache compared to opioids or a combination group with a nonstatistically significant decrease in constipation.

Limitations

One limitation of this study was there was no formal randomization of medications to patients for varying procedures. We elected to provide patients our normal regimen of medications at that time based on the procedure and wait to see what patients elected to fill out in surveys. Once we could see what we felt was an adequate number of surveys being returned, we started to try different regimens to create a different group. We

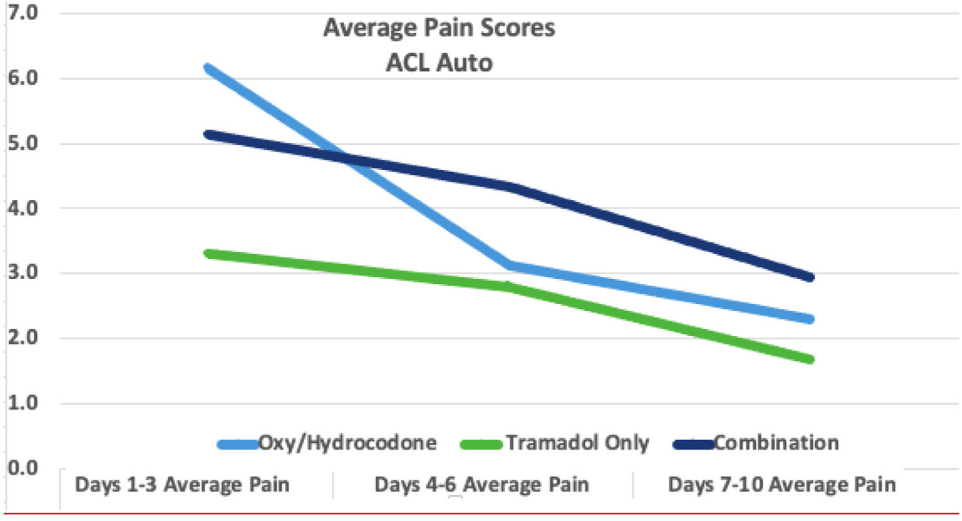

Fig 1. Average VAS pain scores by medication group and time from surgery. ACL, anterior cruciate ligament.

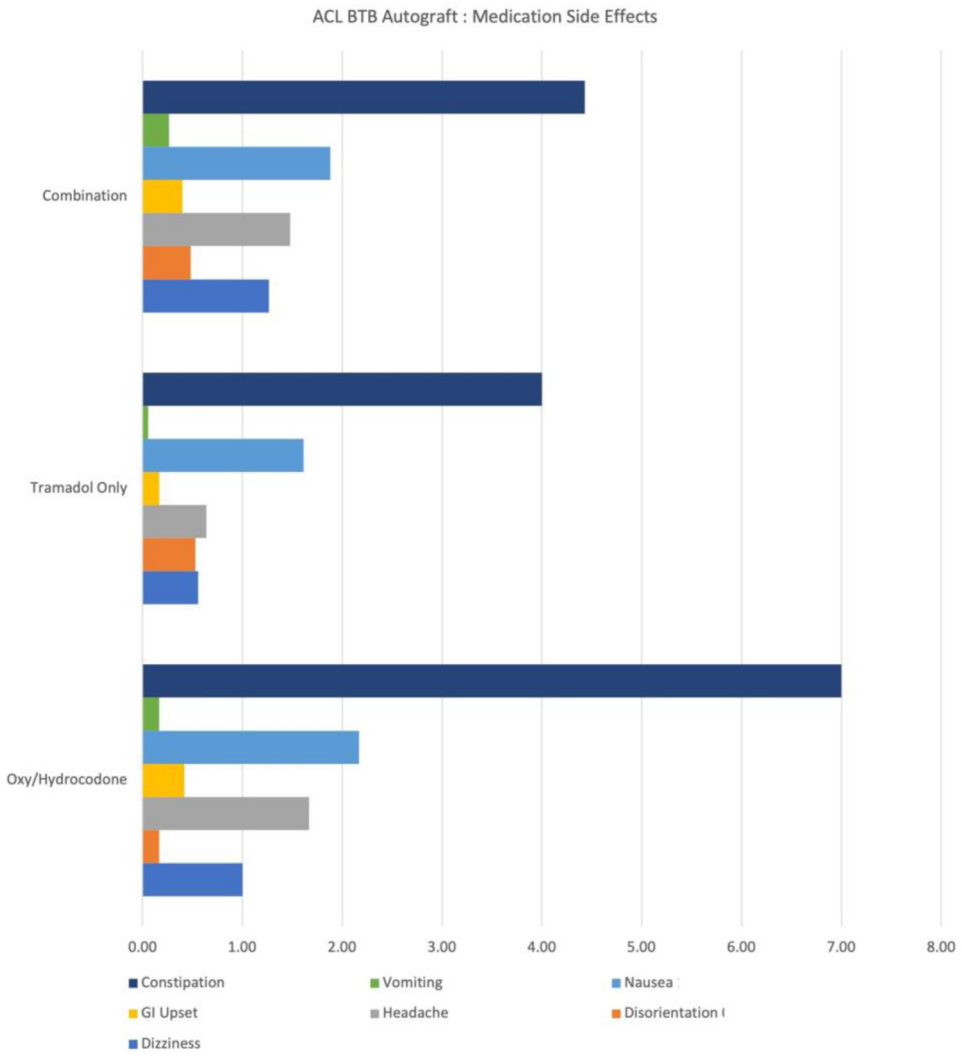

Fig 2. Side effects of medication groups by average days patient experienced the symptom after ACL surgery using BTB autograft. ACL, anterior cruciate ligament; BTB, bone-tendon-bone; GI, gastrointestinal.

recognize the potential bias; however, this was not a randomized study, but more of an observational/retrospective review. Additionally lacking was further confounding factors that may have contributed to postoperative pain. These include factors such as degree of chondral damage or disease, workers' compensation claim, preoperative pain scores, or comorbid psychiatric conditions.

Conclusion

Tramadol provides similar, and in most cases better, pain relief for ACL reconstruction and arthroscopic knee debridements compared to oxycodone (or hydrocodone) alone or a combination of tramadol with oxycodone (or hydrocodone), while providing a lower side-effect profile.

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