



Effect of perioperative acetaminophen on pain management in patients undergoing rotator cuff repair: a prospective randomized study

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Background: Limiting opioid use in perioperative pain management is currently an important focus in orthopedic surgery. The ability of acetaminophen to reduce postoperative opioid consumption while providing acceptable pain management has not been thoroughly investigated in patients undergoing rotator cuff repair (RCR).

Methods: Patients undergoing primary arthroscopic RCR were prospectively randomized to 1 of 3 treatment groups: Group 1 (control) received both 5 mg of oxycodone every 6 hours as needed and 1000 mg of acetaminophen orally every 6 hours as needed after surgery and had the option to take either medication or both. Group 2 (control) received only 5 mg of oxycodone every 6 hours as needed without any additional acetaminophen after surgery. Group 3 received 1000 mg of acetaminophen orally every 6 hours for 1 day prior to and after surgery, which was subsequently decreased to administration every 8 hours during postoperative days 2–5. Group 3 patients were also allowed to take 5 mg of oxycodone every 6 hours as needed after surgery. All patients received interscalene blocks with liposomal bupivacaine (Exparel). Opioid use, pain scores, side effects, and overall satisfaction were assessed daily for the first week after surgery.

Results: A total of 57 patients (mean age, 57.8 ± 9.55 years) were included in this study. Baseline demographic characteristics including age, sex, and body mass index were similar between the groups ($P > .05$). Patients in group 3 took significantly fewer narcotics overall ($P = .017$) and took significantly fewer pills each day compared with group 2. Group 3 also reported significantly better overall pain control compared with the other groups ($P = .040$). There were no significant differences in overall patient satisfaction between the groups ($P > .05$). Additionally, there were no significant differences between groups regarding postoperative medication-associated side effects ($P > .05$).

Conclusion: Perioperative acetaminophen represents an important component of multimodal analgesia in appropriately selected patients undergoing shoulder surgery. In this study, the use of perioperative acetaminophen significantly decreased opioid consumption and improved overall pain control after primary arthroscopic RCR.

This study was approved by the Thomas Jefferson University Institutional Review Board (study no. 18D.712).

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Arthroscopic rotator cuff repair (ARCR) reduces long-term pain and improves quality of life in patients with symptomatic rotator cuff disease.^{9,13,14,16} Nevertheless, ARCR can be associated with significant pain in the early postoperative period, which requires appropriate analgesia.^{2,8} Effectively controlling this pain is an important objective as high levels of postoperative pain can compromise quality of life, as well as early and effective rehabilitation.⁵

Opioids have long been considered the gold standard for achieving adequate analgesia after orthopedic surgery but are also associated with a potential for dependence and abuse, as well as a significant adverse side effect profile.²⁷ In opioid-naïve patients, a cycle of dependence can subsequently develop after opioids are legally prescribed by medical providers, with approximately 9% of such cases being orthopedic patients.²⁴ Side effects associated with opioid medications include nausea, vomiting, constipation, ileus, urinary retention, and pruritus.²⁰ Even more significant complications can occur at higher doses, including hypotension, hypoxia, and respiratory depression.²² Given the potential risks associated with opioid use and the current opioid epidemic, additional options for postoperative pain management warrant investigation.²³

A number of non-opioid options exist for ameliorating pain in the immediate postoperative period. Regional anesthesia including interscalene brachial plexus blocks,¹⁰ patient-controlled analgesia,⁷ and intra-articular local injections³ are such options. An interscalene brachial plexus block may be superior to patient-controlled analgesia but is still limited by an effective duration of 1-2 days.¹⁰ This duration may be extended with liposomal bupivacaine, but regional anesthesia must still be combined with additional analgesic medication for pain control that is needed for a longer duration.²⁸ Nonsteroidal anti-inflammatory drugs are one option for this, but their adverse effects on soft tissue-to-bone healing are well documented.^{6,11} One additional medication is acetaminophen. Although not without its risks, such as the potential for acetaminophen-induced liver toxicity, acetaminophen is generally considered a safe drug with an acceptable side effect profile.¹

The use of acetaminophen to reduce opioid utilization and improve patient satisfaction has not previously been studied after arthroscopic shoulder surgery. We sought to evaluate the ability of preoperative and postoperative acetaminophen to decrease opioid utilization after ARCR. We hypothesized that a pain regimen including perioperative acetaminophen would reduce opioid consumption and provide adequate analgesia after ARCR.

Materials and methods

Patients undergoing primary ARCR at a single institution from June 2019 to March 2020 were approached for enrollment (Fig. 1). The study included all patients aged 30-80 years undergoing primary ARCR of full-thickness rotator cuff tears. The exclusion criteria consisted of any history that would preclude acetaminophen use including active liver disease, a history of alcoholism, phenylketonuria, severe renal impairment, documented caloric undernutrition, previous overdose with acetaminophen, or allergy to acetaminophen. Patients who had a history of chronic narcotic use or who received regional anesthesia with an agent besides liposomal bupivacaine were also excluded. All surgical procedures were performed by 1 of 4 fellowship-trained shoulder and elbow surgeons with patients in the beach-chair position.

Patients were prospectively randomized to 1 of 3 treatment groups at enrollment (Table I). To help eliminate confounding variables, all patients in a given 3-week window were given the same management and assigned to the same treatment group. The assigned group for enrollment rotated every 3 weeks. Group 1 (control) patients were able to take 5 mg of oxycodone every 6 hours as needed and 1000 mg of acetaminophen every 6 hours as needed after surgery. They had the option to take either medication or both. Group 2 (control) patients were able to take 5 mg of oxycodone every 6 hours as needed without any additional acetaminophen after surgery. Group 2 patients who reported taking acetaminophen were considered noncompliant with the protocol and were excluded. Group 3 patients received 1000 mg of acetaminophen every 6 hours for 1 day prior to and after surgery. During postoperative days 2-5, these patients received 1000 mg of acetaminophen every 8 hours. Group 3 patients were also allowed to take 5 mg of oxycodone every 6 hours as needed after surgery. Patients in group 3 who did not take the assigned dose of acetaminophen before and after surgery were also considered noncompliant with the protocol and were excluded. Patients in all groups were instructed not to take other pain medications. Preoperatively, all patients received general anesthesia and interscalene blocks with 10 mL of liposomal bupivacaine (Exparel; Pacira Biosciences, Parsippany, NJ, USA) and 10 mL of 0.5% bupivacaine hydrochloride without epinephrine. The nerve blocks also included 4 mg of dexamethasone. Additionally, all patients received a combination of 4 mg of dexamethasone intravenously and 4 mg ondansetron intravenously per our antiemetic protocol prior to receiving general inhalational anesthesia with an endotracheal tube.

Prior to surgery, all patients received standardized instructions on the survey they would receive each day for the first week after surgery and on how they would need to answer the questions. There were 5 survey questions: (1) Did you take any opioid medication today (yes/no)? (2) If yes how many pills and at what times? (3) How would you rate your pain today (0-100)? (4) If you experienced any side effects, what were they? (5) Are you satisfied with your pain control? (Likert scale). All results were entered



CONSORT 2010 Flow Diagram

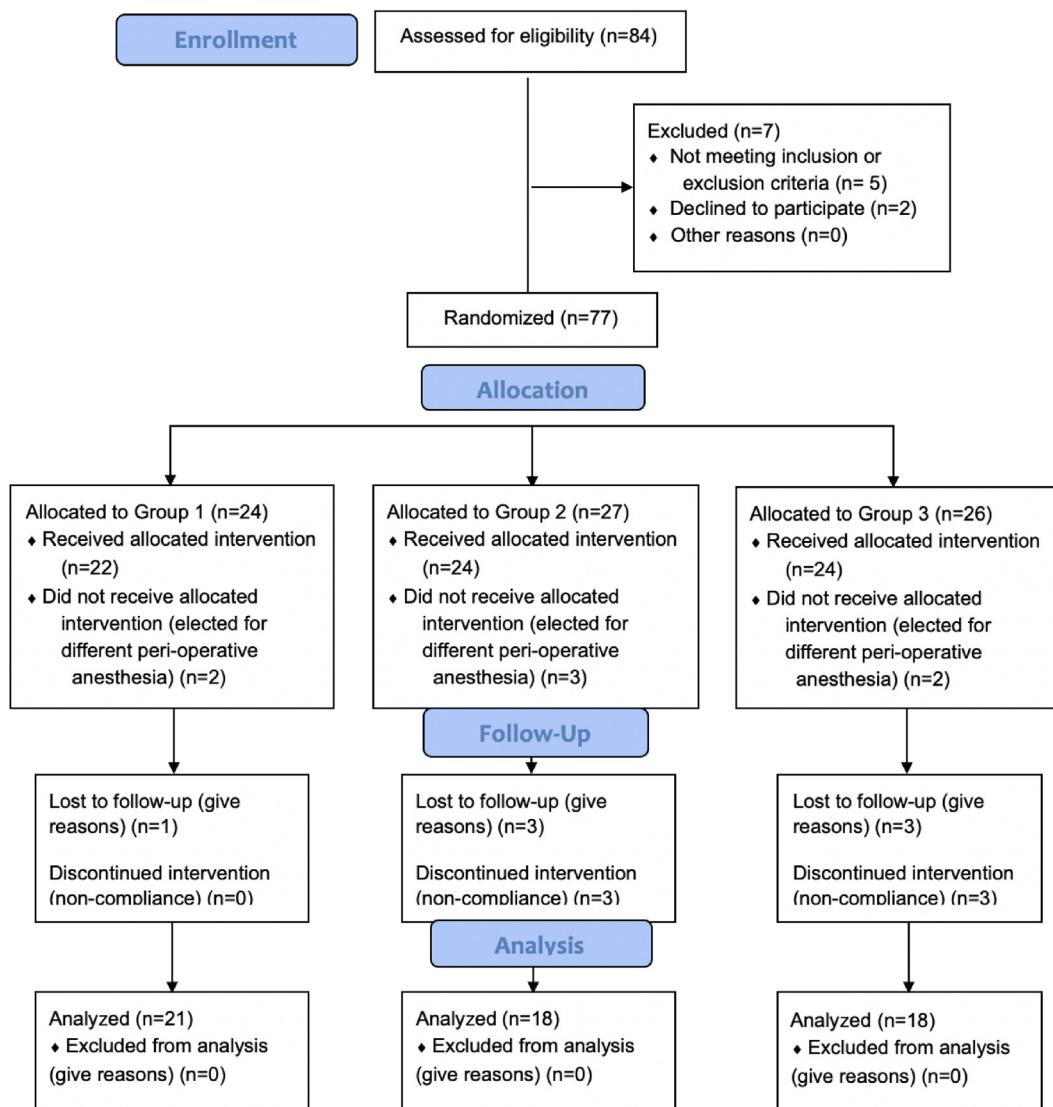


Figure 1 CONSORT (Consolidated Standards of Reporting Trials) guidelines flow diagram.

Table I Study treatment groups

	Group 1	Group 2	Group 3
Preoperative acetaminophen dose	None	None	1000 mg every 6 h for 24 h on day prior to surgery
Postoperative acetaminophen dose	1000 mg every 6 h as needed	None	1000 mg every 8 h on days 2-5, then as needed
Oxycodone dose	5 mg every 6 h as needed	5 mg every 6 h as needed	5 mg every 6 h as needed

into a secure server, REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN, USA), through which the survey questions were e-mailed daily on postoperative days 1-7. Patients were also given the option to take home a paper version of the survey that they could fill out daily and bring to their first postoperative visit.

Adherence to the protocol was confirmed at the first postoperative visit in the clinic or by a phone call. Demographic factors for each patient such as age, sex, and body mass index (BMI) were collected via chart review. Total pills taken (1 pill was defined as 5 mg of oxycodone or 7.5 morphine milligram equivalents), pain scores from 0 to 100, and satisfaction on a Likert scale from day 1 through day 7 postoperatively for each patient were summed and averaged for each group.

Statistical analysis

The primary outcome was the total number of 5-mg oxycodone pills (7.5 morphine milligram equivalents) consumed in the first week after surgery. Secondary outcome measures included daily side effects, level of pain experienced, and satisfaction with pain-control regimen. Power analysis was performed using G*Power (Heinrich Heine University, Dusseldorf, Germany). Post hoc power analysis was performed 10 months from the beginning of enrollment. The effect size was determined based on the mean number of pills consumed over the first week for each study arm and was found to be 0.4; α was set to 0.05 and $1 - \beta$ was set to 0.95, resulting in an actual power of 0.953. This indicated sufficient power had been achieved, and enrollment was concluded.

Descriptive statistics were calculated using SPSS software (IBM, Armonk, NY, USA). To identify differences in survey responses between patients in the 3 arms of the trial, we used χ^2 and analysis-of-variance tests for categorical and continuous variables, respectively. Additionally, we used *t* tests for subgroup analysis and the Kruskal-Wallis test for ordinal variables. A threshold of $P < .05$ was used for statistical significance.

Results

A total of 57 patients (mean age, 57.8 ± 9.55 years) meeting the inclusion and exclusion criteria were evaluated (Fig. 1). Baseline demographic characteristics including age ($P = .58$), sex ($P = .07$), and BMI ($P = .15$) were similar between the groups (Table II). There were 21 female and 36 male patients, and the average BMI was 30.5 ± 5.2 . Additionally, there were no significant differences between groups regarding concurrent biceps procedures performed ($P = .368$) or number of rotator cuff tendons repaired ($P = .317$) (Table III).

Patients in group 3 consumed significantly fewer 5-mg oxycodone pills overall compared with the other treatment groups ($P = .017$). In terms of average opioid pill

consumption per group, patients who consumed acetaminophen before and after surgery took approximately 10 fewer opioid pills in the first postoperative week when compared with patients who took no acetaminophen and about 4 fewer pills than patients who took acetaminophen only after surgery (Table IV). Patients in group 3 also took significantly fewer narcotic pills each day compared with group 2 and took significantly fewer pills than both groups on day 1 (Fig. 2). Furthermore, average pill consumption in group 3 was significantly less than that in both groups 1 and 2 on day 1: 2.1 vs. 3.0 ($P = .03$) and 2.1 vs. 3.2 ($P = .02$), respectively. The same day-by-day breakdown for average pill consumption by group showed that significantly fewer pills were consumed by group 3 vs. group 2 for each of the 7 days postoperatively ($P < .05$) (Fig. 2).

Group 3 patients also reported significantly better overall pain control on a 0-100 scale than patients in the other groups ($P = .040$) (Table IV). There was no significant difference in overall satisfaction on a Likert scale between the groups ($P = .083$). Commonly reported postoperative medication-associated side effects included nausea, constipation, and drowsiness. There were no significant differences between groups regarding medication side effects experienced ($P = .649$) (Table V).

Discussion

The results of this prospective case-control study confirmed our hypothesis that perioperative acetaminophen can significantly reduce postoperative opioid consumption and improve patient satisfaction after ARCR. Our results showed that patients in the study group—those who took acetaminophen before and after ARCR—consumed significantly less opioid medication when compared with patients who took acetaminophen only after surgery or not at all ($P = .017$). Furthermore, patients in the study group reported significantly better pain control, despite taking less opioid medication ($P = .040$). There was no significant difference in overall satisfaction as measured on a Likert scale, although patients in the study group did report the highest satisfaction with their pain regimen ($P = .083$). The use of 2 control groups helped to demonstrate the ability of preoperative acetaminophen to reduce opioid consumption after surgery regardless of the postoperative pain-control regimen.

Acetaminophen is an important component of multimodal analgesia in patients undergoing ARCR, and the results in the study group suggest that acetaminophen has potential use as a premedication, prior to surgery. The reason for the efficacy of acetaminophen taken before surgery in this trial may relate to its pharmacokinetics. Acetaminophen has a plasma half-life of 1.5-2.5 hours at lower doses, but the sulfonation pathway becomes saturated at higher doses (4 g/d), allowing the half-life to increase.¹⁸ The patients in group 3 in this trial took the maximum

Table II Patient demographic characteristics

Parameter	Group 1 (n = 21)	Group 2 (n = 18)	Group 3 (n = 18)	P value
Age at surgery, yr	56.67 (11.45)	57.11 (8.51)	59.72 (8.23)	.580
Sex: F/M	11/10	3/15	7/11	.069
BMI	30.29 (5.06)	32.36 (5.97)	29.01 (4.31)	.153
Laterality: R/L	13/8	5/13	13/5	.019

F, female; M, male; BMI, body mass index; R, right; L, left.

Data are presented as number of patients or mean (standard deviation).

Table III Procedures by group

Parameter	Group 1 (n = 21)	Group 2 (n = 18)	Group 3 (n = 18)	P value
Procedure				.368
RCR only	14	14	15	
RCR and tenodesis	5	4	0	
RCR and tenotomy	2	0	3	
Average No. of tendons repaired	1.29	1.44	1.33	.317

RCR, rotator cuff repair.

The P value for the difference in procedure occurrence was calculated between all groups.

Table IV Opioid use and pain

Parameter	Group 1 (n = 21)	Group 2 (n = 18)	Group 3 (n = 18)	P value
Pills taken	12.97 (10.95)	18.88 (10.85)	8.94 (8.06)	.017
Pain	46.37 (23.63)	59.93 (22.32)	41.49 (19.63)	.040
Satisfaction	2.14 (0.83)	2.42 (0.62)	1.87 (0.67)	.083

Data are presented as mean (standard deviation). One pill was defined as 5 mg of oxycodone. Pain and satisfaction were averaged for postoperative day 1 through day 7. Pain was measured on a scale from 0 to 100. Patient satisfaction with the pain-control regimen was rated from 1 to 5, in which 1 is best.

recommended therapeutic dose (4 g) the day before surgery, and this is still far from the lower threshold for a toxic dose of 12 g, or 150-200 mg/kg.¹² In this study, 5 days was chosen for the scheduled administration of acetaminophen in the study group because of initial uncertainty regarding patient compliance or error. As we become more comfortable with the protocol and patient education, the acetaminophen dose can be tailored to BMI and health history (as high as 4000 mg in any 24-hour period) and the administration can be extended to as many as 10 days postoperatively.

Various studies have shown that larger doses of perioperative oral or intravenous acetaminophen can reduce postoperative opioid use.^{4,21,25} In patients undergoing laparoscopic sleeve gastrectomy, opioid administration decreased from 23.7 to 0.7 mg in patients who were given acetaminophen intraoperatively and postoperatively when compared with controls ($P < .001$).²¹ Among patients undergoing spine surgery, those administered intravenous acetaminophen perioperatively also consumed significantly

less opioid medication than a control group ($P = .015$).²⁵ Moreover, patients undergoing outpatient breast surgery who received preoperative oral acetaminophen showed reduced narcotic use and improved pain scores when compared with patients receiving no preoperative analgesia ($P < .001$).⁴

The ability for multimodal analgesia to reduce opioid consumption in shoulder arthroplasty has also previously been investigated. Patients undergoing elective shoulder arthroplasty were treated with a standard opioid-based regimen or a multimodal analgesia regimen including preoperative and postoperative doses of acetaminophen, and opioid use was tracked for 72 hours.¹⁹ Opioid use was found to be lower in the multimodal cohort on all 3 days ($P < .01$ for all). However, because acetaminophen was not the only drug administered preoperatively, its effect was not isolated.

Although multimodal pain regimens have previously been investigated,^{4,19,21} we are unaware of other literature that has investigated the isolated efficacy of oral

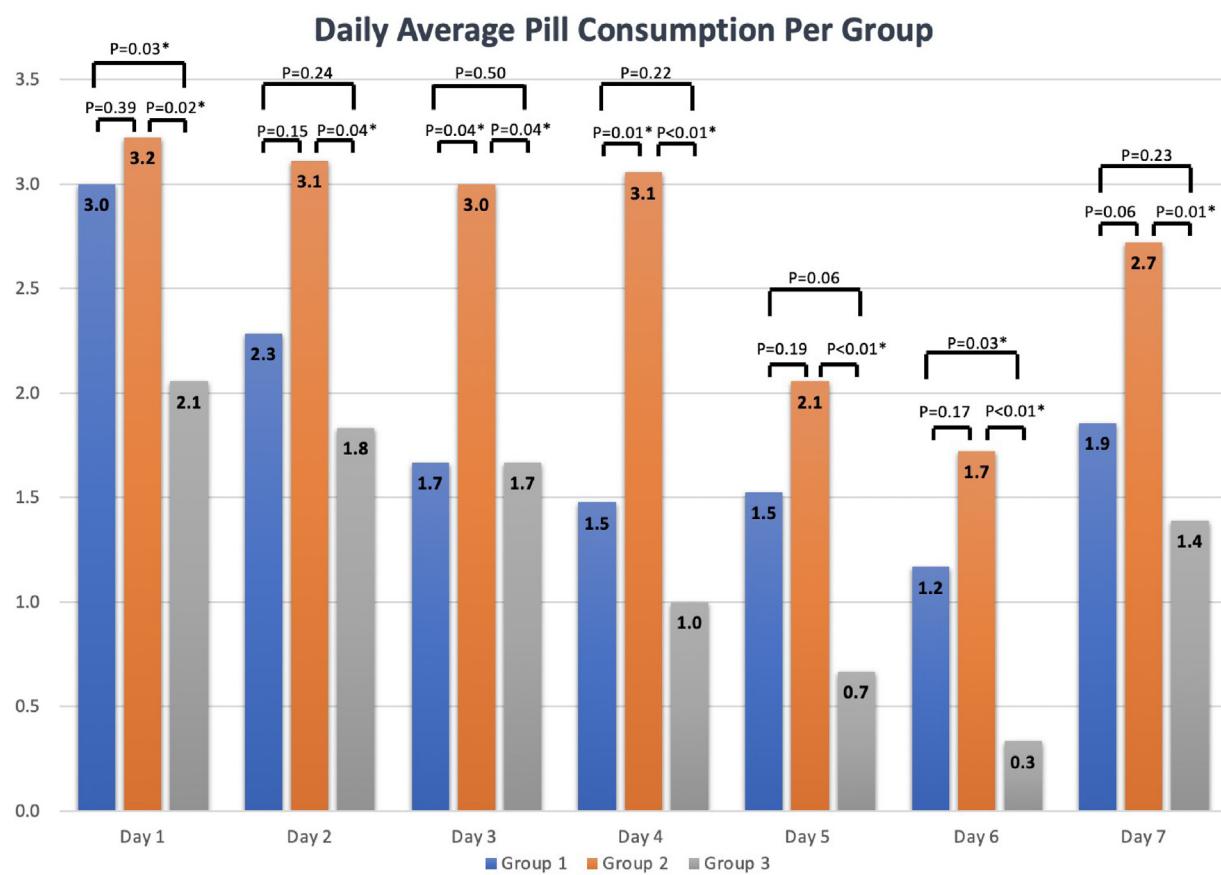


Figure 2 Daily average oxycodone pill consumption by group. *Statistically significant.

Table V Most common side effects experienced

Side effect	Group 1 (n = 21)	Group 2 (n = 18)	Group 3 (n = 18)	P value
None	10	5	5	.649
Nausea	4	2	2	
Constipation	5	7	7	
Drowsiness	2	4	4	

Patients reported side effects daily, if any; the most common side effect per patient is reported.

acetaminophen in reducing the need for opioid medication after ARCR. Although demonstrating efficacy vs. control groups, previous studies have failed to isolate the additional effect of acetaminophen. Furthermore, patient compliance is likely to be better when adding only 1 additional medication to the analgesia regimen rather than 3, as in some previous studies. Of the 77 patients who underwent randomization in our study, 6 (7.8%) did not follow the regimen as directed, and this brings into question how well patients would follow a postoperative regimen involving up to 4 medications rather than just 2, as used in this trial.

An additional reason to add acetaminophen to analgesic regimens is to reduce cost. ARCR is now commonly

performed at ambulatory surgery centers on an outpatient basis, and adequate analgesia is necessary not only to ensure patient comfort but also to minimize the potential for readmission for pain.¹⁵ A review of a cohort of >18,000 patients who underwent outpatient rotator cuff repair found that one of the most common complications resulting in readmission was pain, with 13% of readmissions occurring for this reason.¹⁷ This readmission rate for pain suggests that there is room for improvement to be made in the management of postoperative pain after ARCR.

This study had several limitations. First, it was not a blinded trial. It may be possible to blind both patients and research personnel to the trial arm in which each patient

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was enrolled by using a placebo, which would help to eliminate potential detection bias. Furthermore, the use of a placebo in group 2 would have equalized the total number of pills (including both acetaminophen and opioids) taken between the groups. It is possible that the additional absolute number of pills taken by groups 1 and 3, as compared with group 2, which only took opioid medication, may have had some degree of placebo effect. It is also possible that confounding variables may have been better controlled by performing enrollment in all patient groups simultaneously. Additionally, a nearly significant difference was found in the sex breakdown across groups ($P = .069$). If sex significantly affects perioperative pain and opioid use, then this may have had an effect on the results.

The strengths of this study include the presence of 2 control groups that represent the most common postoperative analgesic regimens. Whether one regimen or the other is more reflective of what is typically followed depends on the level of patient education regarding opioids and patient preferences.^{26,29} Furthermore, selection bias was limited in this study by randomizing enrollment, and the potential for recall bias was reduced by having patients answer survey questions daily.

Conclusion

The use of perioperative acetaminophen significantly decreased opioid consumption and improved overall pain control after primary ARCR. Given the significant side effect profile of opioids, any analgesic regimen that reduces opioid utilization while maintaining a similar level of pain relief will be of great benefit to patients.

Disclaimers

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