The Effect of Initiating a Preventive Multimodal Analgesic Regimen on Long-Term Patient Outcomes for Outpatient Anterior Cruciate Ligament Reconstruction Surgery

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BACKGROUND: Unrelieved postoperative pain may impair rehabilitation, delay recovery, and result in poor outcomes. Preventive multimodal analgesic techniques may improve long-term outcome after surgery.

METHODS: We randomized 200 consecutive patients to receive acetaminophen 1000 mg and either celecoxib 400 mg or placebo 1–2 h before anterior cruciate ligament surgery. All patients received intraarticular analgesics and had an external cooling system applied to the operative knee. After discharge patients were instructed to take acetaminophen 1000 mg every 6 h and either celecoxib 200 mg every 12 h or matching placebo for the first 14 days postoperatively. All patients were enrolled in an accelerated rehabilitation program. Six months postoperatively, the level of activity was assessed, as was the presence of patellofemoral complications including: anterior knee pain, flexion contracture, quadriceps weakness, and complex regional pain syndrome.

RESULTS: More patients in the control group developed patellofemoral complications compared to the celecoxib group ($P = 0.001$) including anterior knee pain (14/96; 15%) vs (4/95; 1%), complex regional pain syndrome (7/96; 7%) vs (1/95; 1%), flexion contractures (9/96; 9%) vs (2/95; 2%), and scar tissue requiring re-arthroscopy (8/96; 8%) vs (2/95; 2%) respectively. More patients in the celecoxib group returned to a higher activity level (84% vs 65%) ($P < 0.01$), were able to participate at a more intense level ($P < 0.02$), and return to full sports activity ($P < 0.05$).

CONCLUSIONS: The administration of celecoxib as a component of a preventive multimodal analgesic technique for anterior cruciate ligament reconstruction reduces long-term patellofemoral complications and increases the likelihood of returning to a preinjury level of activity.

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Arthroscopic reconstruction of the anterior cruciate ligament (ACL) is routinely performed on an outpatient basis and is associated with considerable postoperative pain (1). Unrelieved postoperative pain may impair the ability to participate in rehabilitation programs and delay recovery, resulting in poorer outcome and greater use of health care resources after discharge to home (2). Patients unable to participate in a rehabilitation program after arthroscopic knee surgery are at increased risk for developing postoperative complications such as delay in strength recovery, prolonged stiffness, anterior knee pain, and complex regional pain syndrome (CRPS) (3–7).

There is a continuum of pain after surgery ranging from acute to chronic. Effective treatment of acute pain, especially when accompanied by an antihyperalgesic component, may prevent the development of chronic pain syndromes (8,9). The perioperative nociceptive afferent barrage associated with surgery has been linked to central sensitization that may cause chronic postoperative pain (10). Short-term reductions in pain and opioid use have been reported in patients who received preemptive analgesic interventions designed to block or reduce this surgical nociceptive input from reaching the central nervous system (CNS) (10,11). However, most preemptive analgesic studies have limited their outcomes to the assessment of pain and opioid use in the immediate postoperative period before hospital discharge (10,11). The goal of preventive analgesia is to reduce central sensitization that arises from noxious inputs arising throughout the entire operative and postoperative period and not just from those occurring during the surgical incision (12).

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Effective preventive analgesic techniques may not only be useful in reducing acute pain but also chronic postsurgical pain and disability (13,14).

The goal of this study was to assess the efficacy of administering a preventive multimodal analgesic technique on long-term (6 mo) outcomes for patients undergoing outpatient ACL surgery.

METHODS

After IRB approval, informed written consent was obtained from 200 patients undergoing primary ACL reconstruction surgery for this randomized, double-blind, placebo-controlled study. Patients were excluded if they had other ligament tears, had undergone a previous operation in the same knee, had undergone tibial osteotomy or meniscal reconstruction, had evidence of chondral damage or degeneration, had injured the contralateral knee, complained of patellofemoral symptoms, had an acute lesion of the ACL (defined as interval between the injury and surgery <30 days), were medicated with opioids preoperatively, or had a contraindication to the use of nonsteroidal antiinflammatory drugs (NSAIDs) or oxycodone. Two-hundred consecutive patients were randomized to receive either celecoxib 400 mg ($n = 100$) or matching placebo ($n = 100$) 1–2 h before surgery according to a computer-generated randomization list. The study drugs (celecoxib and placebo supplied by Pfizer, NY, NY, as identical appearing capsules) were prepared by the hospital pharmacy in identical containers marked with the name of the project and consecutive patient numbers. During the study, the randomization list was held in the hospital pharmacy and released only after study completion. Investigators, pharmacists, and clinical staff were blinded to treatment group assignments. All patients were given acetaminophen 1000 mg with celecoxib or placebo 1–2 h before surgery. Anesthesia was induced with propofol (2 mg/kg), fentanyl 2 μg/kg, and ketamine 30 mg and was maintained with 30%–50% N_2O in O_2, and sevoflurane 1%–2% end-tidal concentration delivered via either an endotracheal tube or laryngeal mask airway. All patients received 20 mL of intraarticular bupivacaine 0.25% and clonidine 50 μg before surgical incision. ACL surgery was performed using a bone-tendon-bone central-third patellar tendon autograft. Before awakening, all patients received 20 mL intra-articular bupivacaine 0.25%, morphine 5 mg, and clonidine 50 μg, and an external cooling system was applied to the operative knee.

After discharge from the hospital patients were instructed to take acetaminophen 1000 mg every 6 h and either celecoxib 200 mg every 12 h or matching placebo (according to randomization) for the first 14 days postoperatively. In addition, patients were instructed to take oxycodone 5–10 mg every 3 h for a numerical rating scale pain score ≥3. All patients were enrolled in an accelerated rehabilitation program as described by Shelbourne and Nitz (5). This protocol emphasizes full weight bearing and full knee extension on the first postoperative day with a goal of returning to normal activities including full sports participation by 6 mo.

The present manuscript considered the long-term (6 mo) outcome in this population of patients. In a companion paper we examined the short-term outcome (up to 14 days) in this same population of patients (15).

Patellofemoral Complications

The presence of patellofemoral complications including anterior knee pain, flexion contracture, quadriceps weakness, and CRPS were evaluated at 6 mo after surgery.

Anterior Knee Pain

The test for anterior knee pain was performed with the patient lying supine on an examining table. The medial and lateral patellar facets were palpated by an orthopedic surgeon. Next, the patient's limb was supported on a bolster in 20°–30° of knee flexion. The patella was firmly pressed into the trochlear groove while the patient was asked to actively extend his or her knee and the presence or absence of anterior knee pain was recorded.

Flexion Contracture

The presence of flexion contracture was determined by either one of two methods as described by Sachs et al. (16) Knee extension was evaluated with the patient prone with both lower limbs hanging off the end of the table. If the patient has a unilateral flexion contracture, one knee will be bent and one heel will be higher than the other. Since this angle can be small (1°–5°), we also measured the difference in heel heights. A flexion contracture was defined as asymmetric prone heel heights ≥1 cm. This method has been shown to be a reproducible and accurate method for measuring the presence of a flexion contracture. Patients who demonstrated persistent difficulty in achieving full knee extension equal to the nonoperated knee and who also had associated anterior knee pain were offered surgical intervention. In these patients, arthroscopy was performed to excise scar tissue at the base of the ACL graft and to enlarge the notch anteriorly and laterally if necessary.

Quadriceps Weakness

Isokinetic testing for evaluation of muscle strength was performed with a Cybex II isokinetic dynamometer (Lumex, Ronkonkoma, NY) at 1 and 6 mo postoperatively. The peak quadriceps and flexor torque of the operative knee (five repetitions) was measured and related to the contralateral normal knee at 60, 120, and 180 deg/s. The strength index is expressed as a ratio of the peak torque of the operative knee divided by the peak torque of the normal knee, multiplied by

100. Immediately after isokinetic testing, patients were asked to rate their pain on a numerical rating scale score from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain.

CRPS

The diagnosis of CRPS was based on signs and symptoms outlined by the International Association for the Study of Pain (17). These criteria have a high degree of specificity (94%) in identifying patients with CRPS. These criteria have been used in a previous investigation at our institution to diagnosis CRPS of the knee (7).

Postoperative Level of Activity

Level of activity was assessed preoperatively and at 6 mo using the evaluation of the International Knee Documentation Committee (18). The level of sporting activity before injury and at 6 mo after ACL reconstruction was assessed using two criteria: 1) the functional category of sport according to International Knee Documentation Committee Levels I–IV as daily living activities, straight running, agility sport, and cut and jump; 2) the level of competition as activities of daily living, light recreational, vigorous recreational, and competitive sport. Return to full sports activities was allowed on achievement of at least 70% quadriceps strength compared with that of the contralateral limb, no knee effusion, and obtaining a full range of motion.

Statistical Analysis

Group means for continuous variables were compared with Student's *t*-test for unpaired data. For noncontinuous data, comparisons were made with the Mann–Whitney *U*-test. Tests for association of binary variables were made by χ^2 analysis. Bonferroni corrections for multiple comparisons were used when applicable. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 200 surgical patients nine were unable to return for assessment at ≥1mo postoperatively. Three patients had concomitant surgical procedures (unrelated to ACL surgery) during the 6-mo study period that limited their participation in the prescribed rehabilitation protocol and six patients were lost to follow-up. The results of these nine patients are included in analysis but they are excluded from long-term assessment. The remaining 191 patients remained compliant to the rehabilitation protocol.

As described in the companion manuscript (15) there were no significant differences between the two groups with respect to demographic variables, operative times, operative site (companion manuscript, Table 1), or preoperative level of sports participation (companion manuscript, Table 2). The mean time interval from injury to surgery was 2.7 mo (range, 1–5 mo), which was similar between the two groups.

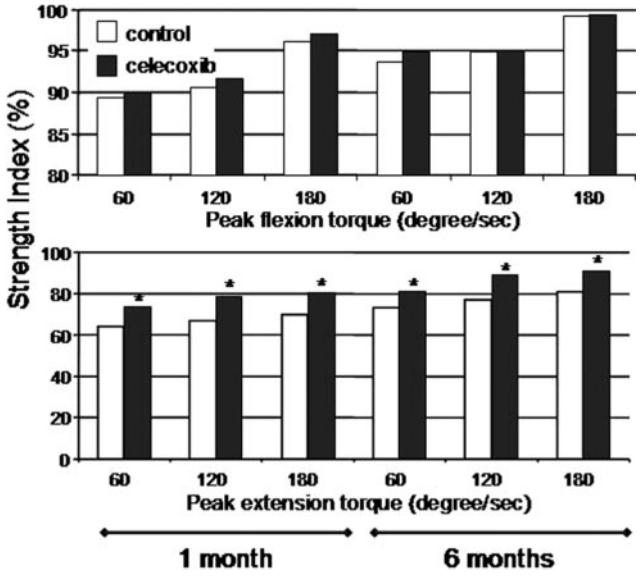

Figure 1. Peak quadriceps and flexor torque of the operative knee was measured and related to the contralateral normal knee at 60, 120, and 180 deg/s at 1 and 6 mo postoperatively. The strength index is expressed as the ratio of the peak torque of the operative knee divided by the peak torque of the normal knee, multiplied by 100. There were no statistically significant differences in peak flexion torque between the celecoxib and control groups. There was a significant (*$P < 0.05$) deficit in peak extension torques at 60, 120, and 180 deg/s at 1 and 6 mo postoperatively for patients in the control group compared to the celecoxib group.

At 6 mo after surgery, significantly more patients in the control group developed patellofemoral complications compared to the celecoxib group ($P = 0.001$). These included a higher incidence of anterior knee pain (14 of 96; 15%) vs (4 of 95; 4%), CRPS (7 of 96; 7%) vs (1 of 95; 1%), flexion contractures (9 of 96; 9%) vs (2 of 95; 2%), and scar tissue requiring arthroscopy (8 of 96; 8%) vs (2 of 95; 2%) for celecoxib versus control groups, respectively. Isokinetic testing for evaluation of knee strength at 1 and 6 mo failed to reveal significant differences in peak flexion torque between the two groups (Fig. 1). However, there was a significant ($P < 0.05$) deficit in peak extension torques at 60, 120, and 180 deg/s at both 1 and 6 mo postoperatively for patients in the control group compared to celecoxib group (Fig. 1). Patients in the celecoxib group reported significantly ($P < 0.05$) lower pain scores than the control group after isokinetic testing at 1 month (3.1 ± 0.6 vs 4.8 ± 1.3) and 6 mo (1.0 ± 0.4 vs 3.2 ± 0.9) respectively

Results from the postoperative level of activity (Fig. 2), revealed more patients in the celecoxib group returned to a Grade III or IV activity level ($P < 0.01$) than in the control group (84% vs 65%). Further, more patients were able to participate at a more intense (competitive) level ($P < 0.02$) and return to full sports activity ($P < 0.05$) in the celecoxib group compared to the control group 1 (Fig. 2).

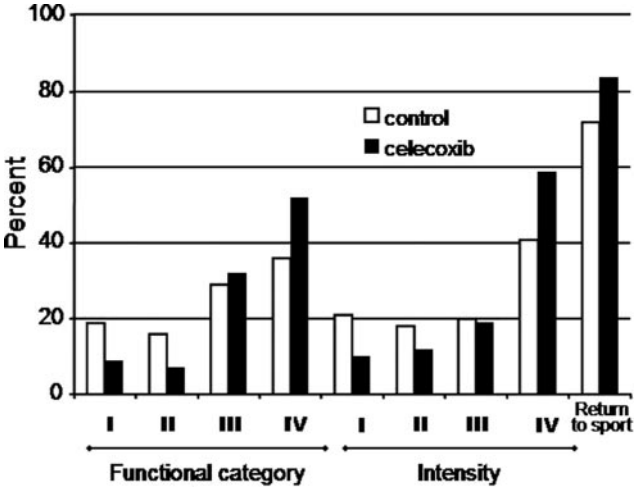

Figure 2. The level of activity 6 mo postoperatively using the evaluation of the International Knee Documentation Committee. The level of sporting activity was assessed using two criteria: 1) the functional category of sport according to Levels I–IV as I = daily living activities, II = straight running, III = agility sport, and IV = cut and jump; 2) the level of competition according to Levels I–IV as I = activities of daily living, II = light recreational, III = vigorous recreational, and IV = competitive sport. More patients in the celecoxib group returned to a Grade III or IV activity level ($P < 0.01$), participated in a more intense (Grade IV) level ($P < 0.02$), and returned to full sports activity ($P < 0.05$) compared to the control group.

DISCUSSION

The sustained administration of celecoxib as a component of a preventive multimodal analgesic technique results in a significant reduction in long-term patellofemoral complications and persistent pain, and increases the likelihood that patients will return to their preinjury level of activity.

Postoperative analgesic strategies aimed at improving pain and long-term outcomes after surgery need to target the afferent barrage of nociceptive pain signals throughout the operative and entire postoperative period. Such strategies should use analgesics that target peripheral and central pain pathways. The perioperative administration of regional nerve blocks, intraarticular analgesics, cryotherapy, NSAIDs, and ketamine and have all proven to be effective in the management of pain after ACL surgery (1).

Sustained administration of NSAIDs (acetaminophen and celecoxib) into the postoperative period may not only reduce acute pain, but also contribute to a reduction in chronic postsurgical pain (19). It has been suggested that early intervention with cyclooxygenase-2 (COX-2) inhibitors may play an integral role in thwarting the processes of peripheral and central sensitization and may prevent the progression of acute pain to chronic pain (20). Even in the setting of regional nerve blocks, NSAIDs may play an important role in reducing central sensitization. We have recently demonstrated that despite adequate spinal anesthesia, CNS levels of prostaglandin E_2 are increased after surgery (21).

There appear to be two forms of nociceptive input from peripheral inflamed tissue to the CNS (22). The first is mediated by electrical activity in sensitized nerve fibers innervating the inflamed area. This input is sensitive to peripherally acting COX-2 inhibitors and to neural blockade with local anesthetics. The second is a humoral signal originating from the inflamed tissue, which acts to produce a widespread induction of COX-2 in the CNS. This input will not be affected by regional anesthesia and will only be blocked by centrally acting COX-2 inhibitors. Therefore, it has been suggested that COX-2 inhibitors that better penetrate the blood–brain barrier may be more efficient analgesics by blocking central sensitization processes (22,23). Celecoxib rapidly crosses the blood–brain barrier both in rodents (24) and humans (25) and therefore may play a role in the reduction of central COX-2 mediated inflammation.

The use of celecoxib as a component of a preventive multimodal analgesic technique allowed these patients to participate to a greater extent in our rehabilitation protocol, which may have contributed to a reduction in long-term patellofemoral complications. After total knee arthroplasty, it has been emphasized that functional recuperation is accelerated and the overall length of stay is shortened by an early intensive rehabilitation program, which is possible only if the patients remain pain free (26). Similarly, patients who were able to participate in an accelerated ACL rehabilitation program, emphasizing immediate restoration of full knee extension, demonstrated a significant reduction in long-term patellofemoral complications (5,26,27). It has been demonstrated that there is a causal relationship between patellofemoral pain and postoperative quadriceps strength (16). A reduction in patellofemoral pain may be associated with a reduction in the incidence of flexion contracture and improved quadriceps strength (16), as observed in our present study. Improved perioperative analgesia observed in patients receiving preventive multimodal therapy may have resulted in diminished patellofemoral pain allowing more patients to participate in an accelerated rehabilitation program. This allowed for more patients to return to their preinjury level of activity including full sports participation at a more intense level.

In addition to reducing patellofemoral pain, we also observed a significant reduction in the incidence of postoperative CRPS of the knee. There are several possible reasons for the reduction in the incidence of CRPS observed in the preventive multimodal group that received celecoxib. It has been hypothesized that one of the pathophysiological mechanisms of CRPS is a continuous barrage of nociceptor input from the peripheral to the CNS leading to a state of central hyperexcitability (28). Preemptive analgesic techniques with NSAIDs may prevent the development of central sensitization (10) and have been shown to be effective in reducing postoperative pain after ACL

surgery (1,29,30). Spinal prostaglandin synthesis is important for the induction and initial expression of spinal cord hyperexcitability (31) and early intervention with COX-2 inhibitors may prevent these processes as well (20). At this time, there is no evidence to indicate that sustaining COX-2 inhibitors beyond the 14-day period of dosing used in our study would confer any additional benefit.

A reduction in the incidence of acute postoperative pain may also contribute to a reduction in the development of chronic pain syndromes (8,9). It is possible that the improved perioperative pain control observed in our patients undergoing ACL surgery with a preventive multimodal analgesic technique contributed to a reduction in the incidence of CRPS. Also, patients unable to participate in a rehabilitation program after arthroscopic knee surgery may be at increased risk for developing postoperative knee complications such as delay in strength recovery, prolonged stiffness, anterior knee pain, and CRPS (3,4,6). Although the use of postoperative physical therapy is a common practice after orthopedic surgical procedures, there are no controlled clinical trials examining its efficacy on reducing the incidence of CRPS (32).

In summary, the use of celecoxib as a component of a preventive multimodal analgesic technique provided for a reduction in the incidence of persistent postsurgical pain and patellofemoral complications (patellofemoral pain, flexion contracture, quadriceps weakness, and CRPS) after ACL surgery. Further, these patients were more likely to return to their preinjury level of activity including full sports participation. These data complement the benefits observed in the first 14 days, reported in our companion manuscript (15). Future prospective, randomized, controlled trials involving preventive multimodal analgesic techniques are needed to determine its efficacy, appropriate timing, as well as its impact on clinical and economic outcomes after surgery.

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