Efficacy of Periarticular Multimodal Drug Injection After Medial Opening-Wedge High Tibial Osteotomy: A Randomized, Controlled Study

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Purpose: The purpose of this study was to evaluate the efficacy of periarticular multimodal drug injection after medial opening-wedge high tibial osteotomy regarding the postoperative pain level. Methods: From January 2011 to January 2012, 70 patients underwent medial opening-wedge high tibial osteotomy. Thirty-five patients were randomly assigned to receive no injection (group I), and 35 patients were assigned to receive periarticular multimodal drug injection (group II). These 2 groups were compared regarding the postoperative pain level, frequency of additional nonsteroidal anti-inflammatory drug injections, total amount of patient-controlled analgesia, and number of times that patients pushed the patient-controlled analgesia button at each time interval. Statistical results were based on multivariate analysis of variance and repeated-measures analyses. Results: Multivariate analysis of variance of mean visual analog scale (VAS) scores over the 2-week postoperative period showed statistical significance ($P < .001$). Repeated-measures analysis yielded a statistically significant difference ($P = .001$) for the time-by-treatment interaction, showing a clear periarticular multimodal drug injection benefit over time based on VAS scores. In addition, the mean number of times that patients pushed the patient-controlled analgesia button differed significantly between groups over time ($P = .01$). The VAS scores, frequency of additional nonsteroidal anti-inflammatory drug injections, mean number of times that patients pushed the patient-controlled analgesia button, and mean total amount of fentanyl consumption differed significantly within each group over time ($P < .001$ for all variables). However, the frequency of additional nonsteroidal anti-inflammatory drug injections and mean total amount of fentanyl consumption did not differ significantly between groups over time ($P = .822$, $P = .529$, and $P = .282$). Opioid- and injection-related complications were not found. Conclusions: This prospective randomized study shows that intraoperative periarticular multimodal drug injections in patients undergoing medial opening-wedge high tibial osteotomy for unicompartmental osteoarthritis of the knee could result in significant reductions in VAS scores at 2 weeks postoperatively. Level of Evidence: Level I, high-quality randomized controlled trial with statistically significant differences.

Multimodal pain management with pre-emptive medication and intra-articular and periarticular injections during arthroscopic surgery or total joint arthroplasty involves the use of multiple agents that act on different regions of the pain pathway and provide appropriate pain relief with less reliance on opioids.1-23 Multimodal drug injection has the potential to minimize postoperative pain while reducing total opioid consumption, with its potential associated adverse effects.1-23 The use of such multimodal therapy has been noted in total knee replacement, and specifically, the lack of such pain control is fraught with potential complications. Medial opening-wedge high tibial osteotomy (MOWHTO) has regained popularity since improvements in the operative techniques used have been made, and special implants for this procedure have been developed.24-27 However, previous studies of multimodal pain management have been performed in patients who had undergone arthroscopic surgery or total joint arthroplasty. There have been debates on the efficacy of periarticular multimodal drug injection in
total knee arthroplasty. However, there are no reports on the efficacy of periarticular multimodal drug injection in the high tibial osteotomy setting. We have used this protocol for arthroscopic procedures and arthroplasty procedures based on several studies.\(^3,^28\)

The purpose of this study was to evaluate the efficacy of periarticular multimodal drug injection after MOWHTO regarding the postoperative pain level. The hypothesis was that periarticular multimodal drug injections in patients undergoing MOWHTO for unicompartmental osteoarthritis of the knee significantly reduce postoperative pain.

**Methods**

This study was a prospective study with a double-blind design. The design and protocol of this prospective study were approved by our institutional review boards, and informed consent was obtained from all patients for participation in the study.

From January 2011 to January 2012, 83 patients who had undergone MOWHTO for symptomatic medial-compartment osteoarthritis were considered eligible for this study. The inclusion criteria for MOWHTO were as follows: symptomatic medial osteoarthritis or articular cartilage lesions of the knee joint in active patients, varus malalignment (minimum of 10 mm of medialization of the weight-bearing axis from the anatomic center of the knee or 3º of varus malalignment), and a lateral joint compartment that was intact or whose cartilage lesions had an International Cartilage Repair Society grade of less than 1 with failure of conservative treatment for 3 months. The exclusion criteria were active infection of the knee, severe osteoarthritis of the patellofemoral joint, a lateral femorotibial angle of 190º (10º anatomic varus alignment) or greater, and a flexion contracture of greater than 15º. We also excluded patients with varus/valgus instability of greater than 10º on a stress view obtained with a Telos device (Telos, Marburg, Germany) and those aged 60 years or older with anterior cruciate ligament insufficiency.

Group I received no injection, and group II received periarticular multimodal drug injection. In this randomized, double-blind study, randomization into 1 of the 2 study groups was performed by use of Microsoft Excel (Microsoft, Redmond, WA) to generate random numbers. Allocations were kept in a set of sealed envelopes. One hour before surgery, the appropriately numbered envelope was opened and the card inside determined the group allocation. Group I received no injection. For group II, a 50-mL periarticular injection cocktail (200 mg of bupivacaine [20 mL]; 10 mg of morphine sulfate [10 mL]; 200 mg of 1:100,000 epinephrine [0.2 mL]; and normal saline solution [19.8 mL]) was prepared in one 50-mL syringe; 15 mL of the cocktail was injected around the medial collateral ligament and pes anserinus tendon sheath; 15 mL was injected into the tissue at the periosteum around the osteotomy site; 10 mL of the injection cocktail was infiltrated into the sheath of the patellar tendon and intrapatellar fat pad; and 10 mL of the injection cocktail was infiltrated into the incision site (Fig 1).

All patients underwent an arthroscopic examination at the time of MOWHTO. However, drilling of a degenerative ulcer or shaving of the articular cartilage was not performed in any case. After arthroscopy, MOWHTO was performed with a TomoFix plate (Synthes, Solothurn, Switzerland). A porous β-tricalcium phosphate wedge (semicircular chronOS; Synthes) was inserted into the osteotomy gap. The TomoFix plate was then inserted into a subcutaneous tunnel formed on the medial side of the tibia and fixed in place with locking screws with minimal invasiveness (Video 1, available at www.arthroscopyjournal.org).

The day after surgery, active and passive range-of-motion exercises with continuous passive motion and muscle strengthening were commenced. Patients were hospitalized as inpatients for 2 weeks. Range-of-motion exercises with continuous passive motion were continued until a maximum flexion angle of 130º or more was obtained within 3 weeks of surgery. Patients were allowed to begin partial weight-bearing exercises with crutches or a walker 1 day after surgery, and they could walk with full weight bearing with a cane 6 weeks after MOWHTO.

To control postoperative pain, intravenous fentanyl was administered by use of a computerized intravenous patient-controlled analgesia system (AutoMed 3300; ACE Medical, Seoul, South Korea). The patient-controlled analgesia was set at a bolus dose of 0.1 mg/kg with a lockout time of 15 minutes and continuous infusion of 0.1 mg·kg\(^{-1}\)·hr\(^{-1}\) (total regimen, 10 mg·kg\(^{-1}\)·100 mL\(^{-1}\)). The patients were instructed to push the button on the patient-controlled analgesia system each time they felt pain. When patients complained of persistent pain with a visual analog scale (VAS) score greater than 3, we injected 75 mg of diclofenac sodium intravenously until a VAS score of less than 3 was achieved. However, an additional 50 mg of tramadol hydrochloride was injected if the VAS score was greater than 3 with initial injection of 75 mg of diclofenac sodium.

The primary outcome variables were pain levels at 6 hours, 12 hours, 18 hours, 1 day, 4 days, 7 days, and 14 days postoperatively. Before surgery, the patients were instructed to use a 10-cm VAS score with end points labeled “no pain” and “worst possible pain” to assess the maximum pain level during the assessment day. To estimate individual pain sensitivity in an objective manner, we assessed the pain level experienced during a preoperative antibiotic skin test using a VAS score ranging from 0 (no pain) to 10 (worst...
The antibiotic skin test was performed by infiltrating 0.2 mL of cefazolin solution intradermally using a 1-mL syringe with a 26-gauge needle. The secondary outcome variables were total amounts of additional nonsteroidal anti-inflammatory drugs (NSAIDs) and patient-controlled analgesia used postoperatively. The frequency of additional NSAID injections was assessed at 6 hours, between 6 and 12 hours, between 12 and 18 hours, between 18 and 24 hours, between 1 and 4 days, between 4 and 7 days, and between 7 and 14 days after surgery. The number of times that the patients pushed the patient-controlled analgesia button and total amounts of patient-controlled analgesia were assessed at 6 hours, between 6 and 12 hours, between 12 and 18 hours, between 18 and 24 hours, between 1 and 2 days, and between 2 and 3 days after surgery. The patients were closely observed postoperatively for fentanyl- and bupivacaine-related side effects. Noted narcotic-related side effects are nausea, vomiting, pruritus, urinary retention, and respiratory depression. Bupivacaine-related side effects comprise blurred vision, hearing problems, peripheral paresthesia, dizziness, uncontrolled muscle contraction, convulsion, hypotension, bradycardia, headache, itching, and chondrolysis.

**Statistical Analysis**

A sample size of 70 patients was determined to yield a population with 80% confidence at a 2-sided $z$ level of .05 based on an assumed difference of 33% between the treatment and control groups for the VAS pain score over the 2-week postoperative period from a prior pilot study.\(^{32,33}\)

The Kolmogorov-Smirnov test was used to determine whether parameters were normally distributed. Both groups were compared with respect to primary and secondary outcomes, age, gender, body mass index,
preoperative varus deformity, preoperative Knee Society knee score, preoperative Knee Society function score, preoperative VAS score, and pain sensitivity. Differences in the outcomes between the groups over time were analyzed by univariate analysis of variance for repeated measures with the Bonferroni post hoc test. The model was adjusted for baseline characteristics by multivariate analysis of variance, and a 2-factor (time × group) analysis was performed to evaluate the overall group effect, overall time effect, and interaction between group and time. Data were analyzed statistically with SPSS software, version 12.0 (SPSS, Chicago, IL). For all tests, \( P < .05 \) indicated a significant difference.

**Results**

From January 2011 to January 2012, 83 patients who had undergone MOWHTO for symptomatic medial-compartment osteoarthritis were considered eligible for this study. On the basis of the inclusion and exclusion criteria for MOWHTO, 13 patients were excluded before enrollment for the following reasons: 7 underwent combined anterior cruciate ligament reconstruction and 6 refused to participate (Fig 2). The remaining 70 knees (70 patients) were randomly assigned to 1 of 2 groups. So, the number of patients was sufficient to yield a population with 80% confidence at a 2-sided \( \alpha \) level of .05 based on an assumed difference of 33% between the treatment and control groups for the VAS pain score over the 2-week postoperative period from a prior pilot study. Age, gender, body mass index, preoperative varus deformity, preoperative pain sensitivity, and preoperative knee score did not differ between the groups (Table 1). We determined whether parameters were normally distributed according to the Kolmogorov-Smirnov test. There was a normal distribution in the pain experience in both groups. The VAS score, frequency of additional NSAID injections, mean number of times that the patients pushed the patient-controlled analgesia button, and mean total amount of fentanyl consumption differed significantly within each group over time (\( P < .001 \) for all variables). The mean VAS score and number of times that the patients pushed the patient-controlled analgesia button differed significantly between groups over time (\( P < .001 \) and \( P = .01 \), respectively) (Figs 3 and 4). Repeated-measures analysis yielded a statistically significant difference (\( P = .001 \)) for the time-by-treatment interaction, showing a clear injection benefit over time based on VAS scores. The frequency of additional

| Table 1. Demographic and Preoperative Patient Data |
|---------------------------------|-----------------|--------|---------|--------|
|                                | Group I          | Group II | 95% CI  | \( P \) Value |
| Age [mean (range)] (yr)        | 60.4 ± 8.9 (37 to 80) | 58.8 ± 7.2 (43 to 71) | -2.626 to 5.674 | .466 |
| Gender (male/female)           | 3:32             | 2:33    | 0.445 to 9.027 | .500 |
| Body mass index [mean (range)] (kg/m²) | 25.5 ± 2.6 (21.3 to 32.3) | 23.7 ± 3.5 (12.1 to 29.7) | -0.359 to 1.412 | .242 |
| Preoperative varus deformity [mean (range)] (°) | -5.6 ± 2.9 (-12.7 to -1) | -4.5 ± 3.5 (-13 to -1) | -0.556 to 2.693 | .193 |
| Preoperative KSS [mean (range)] | 57.6 ± 12.6 (40 to 70) | 58.7 ± 12.0 (40 to 70) | -6.639 to 7.655 | .889 |
| Preoperative KSSF [mean (range)] | 54.9 ± 23.4 (40 to 70) | 52.1 ± 24.4 (40 to 65) | -1.544 to 6.532 | .225 |
| Preoperative pain sensitivity [mean (range)] | 3.3 ± 1.8 (1 to 8) | 4.3 ± 2.4 (1 to 10) | -2.252 to 0.032 | .057 |
| Preoperative VAS [mean (range)] | 5.1 ± 1.4 (1 to 8) | 5.5 ± 1.3 (3 to 8) | -0.556 to 2.693 | .239 |

CI, confidence interval; KSS, Knee Society knee score; KSSF, Knee Society function score.
NSAID injections and mean total amount of fentanyl consumption did not differ significantly between groups over time ($P = .822$, $P = .529$, and $P = .282$; repeated-measures analysis) (Figs 5-7). After adjustment for baseline characteristics (age, gender, body mass index, preoperative varus deformity, preoperative pain sensitivity, and preoperative knee score), the mean VAS score and number of times that the patients pushed the patient-controlled analgesia button differed significantly between groups over time ($P < .001$ and $P = .01$, respectively). The mean VAS score at 6 hours postoperatively was 6.5 ± 1.9 (range, 3 to 10) in group I and 3.8 ± 1.8 (range, 0 to 8) in group II (95% confidence interval, 2.302 to 4.237; $P = .012$). The highest pain level in group I occurred at 6 hours postoperatively and gradually diminished with time. In contrast, the highest pain level in group II occurred at 12 hours postoperatively and gradually diminished with time. The mean number of times that the group II patients pushed the patient-controlled analgesia button (2.2 ± 2.4; range, 0 to 9) was 48% less than the mean number of times that the group I patients pushed it (4.2 ± 3.6; range, 0 to 18) (95% confidence interval, 0.237 to 1.835; $P = .012$). The administration of patient-controlled analgesia was stopped at 3 or 4 days after surgery. Opioid-related complications such as nausea, vomiting, and dizziness were not found in either group. Injection-related complications such as wound infection were not found in this study. Bupivacaine-related side effects including chondrolysis were not found. Finally, skin necrosis from the epinephrine administration was not found.
Discussion

The principal findings of this study showed that periarticular multimodal drug injection after MOWHTO reduced postoperative pain as shown by VAS scores at 2 weeks postoperatively. According to our study, we could confirm our hypothesis that periarticular multimodal drug injections in patients undergoing MOWHTO for unicompartmental osteoarthritis of the knee significantly reduce postoperative pain at 6 hours.

Numerous intervention studies have been performed over the past 2 decades to find ways to reduce postoperative pain and improve effective rehabilitation after knee surgery. Although there has been increasing interest in multimodal pain management for postoperative pain control and reduction of opioid consumption after arthroscopic surgery and arthroplasty, no articles have been published concerning the efficacy of periarticular multimodal drug injection after osteotomy. A systemic review and meta-analysis concerning the clinical efficiency and safety of periarticular multimodal pain injection suggested that periarticular multimodal drug injection in total knee arthroplasty provides short-term advantages in pain relief, straight-leg raises, and postoperative complications. In our study the periarticular multimodal drug injection group had a significant pain level reduction during the 2-week postoperative period. Our findings suggest that periarticular multimodal drug injection is limited in terms of its ability to provide long-lasting pain relief in the high tibial osteotomy setting, which is similar to the total knee arthroplasty setting. Moreover, the pain levels in group II increased between 6 and 12 hours postoperatively and gradually diminished with time. This so-called rebound phenomenon observed in the periarticular multimodal drug injection group was similarly found in previous studies concerning the effectiveness of periarticular multimodal drug injections after total knee arthroplasty. On the basis of this finding, we speculate that additional and pre-emptive pain management (more aggressive pain control modalities) between 6 and 12 hours postoperatively is necessary to decrease the pain level in the injection group between 6 and 12 hours. This study focused on...
the early postoperative period. Additional study is required to evaluate whether reduced pain scores and fentanyl consumption translate into a lower incidence of chronic pain development. We did not use special monitoring devices to detect side effects related to the use of bupivacaine; instead, patients were monitored closely for clinical symptoms. However, bupivacaine-related side effects or complications did not develop in any patients, and the 200-mg dose used in this study was smaller than the 400-mg dose used in previous studies concerning the efficacy of multimodal drug injection after total knee arthroplasty.²⁸

Postoperative pain levels determined with VAS scores are subjective and might be influenced by psychological and cultural factors, personal experiences, and operative technique. Le Resche et al.³⁴ reported that participants given the same pain stimulus rated the severity of pain differently from one another and that the same participants assessed pain produced by the same level of stimulus quite differently at different times. In our study we assessed the frequency of use of patient-controlled analgesia, which provided an indicator of total pain intensity. The total amount of patient-controlled analgesia determined by a computerized system and frequency of use of patient-controlled analgesia at 6 hours postoperatively were 24% and 48% lower in group II than in group II. However, the mean total amount of fentanyl consumption did not differ significantly at the following time intervals. The groups did not differ regarding additional NSAID injections at each time interval.

**Limitations**

This study has a limitation. Regarding the study population, 92.8% (65 of 70 patients) were women. As has been previously reported, women are predominant among Korean patients undergoing MOWHTO for some unknown reason.

**Conclusions**

This prospective randomized study shows that intraoperative periarticular multimodal drug injections in patients undergoing MOWHTO for unicompartamental osteoarthritis of the knee could result in significant reductions in VAS scores at 2 weeks postoperatively.

**References**


