# Intrathecal Morphine and Its Impact on Length of Stay in Joint Arthroplasty Surgery: A Double-Blind Randomized Clinical Trial

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The changing health economy has driven the need for greater patient throughput, rapid turnover, and shorter hospital stays while retaining high-quality medical care. A high-volume inpatient procedure, such as total knee arthroplasty, is a common target for improving cost efficiencies.[1] Intrathecal morphine (ITM) is common in spinal anesthesia for joint arthroplasty, particularly within in-hospital enhanced recovery after surgery (ERAS) protocols, to provide prolonged postoperative analgesia while reducing reliance on systemic opioids.[2,3] However, ITM also has adverse effects which may prolong the length of hospital stay (LOS).[3,4]

In this study, we hypothesize that avoiding ITM leads to shortened LOS.

## METHODS

After approval by the Mount Sinai Hospital Research Ethics Board (REB 18_0116_A), a prospective, double-blind, randomized trial was conducted. Written informed consent was obtained from all trial participants. patients 18 to 85 years old, body mass index (BMI) of 18 to 40, undergoing elective, nontraumatic, primary and revision knee and hip arthroplasties under regional anesthesia were eligible for inclusion. Exclusion criteria included planned discharged on day of surgery, increased risk for respiratory depression (central apnea), women of childbearing potential not on birth control, morphine allergy, alcohol and/or other substance dependence, cognitive impairment, chronic pain, preexisting urinary problems (BPH, prior bladder or ureter surgery). The first patient was enrolled but not randomized on January 19, 2019, after which there was a delay in patient recruitment due to significant administrative staff changes and coronavirus disease-2019 (COVID-19). The study was registered with the clinical trial registry (NCT05105074, principal investigator: Dr N. Siddiqui) on October 29, 2021, before further patient enrollment. The first patient was randomized on November 3, 2021.

Patients were randomized into treatment groups, stratified by surgery type (knee and hip). Preoperatively, all patients received celecoxib and acetaminophen. Participants received intrathecal bupivacaine (13–15 mg) and fentanyl (15 mcg), along with either 100 mcg ITM or saline placebo. Patients could receive propofol sedation, but no patients received general anesthesia. Propofol sedation was titrated intraoperatively according to the Ramsay Sedation Scale scores of 3 to 4 ensuring a uniform approach across groups.

The primary outcome was LOS. Secondary outcomes were intermittent bladder catheterization, pain scores, patient satisfaction scores, and side effects.[5] The bladder management protocol is described in Supplemental Digital Content 1, Supplemental File S1, https://links.lww.com/AA/F345.

Standardized institutional protocol guided discharge criteria (ambulatory with assistance, effective pain management, absence of side effects, and successful voiding).

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### Statistical Analysis

Sample size justification was based on the primary outcome (Supplemental Digital Content 2, Supplementary File S2, https://links.lww.com/AA/F344). Analyses were based on the intention-to-treat principle. The differences in medians of continuous outcomes or in rate/risk of binary outcomes between treatment groups were assessed using univariate quantile linear regression (due to data skewness) and univariate linear probability regression models, respectively.[6,7] The variation in treatment effect across surgery type was examined by including an interaction term in the models. Side effects were compared using $\chi^2$ or Fisher exact test. Subgroup analyses stratified by surgery type were conducted for LOS and satisfaction scores. Analyses were performed using SAS 9.4 (SAS Institute Inc). A 2-sided $P < .05$ was used for statistical significance without adjustment for multiple comparisons for secondary outcomes.

## RESULTS

Due to the COVID-19 pandemic, we were not able to recruit our target sample size in the planned study period. A total of 164 patients were recruited, with 125 completing the study, out of which 70 underwent knee surgery and 55 underwent hip surgery (Supplemental Digital Content 3, Supplemental Figure S1, https://links.lww.com/AA/F346).

No difference in baseline patient/clinical characteristics was observed between ITM (59 patients) and non-ITM (66 patients) groups (Table 1).

The ITM group had a significantly reduced median LOS at 30.0 hours compared to 44.2 hours in the non-ITM group (difference in medians: −13.8 hours (95% confidence interval [CI] −24.2, −3.4), $P = .01$, Table 2), with no difference in treatment effect across surgery types ($P = .17$ for interaction). Subgroup analysis also did not show a significant difference in LOS between treatments for each surgery type (Table 2).

No difference was observed between treatment groups in the rate of first or second in and out catheterization, pain scores at rest except reduced pain at 48 hours in the non-ITM group ($P = .01$), pain scores at movement, satisfaction scores, or incidence of side effects (Table 2; Supplemental Digital Content 4, Supplemental Table S1, https://links.lww.com/AA/F347).

## DISCUSSION

Our findings suggest that ITM in an ERAS protocol for in-hospital elective joint arthroplasty surgery is associated with reduced LOS, within 48 hours postoperatively, with no significant difference in side effects, patient satisfaction, pain scores, and catheterization requirements.

Our LOS findings differ from previous studies which used nonstandardized anesthetic doses, high morphine doses, or lacked intraoperative local infiltration.[8,9] We used 100 mcg and standardized management, avoiding such confounders. Given our study's lack of difference in the quality of analgesia and other secondary outcomes, it is unclear how the ITM group had shorter LOS. LOS is a complex variable affected by

**Table 1. Comparison of Baseline Characteristics**

| | Treatment | | |
|---|---|---|---|
| | ITM | Non-ITM | Total |
| Sample size, n | 59 | 66 | 125 |
| Sociodemographic characteristics | | | |
| Age in years | | | |
| Mean (SD) | 65.1 (10.5) | 64.4 (12.2) | 64.7 (11.4) |
| Median (IQR) | 65.0 (58.0–73.0) | 66.5 (60.0–73.0) | 66.0 (59.0–73.0) |
| BMI | | | |
| Mean (SD) | 29.9 (4.9) | 31.6 (5.4) | 30.8 (5.2) |
| Median (IQR) | 29.0 (26.1–33.0) | 31.0 (27.1–35.0) | 30.0 (27.0–34.0) |
| Sex, n (%) | | | |
| Female | 28 (47.5) | 29 (43.9) | 57 (45.6) |
| Male | 31 (52.5) | 37 (56.1) | 68 (54.4) |
| Surgical characteristics | | | |
| ASA, n (%) | | | |
| II | 26 (44.1) | 23 (34.9) | 49 (39.2) |
| III | 31 (52.5) | 43 (65.2) | 74 (59.2) |
| IV | 2 (3.4) | 0 (0.0) | 2 (1.6) |
| Pain score,[a] screening day, at rest | | | |
| Mean (SD) | 2.4 (2.2) | 2.5 (2.8) | 2.5 (2.5) |
| Median (IQR) | 2.0 (0.0–4.0) | 2.0 (0.0–4.0) | 2.0 (0.0–4.0) |
| Pain score, screening day, at movement | | | |
| Mean (SD) | 5.7 (2.25) | 6.2 (2.5) | 6.0 (2.4) |
| Median (IQR) | 6.0 (4.0–8.0) | 6.0 (5.0–8.0) | 6.0 (5.0–8.0) |

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; IQR, interquartile range; ITM, intrathecal morphine; SD, standard deviation.

[a]Pain scores were measured using a visual analog scale scoring system (0–10).

**Table 2. Comparison of Outcomes**

| | Treatment | | | |
|---|---|---|---|---|
| | ITM | Non-ITM | Diff (95% CI)[a] ITM vs non-ITM | *P* value[a] |
| All patients, n | 59 | 66 | | |
| Median (IQR) LOS in hrs | 30.0 (23.5–51.0) | 44.2 (23.9–68.5) | −13.8 (−24.2 to −3.4) | .01 |
| Satisfaction score[b] ≥5, n (%) | 54 (91.5) | 61 (92.4) | −0.01 (−0.1 to 0.09) | .85 |
| First in and out catheterization, n (%) | 23 (39.0) | 21 (31.8) | 0.07 (−0.1 to 0.2) | .40 |
| Second in and out catheterization, n (%) | 04 (6.8) | 02 (3.0) | 0.04 (−0.04 to 0.1) | .34 |
| T1 (time from spinal anesthesia to first in and out/Foley catheterization in h) | | | | |
| Median (IQR) | 5.9 (4.3–9.8) | 5.6 (4.7–6.8) | 0.3 (−1.3 to 1.9) | .73 |
| n (n missing) | 23 (36) | 21 (45) | | |
| Pain score,[c] 24 h postoperative, at rest | | | | |
| Median (IQR) | 3.0 (1.0–5.0) | 3.0 (1.0–5.0) | 0 (−1.7 to 1.7) | .99 |
| n (n missing) | 58 (1) | 66 (0) | | |
| Pain score, 36 h postoperative, at rest | | | | |
| Median (IQR) | 4.0 (2.0–6.0) | 3.5 (2.0–4.0) | 0 (−1.6 to 1.6) | .99 |
| n (n missing) | 30 (29) | 44 (22) | | |
| Pain score, 48 h postoperative, at rest | | | | |
| Median (IQR) | 4.0 (3.0–5.0) | 2.0 (2.0–4.0) | 2 (0.6 to 3.4) | .01 |
| n (n missing) | 21 (38) | 33 (33) | | |
| Pain score, 24 h postoperative, at movement | | | | |
| Median (IQR) | 5.0 (3.0–8.0) | 6.0 (3.0–7.0) | −1 (−2.3 to 0.3) | 0.14 |
| n (n missing) | 58 (1) | 66 (0) | | |
| Pain score, 36 h postoperative, at movement | | | | |
| Median (IQR) | 6.0 (5.0–8.0) | 6.0 (5.0–7.0) | 0 (−1.4 to 1.4) | .99 |
| n (n missing) | 30 (29) | 44 (22) | | |
| Pain score, 48 h postoperative, at movement | | | | |
| Median (IQR) | 6.0 (5.0–8.0) | 6.0 (5.0–7.0) | 0 (−1.8 to 1.8) | .99 |
| n (n missing) | 21 (38) | 32 (34) | | |
| Patients who had hip surgery, n | 22 | 33 | | |
| Median (IQR) LOS in h | 33.7 (25.2–77.9) | 52.3 (30.4–74.0) | −17.33 (−39.3 to 4.6) | .12 |
| Satisfaction score ≥5, n (%) | 21 (95.5) | 32 (97.0) | −0.02 (−0.1 to 0.09)[b] | .78 |
| Patients who had knee surgery, n | 37 | 33 | | |
| Median (IQR) LOS in h | 27.5 (23.1–46.8) | 27.5 (23.2–45.8) | −0.01 (−15.8 to 15.8)[b] | .99 |
| Satisfaction score ≥5, n (%) | 33 (89.2) | 29 (87.9) | 0.01 (−0.1 to 0.2) | .86 |

Abbreviations: CI; confidence interval; Diff, difference; IQR, interquartile range; ITM, intrathecal morphine; LOS, hospital length of stay.

[a]The reported *P*-values and the differences (95% CI) in the medians and rates (%) were based on the comparisons between the 2 treatment groups using quantile regression (generating the absolute difference in the outcomes) and linear probability regression models (generating the difference in the probability of the outcomes), respectively.

[b]Patient satisfaction scores were measured on a Likert scale of 1 to 6, with 1 being very dissatisfied and 6 being very satisfied).

[c]Pain scores were measured using a visual analog scale scoring system (0–10).

multiple patient and logistical factors. ITM may support enhanced comfort or aspects of functional recovery beyond pain metrics alone, aligning with previous studies highlighting ITM's role in multimodal analgesia to reduce reliance on systemic opioids and support early mobilization.[2,3,8] Future research could explore specific mechanisms by which ITM influences recovery milestones, such as ambulation and postoperative comfort.

The optimal dose of ITM is uncertain, but our findings complement the Procedure Specific Postoperative Pain Management (PROSPECT) Working Group that recommends 100mcg ITM only be considered when regional techniques and local infiltration analgesia cannot be used.[10]

This study was conducted during the COVID-19 pandemic, impacting recruitment and resulting in a total number of participants slightly below the target sample size. Other limitations were excluding patients with preexisting urinary issues limiting the applicability of findings to higher-risk populations such as older men with prostate hypertrophy, and the absence of pain assessments before 24 hours, possibly missing ITM's peak analgesic effects. Future studies would benefit from earlier evaluations.

The use of 100 mcg ITM in joint arthroplasty when added to intrathecal bupivacaine and intrathecal fentanyl was associated with shorter LOS without an increase in side effects, rates of bladder catheterization, or pain scores. Although ITM did not demonstrate effects on pain improvement, our findings suggest it is a safe and effective modality in the context of in-hospital ERAS for arthroplasty.

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## DISCLOSURES

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