Intra-articular Morphine and Clonidine Injection after Hip Arthroscopy: A Randomized, Triple-Blind Controlled Trial

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Abstract

Hip arthroscopy is an increasingly common outpatient procedure for which postoperative pain control remains a vital component of patient care and surgical outcome. The objective of this study was to determine the effect of intra-articular morphine and clonidine injection as compared with placebo on postoperative opioid requirement after hip arthroscopy. Seventy patients undergoing primary hip arthroscopy were randomized to receive an 11mL intra-articular injection of 10mg morphine + 100mcg clonidine (study) or normal saline (control) at the conclusion of arthroscopy. The primary outcome was opioid consumption during recovery in the post-anesthesia care unit (PACU). Mean PACU opioid consumption in oral morphine equivalents (mEq) in the study group was 37.0 [95% CI: 28.8-45.3] compared to 40.1 [95% CI: 31.8-48.4] in the control group (P=0.29). With the numbers available, intraoperative intra-articular morphine and clonidine injection showed no statistically significant difference in PACU postoperative opioid consumption compared to normal saline control after hip arthroscopy.

Keywords: Intra-articular injection; Morphine; Clonidine; Hip arthroscopy; Opioid consumption.

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Introduction

The application of hip arthroscopy as a treatment for various hip conditions is becoming increasingly popular(1, 2). With most of these cases being performed in the outpatient setting, pain control remains a high priority for both the patient and the care team. Many patients with pain after hip arthroscopy require significant doses of opioid analgesic in the post-anesthesia care unit (PACU), which is effective in short-term pain relief but increases systemic opioid complications and length of stay (3). Furthermore, many patients are sent home with opioids for further pain relief in the days to weeks following surgery. As a result, reducing postoperative pain and shortening recovery times, while limiting systemic exposure to opioids, remains a challenge from both a patient satisfaction and case management perspective.

A variety of preoperative and intraoperative techniques, such as femoral nerve block and intra-articular (IA) bupivacaine injections, have been proposed to decrease pain and opioid consumption in the postoperative setting. Though these techniques limit the exposure to systemic opioids, femoral nerve blockade increases fall risk and IA local anesthetic injections, including ropivacaine, have been shown to be chondrotoxic, limiting the utility of these techniques (4-7). One study in rats showed that compared to saline-injected knees, healthy knees injected with 0.5% bupivacaine demonstrate up to a 50% decrease in density of chondrocytes in the joint (8). Morphine binds to μ-opioid receptor at both central and peripheral tissues. While perhaps the most notable opioid receptors exist in the brain and gastrointestinal tissues, evidence also supports presence of opioid receptors in the joint space (9-11). Furthermore, the poor lipid solubility of morphine inhibits its distribution across the synovial membrane and out of the joint after IA injection, which decreases systemic exposure (12). It also has the added benefits of circumventing both chondrotoxicity and impaired neuromuscular function. In regards to clonidine, a 2014 systematic review by Sun et al demonstrated an immediate postoperative analgesic effect after knee arthroscopy without any evidence of chondrotoxic side effects (13). Clonidine binds to α2-adrenergic receptors, leading to a decrease in nerve signaling from C and Aδ pain fibers. Multiple studies have demonstrated an analgesic effect of clonidine after knee arthroscopy, and in one study by Joshi et al the combination of clonidine to IA morphine injection has been shown to potentiate the analgesic effects of morphine 5-fold (14, 15). While supporting literature and evidence regarding IA morphine injections for postoperative pain control in knee arthroscopy is quite robust (9, 16, 17), there remains a paucity of data for such techniques in hip arthroscopy. One prior retrospective study demonstrated a nearly 43% decrease in PACU opioid requirement with use of IA morphine and clonidine injection, which highlights the potential for pain reduction and clinical significance of this intervention (18).

The purpose of this study is to determine the efficacy of intra-articular (IA) morphine and clonidine hip injection immediately after hip arthroscopy in reducing opioid consumption in the immediate and extended postoperative period. We hypothesized that patients who received the IA injection of morphine and clonidine would have reduced opioid consumption in the postoperative recovery period.

Materials and Methods

Participants

After approval from our university's institutional review board was obtained, patients undergoing primary hip arthroscopy by a single, fellowship-trained orthopaedic surgeon between December 2015 and December 2016 were considered eligible for enrollment in this prospective, parallel, randomized, triple-blind, controlled trial. This study was registered with www.clinicaltrials.gov (NCT02530151 approved 8/18/2015) where a full trial protocol can be found. No major changes were made to the trial design after commencement of the study. All patients were considered eligible for this study except for pregnant women, patients under 18 years of age, and those

undergoing revision procedures. All data was collected at a single, academic institution in a major US city. Of note, funding for drug supply and drug administration came from an annual educational grant from Smith & Nephew, though their company had no other role in the design, methods, or outcomes of the trial.

On the day of surgery, a member of the research team enrolled patients into the study. Following patient's written consent on the day of surgery, a computer-generated list sequentially randomized patients into either the control or the study group. The list was created by pharmacists who were not involved in patient care. The pharmacists then prepared the IA injection in accordance with the respective group—the control group received 11 mL of 0.9% NaCl solution and the study group received 11 mL of 10 mg morphine and 100 mcg clonidine in 0.9% NaCl solution. After preparation, the solution marked "Investigational Protocol 11 mL IA injection" was delivered to the operating room for IA injection at the conclusion of the case. The surgeon, surgical staff, perioperative nurses, research team, and the patient were blinded to the contents of the injection. A sequential list of the random allocation sequence and respective participants was kept by the investigational pharmacy in a separate location from the operating room pharmacy and was only unblinded at the time of statistical analysis.

A standard preoperative pain treatment protocol was administered for all patients enrolled in the study. This regimen consisted of 400 mg celecoxib and 1000 mg acetaminophen given orally 1 hour prior to the scheduled time of surgery. No patients underwent femoroplasty or T-shaped capsulotomy, as osteoplasty was focused solely on the central compartment for all patients, which is consistent with a recent study demonstrating the efficacy of isolated acetabuloplasty alone in treating combined-type FAI (19). The intraoperative IA injection was administered under visualization through the anterior portal at the conclusion of the arthroscopic procedure but prior to removing the hip from traction to ensure proper placement within the hip joint. All intraoperative and postoperative treatment protocols were identical between both the control and study groups. All patients received postoperative ondansetron and dexamethasone (0.1mg/kg; maximum dose 8mg) per anesthesia protocol for nausea and vomiting in the PACU.

The postoperative pain control protocol included intravenous medication (fentanyl, hydromorphone, meperidine) as needed for breakthrough pain, assessed by the PACU nursing staff as a result of patient reported pain levels. Additionally, oral opioids (hydromorphone, hydrocodone/acetaminophen) were administered for longer lasting relief upon discharge from the outpatient care center. All patients were sent home with a standard multimodal pain control regimen, including Norco (hydrocodone 5mg-acetaminophen 325mg), naproxen 500mg twice daily, and aspirin 325mg twice daily (primarily prescribed for deep vein thrombosis prophylaxis).

A total of 180 patients underwent hip arthroscopy from a single surgeon at our institution between the start of recruitment in December 2015 and the end of recruitment in December 2016.

Between the two groups, baseline characteristics were similar, including age, BMI, duration of surgery, and concomitant procedures (Table 1). All patients in the study underwent hip arthroscopy, labral repair, and acetabuloplasty. Intraoperative opioid requirement between both groups was similar (Table 2).

Outcomes Assessed

Opioid consumption during the immediate postoperative period in the PACU was assessed as the primary outcome, and was measured in oral morphine equivalents (mEq) calculated using the respective conversion factor from http://www.globalrph.com/narcotic.cgi (20). All postoperative pain scores and medication administration were assessed by PACU nurses and recorded in the EMR in actual time for eventual data collection by the research team. Secondary outcomes included: postoperative opioid consumption at 6, 18, 24, 48 hours, and 7 days; patient reported pain scores were assessed via Numeric Pain Rating (NPR) scores in the immediate postoperative period and 6, 18, 24, 48 hours, and 7 days postoperatively; time until ready for discharge from the PACU; Quality of Recovery (QoR) scores were assessed in the preoperative waiting area as well as 24 hours post operation using the QoR-15 questionnaire, a validated questionnaire for surgical recovery (21).

Additional data recorded included duration and type of procedure, intraoperative analgesic consumption, and all patients were sent home with a postoperative diary for recording pain scores, medication usage, 24-hour QoR evaluation, and potential side effects, including postoperative nausea, vomiting, constipation, itching, and dyspnea. Patients were asked to return their diary at their first postoperative follow-up appointment. Upon discharge from the PACU, they were

Table 1 Demographics and procedures.

	Control Group	Study Group	P-value
Age (years)	36 [32, 40]	40 [36, 45]	0.18
Gender			
Male	14 (42)	12 (32)	0.39
Female	19 (58)	25 (68)	
Smoker			
No	30 (91)	35 (95)	0.55
Yes	3 (9)	2 (5)	
BMI (kg/m^2)	26 [24, 27]	26 [25, 27]	0.99
Surgical duration (min)	42 [39, 46]	44 [39, 49]	0.59
Concomitant Procedures			
Iliopsoas lengthening	11 (33)	5 (14)	
IT band windowing/ trochanteric bursectomy	6 (18)	11 (30)	
Loose body removal	0 (0)	1 (3)	
Recovery time (min)	172 [157, 187]	172 [158, 186]	0.49

Data reported as mean [95% Confidence Interval] or as absolute values, N (%)

Table 2 Total Opioid consumption in oral morphine equivalents.

	Control Group	Study Group	P-value
Intraoperative	56.0 [47.6, 64.4]	57.3 [50.6, 63.9]	0.40
Postoperative			
PACU	40.1 [31.8, 48.4]	37.0 [28.8, 45.3	0.29
6 hours	5.3 [3.0, 7.6]	5.5 [3.7, 7.3]	0.44
18 hours	13.8 [8.7, 18.9]	14.5 [10.6, 18.4]	0.41
24 hours	20.0 [12.1, 27.8]	19.5 [13.9, 25.1]	0.46
48 hours	35.6 [18.3, 52.9]	27.7 [19.5, 35.9]	0.26
7 days	73.8 [31.6, 115.9]	50.7 [29.6, 71.7]	0.99

reminded once to complete and return the diary, but no patients were asked to complete their diary if they had not done so at their first postoperative appointment due to concern for recall bias. No changes were made to the collected outcomes after the study commenced.

Statistical Analysis

Sample size calculation was drawn from the results of the only known prior retrospective study assessing IA morphine and clonidine injections in hip arthroscopy, where median PACU opioid consumption was 40 mEq (IQR 28-60) (18). The effect size (0.97) was calculated using the correlative mean and standard deviation data from the aforementioned retrospective cohort. With the assumption that IA morphine and clonidine injection reduces opioid consumption, and considering a 30% reduction to be clinically significant, an a priori power analysis estimated 42 total patients required with an α coefficient of 0.05 and a power of 0.8. An allocation ratio of 1.05 was used to reflect the distribution of the retrospective cohort. Recruiting was extended beyond the a priori analysis to help account for loss to follow-up.

Statistical comparison was performed using the Student's t-test for continuous variables and a chi-square analysis for categorical variables. Significance was defined as an alpha level of <0.05. All P-values for primary and secondary outcomes data were reported using the 1-tailed t-test as our goal was to determine whether patients receiving the morphine and clonidine injection had decreased scores compared to those who did not. All demographic data was analyzed using a 2-tailed t-test.

Results

Mean postoperative opioid consumption in the PACU was 37.0 oral morphine equivalents (95% CI [28.8,45.3]) in the study group compared to 40.1 oral morphine equivalents (95% CI [31.8,48.4]) in the control group (P=0.29, N=70) (Table 2). At 6, 18, and 24 hours, opioid consumption was similar between groups. At 48 hours, mean opioid consumption was 7.9 mEq lower in the study group (P=0.26, N=33). At 7 days, mean opioid consumption was 23.1 mEq lower in the study group (P=0.16, N=33) (Table 2).

Mean NPR score immediately postoperatively was 3 (95% CI [2,4]) in the study group compared to 4 (95% CI [3,5]) in the control group (p=0.19, N=70). One hour postoperatively the mean NPR score was 4 (95% CI [3,5]) in the study group compared to 5 (95% CI [4,5]) in the control group (P=0.08, N=70). With the numbers available, there were no statistically significant NPR pain score differences at any other time points. Mean preoperative QoR-15 score in the control group was 131 (95% CI [125,137]) compared to 123 (95% CI [108,138]) in the study group (P=0.29, N=70). At 24 hours postoperatively, the mean decrease in control group QoR-15 score was 20 (95% CI [10,29]) compared to 22 (95% CI [9,35]) in the study group (P=0.74, N=33).

Both groups had a mean time until ready to PACU discharge of 172 minutes (Table 1). Of note, all patients were discharged home from the PACU of the same-day surgery center. Four patients in the study group compared to zero patients in the control group reported nausea at 48 hours, though neither group reported any vomiting. With the numbers available there were no significant differences in nausea, constipation, dyspnea, or itching at any other timepoints.

Discussion

The results of this triple-blind, randomized controlled trial of 10mg IA morphine and 100mcg clonidine injection versus placebo during hip arthroscopy showed no significant decrease in postoperative opioid consumption in the PACU for the study group.

A modest average decrease in opioid consumption of roughly 3 oral morphine equivalents was noted in the study group in the PACU, which was not statistically or clinically significant. At 2 and 7 days postoperatively, a more pronounced difference of 8mEq and 23mEq, respectively, was observed in favor of the study group. No statistical significance was found, as these comparisons outside of the PACU were underpowered due to relatively low rates of completion of postoperative diaries—33 of 70 patients returned their diary at the first postoperative appointment. We would argue, however, that this finding is important to consider. A difference of 23mEq translates to four to five 5mg hydrocodone tablets or 1.25mg IV hydromorphone, as well as a 30% decrease from the control group. A study by Cunningham et al assessed total opioid pills taken 2 weeks postoperatively for arthroscopic treatment of FAI, showing that patients without a history of prior opioid use took an average of twenty 5mg oxycodone, or 150mEq, by the 2-week mark (22). A 23 mEq decrease, as we observed at the 1-week mark, would represent at least a 15% decrease. Given the concern for opioid prescription overuse and misuse, it is important to consider all modalities which may decrease the need for additional or unnecessary home opioids.

A previous retrospective cohort study of a similar patient population showed a mean decrease of 17mEq opioid consumption in the PACU for the study group following the morphine/clonidine injection (18). This discrepancy with data from this prospective randomized study is likely due to lack of blinding in the retrospective cohort and resulting possibility for bias in opioid administration following surgery. The retrospective study did not collect further data at home in the days following surgery, which is also an important period for pain control and reasonable opioid consumption.

Regarding recovery time, there was no difference in time spent in the PACU between study and control groups, which was not a surprising result given the similar pain scores and the use of standard discharge protocols at a single, university-affiliated outpatient surgical center. A

proposed benefit of improved postoperative pain control is decreased recovery times; however, this study was an effectiveness trial based upon clinical practice, and at a large hospital with standardized institutional criteria for PACU discharge, recovery times may not accurately reflect true patient recovery.

The proposed mechanism for effectiveness of IA morphine is due to the presence of μ-opioid receptors in chondrocytes, which inhibit sensory neuron activity from the joint. Unlike other agents commonly used as pain control modalities, such as local anesthetic or NSAIDs, morphine has been shown to be safe in the joint space (23). Additionally the poor lipid solubility of morphine inhibits its distribution across the synovial membrane and out of the joint space after IA injection (9, 12). By injecting the IA solution through the trochar without violation of the capsule beyond trochar placement, it is believed that the injectate remains primarily in the hip joint. One study by Brandsson et al demonstrated very low circulating serum levels of morphine following IA injection for patients undergoing ACL reconstruction, which demonstrates the localization of the injection and also supports the peripheral effect of opioids in the joint space (10). This also decreases the potential for systemic opioid exposure and related side effects.

Postoperative pain control remains a significant factor in patient recovery, satisfaction, and outcomes in orthopaedic surgery, particularly in regards to hip arthroscopy (24). In a healthcare environment that is increasingly driven by patient reported outcomes and satisfaction scores, pain control is an important component of healthcare delivery. A recent systematic review by Shin et al demonstrated the importance of a multimodal approach to pain control after hip arthroscopy, citing numerous modalities of pain control such as femoral nerve block, IA injection, periacetabular injection, and preoperative celecoxib (24, 25). This systematic review drew a few important conclusions, and the most important was that—given a lack of superiority for one particular form of pain control—a multimodal approach remains the best option for decreasing postoperative pain. The available data from our trial do not show a significant decrease in opioid consumption or pain scores in the PACU after IA morphine and clonidine injections, it does suggest a decreased opioid consumption one week after surgery, thus warranting further analysis. The low risk profile of IA morphine and clonidine injection make it an attractive option to be included in a multimodal regimen as well.

Limitations

The conclusions of this study can only be interpreted within the confines of its limitations. First this study was subject to a problem that all postoperative pain management studies endure, which is the heterogeneity of the pain response. This makes it difficult to collect unbiased and consistent markers of pain control. We tried to compensate for this problem by recording multiple outcomes. Regarding quality of recovery measurements, the 24-hour mark may have been too soon to assess quality of recovery, as many of the questions ask about activities of daily living that may not have been tested yet. The decision to test at 24 hours was made based upon prior studies of postoperative pain control in hip arthroscopy, but our data indicate that testing at 48 hours or 7 days may yield more clinically applicable data (26). Additionally, patients were not screened ahead of time for chronic opioid use, which increases generalizability of the study but may mask potential effects of the intervention and postoperative opioid requirements. Unlike the retrospective analysis, this study extended timepoints beyond the PACU period. However, there was a low yield on return of patient diaries, as most patients simply forgot to fill out or return their diary despite multiple reminders, which may have affected the results. However, each group demonstrated similar rates of diary completion, making it unlikely that one group was affected disproportionately from the other. Lastly, this analysis was a single center trial, and no data exist for prospective or retrospective studies outside this practice.

Conclusion

Data during the immediate postoperative period does not show a significant benefit to the IA injection of morphine and clonidine after hip arthroscopy, but a trend toward decreased opioid consumption in the study group was seen at seven days and as early as two days after surgery. Given the potential benefit of these injections in reducing opioid consumption in the week following hip arthroscopy, in combination with the low risk profile of IA morphine and clonidine and the current opioid epidemic, IA morphine and clonidine injections play an important role in multimodal anesthesia. Further pain management research including analyzing opioid consumption in the weeks following hip arthroscopy is warranted.

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