Dexmedetomidine during total knee arthroplasty performed under spinal anesthesia decreases opioid use: a randomized-controlled trial

Réduction de la consommation d'opioïdes grâce à l'administration de dexmédétomidine pendant une arthroplastie totale du genou réalisée sous rachianesthésie: une étude randomisée contrôlée

Ian A. Chan, MD · Jurgen G. Maslany, MD ·
Kyle J. Gorman, MD · Jennifer M. O'Brien, PhD ·
William P. McKay, MD

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Abstract

Background It remains unclear whether the opioid-sparing effects of dexmedetomidine seen in patients undergoing general anesthesia are reproducible in patients undergoing spinal anesthesia. We hypothesized that the administration of intravenous dexmedetomidine for sedation during total knee arthroplasty under spinal anesthesia would decrease postoperative morphine consumption in the first 24 hr following surgery.

Methods We conducted this prospective double-blind randomized-controlled trial in 40 patients (American Society of Anesthesiologists physical status I–III) undergoing total knee arthroplasty with a standardized spinal anesthetic. Patients were randomized to receive either a dexmedetomidine loading dose of $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ over ten minutes, followed by an infusion of $0.5 \mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$ for the duration of the surgery, or a normal saline loading dose and an infusion of an equivalent volume. The primary outcome was the consumption of morphine delivered via patient-controlled analgesia in the first 24 hr following surgery.

Results The mean (SD) cumulative morphine at 24 hr in the dexmedetomidine group was 29.2 (11.2) mg compared with 61.2 (17.2) mg in the placebo group (mean difference,

32.0 mg; 95% confidence interval, 22.7 to 41.2; $P < 0.001$). In the dexmedetomidine group, there was a delay in the time to first analgesic request ($P = 0.003$) and a reduction in the mean morphine use at six and 12 hr following surgery (both $P < 0.001$).

Conclusions Dexmedetomidine was associated with a significant decrease in morphine use in the first 24 hr following total knee arthroplasty. Our study shows that an intraoperative infusion of dexmedetomidine for sedation in patients receiving spinal anesthesia can produce postoperative analgesic effects. This offers another potential adjunct in the multimodal pain management of these patients. This trial was registered at ClinicalTrials.gov (identifier NCT02026141).

Résumé

Contexte Nous ne savons pas si les effets de réduction de la consommation d'opioïdes qu'on observe lors de l'administration de dexmédétomidine aux patients subissant une anesthésie générale s'appliquent également chez les patients subissant une rachianesthésie. Nous avons émis l'hypothèse que l'administration de dexmédétomidine par voie intraveineuse pour la sédation pendant une arthroplastie totale du genou sous rachianesthésie réduirait la consommation postopératoire de morphine au cours des premières 24 h après la chirurgie.

Méthode Nous avons réalisé cette étude randomisée contrôlée prospective à double insu chez 40 patients (statut physique I–III selon l'American Society of Anesthesiologists) subissant une arthroplastie totale du genou avec un anesthésique rachidien standardisé. Les patients ont été randomisés à recevoir soit une dose de

I. A. Chan, MD (✉) · J. M. O'Brien, PhD · W. P. McKay, MD
Department of Anesthesiology, RUH, University of
Saskatchewan, G525-103 Hospital Drive, Saskatoon,
SK S7N 0W8, Canada
e-mail: Ian.chan@usask.ca

J. G. Maslany, MD · K. J. Gorman, MD
Department of Anesthesiology, University of Saskatchewan,
Regina, SK, Canada

charge de dexmédétomidine de $0,5 \mu\text{g}\cdot\text{kg}^{-1}$ sur une période de 10 minutes, suivie par une perfusion de $0,5 \mu\text{g}\cdot\text{kg}\cdot\text{h}^{-1}$ pour la durée de la chirurgie, ou une dose de charge de sérum physiologique et une perfusion de volume équivalent. Le critère d'évaluation principal était la consommation de morphine administrée par analgésie contrôlée par le patient au cours des premières 24 h suivant la chirurgie.

Résultats La dose cumulative moyenne (ÉT) de morphine consommée à 24 h dans le groupe dexmédétomidine était de 29,2 (11,2) mg, par rapport à 61,2 (17,2) mg dans le groupe placebo (différence moyenne, 32,0 mg; intervalle de confiance 95 %, 22,7 à 41,2; $P < 0,001$). Dans le groupe dexmédétomidine, on a observé un délai jusqu'au moment de première demande d'analgésique ($P = 0,003$) et une réduction de l'utilisation moyenne de morphine à six et 12 h après la chirurgie (les deux $P < 0,001$).

Conclusion La dexmédétomidine a été associée à une réduction significative de la consommation de morphine au cours des premières 24 h suivant une arthroplastie totale du genou. Notre étude montre qu'une perfusion peropératoire de dexmédétomidine pour la sédation de patients recevant une rachianesthésie peut avoir des effets analgésiques postopératoires. Voici donc un autre adjuvant potentiel à la prise en charge multimodale de la douleur de ces patients. Cette étude est enregistrée au ClinicalTrials.gov (identifiant NCT02026141).

Patients receiving spinal anesthesia for surgical procedures often request sedation to alleviate anxiety.¹ Anesthesiologists must balance patient satisfaction vs the risk of respiratory depression associated with oversedation. A review of closed claims has revealed that respiratory depression from oversedation has caused catastrophic adverse events such as brain damage and death.² Dexmedetomidine, an alpha-2 adrenergic agonist, may be ideally suited to provide sedation during surgery as it offers sedation and analgesia without causing significant respiratory depression.³ Compared with frequently used sedatives for procedural sedation (e.g., propofol and midazolam), use of dexmedetomidine resulted in less hypoxemia and increased patient satisfaction.^{4,5} A recent meta-analysis also showed improved patient sedation when dexmedetomidine was used during burn procedures.⁶

The analgesic properties of dexmedetomidine may also be beneficial, especially for procedures with significant postoperative pain.⁷ Patients sensitive to the respiratory depressant effects of opioids, such as the elderly or patients with obstructive sleep apnea, may also benefit.^{8,9} The use of intravenous dexmedetomidine for sedation during spinal

anesthesia has been studied to some extent, evidenced by its prolonging effect on the duration of sensory and motor block.¹⁰ A delayed time to first analgesic request was observed in patients undergoing transurethral prostatic resection with spinal anesthesia.¹¹ Despite the significant decreases seen following general anesthesia, there is a lack of randomized-controlled trials (RCTs) studying the effects of dexmedetomidine on opioid consumption after spinal anesthesia.¹²

To investigate a potential dexmedetomidine-mediated opioid-sparing effect after spinal anesthesia, we studied opioid requirements of patients undergoing total knee arthroplasty performed under spinal anesthesia—a common operation associated with severe postoperative pain.^{13,14} We hypothesized that sedation with dexmedetomidine during total knee arthroplasty under spinal anesthesia would decrease postoperative morphine consumption during the first 24 hr after surgery.

Methods

In December 2013, the University of Saskatchewan Biomedical Research Ethics Board gave approval for this single-centre randomized double-blind placebo-controlled parallel-group trial. This project was completed at our tertiary care hospital where approximately 700 total knee replacements are performed annually. Inclusion criteria were adults aged 18–85 yr, American Society of Anesthesiologists (ASA) physical status class I–III, and scheduled for elective unilateral primary total knee arthroplasty under spinal anesthesia. Exclusion criteria included patients with relative contraindications to dexmedetomidine (e.g., allergy, heart block, and significant renal and hepatic impairment), patients with contraindications to morphine or spinal anesthesia, patients preferring general anesthesia, and patients taking narcotics.

The primary outcome was the consumption of morphine delivered via a patient-controlled analgesia (PCA) pump (LifeCare PCATM Infusion System, Hospira, Lake Forest, IL, USA) in the first 24 hr following surgery. Secondary outcomes included morphine consumption at six and 12 hr postoperatively, time to first analgesic request via PCA, resting visual analogue scale (VAS) [(0–10) where 0 = no pain, 10 = worst imaginable pain] scores at six, 12, and 24 hr, discharge readiness time from the postanesthesia care unit (PACU), patient satisfaction with their analgesia in the first 24 hr, hemodynamic and respiratory changes intraoperatively and in the PACU, and opioid-related adverse effects (i.e., nausea, vomiting, pruritus) in the first 24 hr. All the outcomes were pre-specified prior to the start of the trial; however, the research team did not update the protocol at clinicaltrials.gov prior to the study in order to reflect all these non-primary outcome decisions.

Prior to entering the operating room, a member of the research team recruited the patients and obtained written informed consent. A computerized random number generator (www.random.org) was used to randomize the patients to either the dexmedetomidine or the placebo group in a 1:1 ratio. Access to the random number sequence and preparation of the series of sealed numbered envelopes was entrusted to a research coordinator not involved in patient recruitment, clinical care, or data collection. The patient, anesthesiologist, surgeon, and research team member involved with the patient were blinded to the group allocation. Once a patient was enrolled in the study, an anesthesiologist, who was not involved in the project or patient care, prepared a syringe (containing either normal saline or dexmedetomidine) according to the instructions provided in the sealed numbered envelope. The anesthesiologist then provided this numbered syringe to the attending anesthesiologist involved in the patient's care.

Prior to entering the operating room, all patients were familiarized with the VAS and instructed on the use of the PCA pump. They were instructed to press the PCA demand button if their pain was ≥ 4 on the VAS.

All patients received oral premedication with acetaminophen 975 mg and naproxen 500 mg as well as an intravenous bolus of Ringer's Lactate 500 mL 30 min prior to their scheduled operation time.

In the operating room, electrocardiography, noninvasive blood pressure, and pulse oximetry monitors were applied. In the dexmedetomidine group, patients received a loading dose of intravenous dexmedetomidine $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ over ten minutes, followed by an infusion of $0.5 \mu\text{g}\cdot\text{kg}\cdot\text{hr}^{-1}$ delivered by a Medfusion® 3500 infusion pump (Smiths Medical, St. Paul, MN, USA). In the placebo group, patients received a loading dose and infusion of the equivalent volume of normal saline. Oxygen was delivered to all patients at $3 \text{ L}\cdot\text{min}^{-1}$ via nasal prongs. Once the loading dose of the study drug was started, spinal anesthesia was obtained in the sitting position using 0.75% hyperbaric bupivacaine 12.75 mg and fentanyl 10 μg . The anesthesiologist providing care for the patient continually assessed the intraoperative level of sedation and targeted a moderate level of sedation defined by the ASA¹⁵ (i.e., depression of consciousness with maintenance of purposeful responses to verbal commands/ light tactile stimulation, an unassisted patent airway, adequate spontaneous ventilation, and cardiovascular function). Intravenous midazolam 0–4 mg was available to both groups intraoperatively in order to achieve this goal, and no other intraoperative narcotics or sedatives were to be used. Phenylephrine and ephedrine were available at the discretion of the anesthesiologist in the event of hemodynamic changes. Although there were no specific hemodynamic targets with respect to the administration of

phenylephrine and ephedrine, all anesthesiologists were informed of the potential for bradycardia and hypotension with dexmedetomidine and were instructed to provide hemodynamic support as per their clinical judgement. No peripheral nerve blocks were performed on the study subjects, and the surgeons did not administer local anesthetic infiltration during the procedures.

Postoperatively, the infusion was discontinued once the final dressing was applied. Patients were then transferred to the PACU and PCA was initiated. Delivery of morphine was standardized to 1.5 mg with a lockout of eight minutes. This PCA setting differs from our initial protocol registered with clinicaltrials.gov to account for convenience of using the institution's standardized PCA order forms. This decision was made prior to patient enrolment, and all patients enrolled in the study received the same PCA orders. No supplemental analgesics were ordered for the first 24 hr following surgery. Dimenhydrinate 50 mg and ondansetron 4 mg were available if a patient experienced postoperative nausea or vomiting. Patients were discharged from the PACU once discharge criteria were met as per the modified Aldrete scoring system.¹⁶

All patient data and satisfaction scores were collected for 24 hr postoperatively by a research member who was blinded to the group assignment and not involved with the perioperative or postoperative care of the patient. Patient satisfaction was assessed by directly asking the patients to rate their satisfaction with the adequacy of analgesia in the last 24 hr as excellent, good, acceptable, or poor. Nursing staff blinded to group allocation assessed and recorded the VAS scores.

Statistical analysis

Statistical analysis was performed using SigmaPlot® version 13.0 (Systat Software Inc., San Jose, CA, USA).

Sample size was calculated using a previously published study in which mean [standard deviation (SD)] 24-hr morphine consumption for total knee arthroplasty was 58.6 (27.3) mg.¹⁷ A 50% reduction in morphine consumption was considered clinically significant as well as consistent with previously published studies showing decreased use of opioid analgesics following a dexmedetomidine infusion in patients undergoing general anesthesia.¹² Using a two-sided test with an alpha of 0.05 and a power of 0.9, the required sample size for a two-sample comparison of means was estimated at 19 patients per group. The decision was made to enrol 20 patients per group to allow for potential patients who drop out.

Data were tested for normality using the Shapiro-Wilk test with a cut-off of 0.05. Student's *t* tests were used to analyze the outcomes in data with normal distribution, including our primary outcome. The Mann-Whitney U test

Fig. 1 Flow diagram of screened, excluded, and recruited patients

was used for data that were not normally distributed, and a Wilcoxon rank-sum test was used to analyze patient satisfaction.

Results

In May 2014, 49 consecutive patients undergoing total knee arthroplasty were approached for enrolment in this study. Patient flow is depicted in the CONSORT diagram (Fig. 1). Nine patients were excluded from the study. Seven patients preferred a general anesthetic, one patient had an allergy to morphine, and one patient was taking opioids. Twenty patients were enrolled in each of the dexmedetomidine and placebo groups. Spinal anesthesia could not be performed on one patient in the placebo group due to difficulty finding the intrathecal space. This patient received a general anesthetic but was included in the intention-to-treat analysis. This patient's age (65 yr) and 24-hr morphine use (62 mg) was similar to that of the overall placebo group. Patient demographics and duration of surgery were similar between both groups (Table 1).

There was no difference in the mean (SD) dose of midazolam used by both groups [1.0 (1.0) mg, dexmedetomidine group vs 1.5 (1.2) mg, placebo group; $P = 0.153$].

With respect to the primary outcome, the mean (SD) cumulative morphine at 24 hr in the dexmedetomidine group was 29.2 (11.2) mg compared with 61.2 (17.2) mg in the placebo group (mean difference, 32.0 mg; 95% confidence interval [CI], 22.7 to 41.2; $P < 0.001$). The mean (SD) morphine consumption at six hours in the dexmedetomidine group was 6.5 (5.1) mg compared with 14.6 (8.4) mg in the placebo group (mean difference, 8.1 mg; 95% CI, 3.6 to 12.6; $P < 0.001$). At 12 hr postoperatively, the mean (SD) morphine use in the dexmedetomidine group was 16.0 (6.8) mg compared with 29.2 (10.9) mg in the placebo group (mean difference, 18.1 mg; 95% CI, 12.9 to 23.3; $P < 0.001$) (Fig. 2).

The mean (SD) time to first analgesic request was delayed in the dexmedetomidine group compared with the placebo group [240 (77) min vs 166 (70) min, respectively; mean difference, 74 min; 95% CI, 27 to 121; $P = 0.003$] (Table 2). There were no significant differences in VAS

Table 1 Patient demographics and intraoperative characteristics. Continuous values are represented by mean (SD)

	Dexmedetomidine group (n=20)	Placebo group (n=20)
Age	66.2 (11.4)	66.1 (8.6)
Sex, Female	16(80%)	12(60%)
BMI	34.3 (6)	36.3 (7.2)
ASA		
I	0	2(10%)
II	12(60%)	12(60%)
III	8(40%)	6(30%)
Pain at rest	1.8 (2)	1.9 (2.3)
Pain with movement	5.1 (2.4)	5.3 (2.6)
Medical Comorbidities		
Sleep Apnea	1(5%)	3(15%)
CAD	2(10%)	1(5%)
CVD	0	1(5%)
COPD	1(5%)	0
Asthma	1(5%)	0
Heart rate (baseline) beats·min ⁻¹	76.8 (9.2)	76.8 (10.8)
Mean arterial pressure (baseline) mmHg	99.8 (9.9)	102.4 (10.9)
Surgical time (min)	63.8 (8.9)	59.6 (15.2)

Categorical variables are represented by *n* (%). Heart rate and mean arterial pressure were measured prior to entering the operating room. ASA = American Society of Anesthesiologists physical status classification; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease

Fig. 2 Mean morphine consumption in the dexmedetomidine group at six hours was 6.5 mg vs 14.6 mg in the placebo group. At 12 hr, the mean consumption in the dexmedetomidine group was 16 mg vs 29.2 mg in the placebo group. At 24 hr, the mean consumption in the dexmedetomidine group was 29.2 mg vs 61.2 mg in the placebo group

scores at six, 12, or 24 hr (Table 2). Time to discharge from the PACU was delayed in the dexmedetomidine group compared with the placebo group [163 (52) min vs

116 (46) min, respectively; mean difference, 47 min; 95% CI, 16 to 78; $P = 0.004$] (Table 2). Patient satisfaction with their quality of analgesia at 24 hr was found to be significantly higher in the dexmedetomidine group ($P = 0.019$) (Table 2).

Intraoperatively, there were no hemodynamic differences between the two groups, with similar lowest mean arterial pressure (MAP) and heart rate. There were also no differences in estimated blood loss or amount of intravenous fluid given perioperatively (Table 3). Nevertheless, in the PACU, patients in the dexmedetomidine group were found to have a lower MAP compared with those in the placebo group; heart rate was maintained across both groups (Table 3). In the PACU, there was no difference between groups in the number of patients with hypotension (i.e., > 20% drop in MAP from baseline) or in the number of patients receiving phenylephrine or ephedrine (Table 3). No patient in either group had an episode of oxygen desaturation (i.e., < 92%), either intraoperatively or in the PACU. There were more postoperative opioid-related side effects observed in the placebo group, including more nausea, vomiting, and pruritus (Table 2).

Discussion

In this RCT, patients receiving intravenous dexmedetomidine for procedural sedation during total knee arthroplasty under spinal anesthesia showed a significant reduction in postoperative opioid use in the first 24 hr following surgery. Our 24-hr morphine reduction of 32 mg (95% CI, 22.7 to 41.2), which was 53% less than that in the placebo group, is comparable with previous studies showing less postoperative opioid consumption in patients receiving dexmedetomidine infusions during general anesthesia.¹² This reduction is also comparable with other modalities previously studied during total knee arthroplasty, for example, a 50% decrease in the use of periarticular infiltration.¹⁸ This 24-hr reduction in morphine use is similar to that using a single-shot femoral nerve block with a sciatic block. This approach was reported in a recent meta-analysis of femoral nerve blocks highlighting morphine reductions from a single-shot femoral nerve block (20-mg reduction), a single-shot femoral nerve block with a sciatic block (31-mg reduction), and a continuous femoral nerve block (15-mg reduction).¹⁹

The decrease in morphine use in the dexmedetomidine group in the first 24 hr is clinically relevant for a number of reasons. Total knee arthroplasty is an operation associated with significant postoperative pain. Actually, 60% of patients describe the postoperative pain as severe.¹³ Opioids typically play a large role in the treatment of

Table 2 Secondary outcomes

	Dexmedetomidine	Placebo	Mean difference	95% Confidence intervals	P value
Time in recovery unit (min)	162.6 (51.8)	115.7(45.9)	46.9	(15.5 to 78.2)	0.004
Time to first PCA request (min)	239.5 (77.3)	165.5 (69.8)	74.0	(26.9 to 121.1)	0.003
Postoperative VAS score at 6 hr	4.4 (2.7)	5.0 (1.8)	−0.6	(−2.1 to 0.90)	0.410
Postoperative VAS score at 12 hr	4.3 (2.0)	5.1(1.6)	−0.9	(−2.1 to 0.4)	0.170
Postoperative VAS score at 24 hr	4.8 (2.4)	5.0 (2.3)	−0.2	(−1.7 to 1.3)	0.790
Itchiness (first 24 hr)	1 (5%)	6 (30%)	Odds ratio:0.12	(0.01 to 1.14)	0.015
Nausea + vomiting (first 24 hr)	1 (5%)	7 (35%)	Odds ratio:0.09	(0.01 to 0.89)	0.005
Excellent patient satisfaction with analgesia	4	0			
Good patient satisfaction with analgesia	7	5			
Acceptable patient satisfaction with analgesia	6	7			
Poor patient satisfaction with analgesia	3	8			

Continuous values are represented by mean (SD). Categorical variables are represented by *n* (%). PCA = patient-controlled analgesia; VAS = visual analogue scale

Table 3 Hemodynamic variables intraoperatively and postoperatively

	Dexmedetomidine	Placebo	P value
Lowest MAP (mmHg) intraoperatively	76.3 (10.3)	79 (14.6)	0.511
Lowest heart rate (beats·min ^{−1}) intraoperatively	60.4 (8.7)	62.2 (10.9)	0.556
Bradycardia intraoperatively	6 (30%)	2 (10%)	0.051
Lowest MAP (mmHg) in PACU	64.5 (9.0)	77.1 (13.9)	0.002
Hypotension in PACU	17 (85%)	13 (65%)	0.067
Lowest heart rate (beats·min ^{−1}) in PACU	57.7 (7.3)	58.4 (8.8)	0.787
Bradycardia in PACU	6 (30%)	8 (40%)	0.361
Phenylephrine/ephedrine use	6 (30%)	7 (35%)	0.639
Estimated intraoperative blood loss (mL)	182.0 (165.1)	212.7 (192.8)	0.591
Intraoperative intravenous fluid administered (mL)	1,490.0 (390.2)	1,251.3 (395.2)	0.062

Continuous values are represented by mean (SD). Categorical variables are represented by *n* (%). Bradycardia was defined as heart rate < 55 beats·min^{−1}. Hypotension defined as a 20% drop in mean arterial pressure from patient's baseline. MAP = mean arterial pressure; PACU = postanesthesia care unit

postoperative pain after total knee arthroplasty, which may place patients at increased risk of postoperative respiratory depression.²⁰ In a recent closed claims analysis of postoperative opioid-induced respiratory depression, Lee *et al.* make note that 88% of closed claims involving postoperative opioid-induced respiratory depression events occurred within 24 hr of the surgical procedure.²¹ As well, Chung *et al.* found that, during the first postoperative night, increases in the central apnea index and obstructive apnea index in non-obstructive sleep apnea patients are correlated with the first 24-hr opioid requirement.²² To compound this issue, recent data have shown that the increasing demand for total knee arthroplasty appears to be linked to obesity,²³ thereby placing these patients at even greater risk of adverse respiratory events.²⁴ Lessening postoperative opioid use not only decreases opioid-related side effects²⁵ but may also decrease the risk of postoperative respiratory depression.²⁶

Morphine consumption was significantly reduced during all three cumulative time intervals (six, 12, and 24 hr). This suggests that the analgesic effect of dexmedetomidine is present throughout the first 24 hr and that the analgesic benefits of dexmedetomidine extend past its biological half-life of two hours.²⁷

The significant increase in the time to first analgesic request in the dexmedetomidine group was consistent with the reduction in the use of morphine. This delayed analgesic request parallels the delay in patients receiving dexmedetomidine during general anesthesia.²⁸ It is important to emphasize that, although the level of sedation was measured in the operating room as well as in the PACU, in every case, the first analgesic demand occurred on the ward via PCA where the patient's level of sedation was not measured.

It is also interesting to point out that VAS scores were not significantly different between both groups, even

though the increased morphine consumption in the placebo group would suggest they were experiencing more pain than those in the dexmedetomidine group. This may be explained by the patient's proper use of their PCA, as they were instructed to use the PCA to achieve a VAS score of < 4.

Patient satisfaction with analgesia in the first 24 hr was significantly higher in the dexmedetomidine group, which may be due to the decrease in opioid-related side effects, in particular, significantly less nausea and vomiting. The decrease in opioid-related adverse effects observed in our study is supported by similar results in a recent meta-analysis.⁶

One potential limitation to the widespread use of dexmedetomidine may be a delayed discharge from the PACU. We recognize that this delay could lead to inefficiencies in postoperative patient disposition and operating room flow. The primary reason for this delayed discharge can be attributed to the MAP in the dexmedetomidine group observed in the PACU. Although the delay in PACU discharge time is significant, an evaluation is needed to determine whether the benefits of decreased opioid use in the first 24 hr outweigh the slower turnover period in the PACU, especially with respect to patients with opioid sensitivities.

As per discharge criteria at our institution, patients' MAPs must return to within 20% of their preoperative baseline prior to PACU discharge. Although there were no statistically significant differences between the two groups in the number of patients whose MAP fell > 20% below baseline, the dexmedetomidine group had a significantly lower overall mean MAP in the PACU and took longer for their MAP to return to within 20% of baseline. The hypotension observed in the PACU was likely potentiated by the direct pharmacological effects of dexmedetomidine as well as its ability to increase the level of sensory blockade during spinal anesthesia.²⁹

In our experience, the effect of dexmedetomidine on lowering MAP was expected. Nevertheless, our results were inconsistent with a previous meta-analysis suggesting that the use of dexmedetomidine during spinal anesthesia did not show significant hemodynamic differences.³⁰ This discrepancy with our study may be explained by the fact that the previous meta-analysis contained a combination of major and minor surgeries not associated with significant blood loss. Furthermore, the hypotension seen in the PACU in our study may have been compounded by deflating the tourniquet at the end of the surgery.

It is important to emphasize that there were no differences observed between the groups regarding the administration of phenylephrine or ephedrine for intraoperative hypotension. Our protocol did not allow for adjustment of the dose of the study infusion in the case

of hemodynamic changes, and therefore, some patients may have had fewer hemodynamic changes in the PACU if they had smaller doses intraoperatively. Further dose-ranging studies should be performed to determine the optimal dose of dexmedetomidine that would offer the opioid-sparing benefits observed in our study while avoiding delayed discharge times and the hemodynamic changes seen in the PACU.

A limitation of our study was that the patients' level of sedation was not measured on the ward. It may be that patients in the dexmedetomidine group used less morphine due to their increased level of sedation. This seems unlikely to us since opioid consumption was decreased in all time intervals (six, 12, and 24 hr postoperatively). If sedation had played a major role, we would expect a greater reduction in opioid use during the first time interval, in keeping with the biological half-life of dexmedetomidine.²⁷ Furthermore, patients met Aldrete's discharge criteria of being "wide awake" prior to being transferred from the PACU to the ward. The end result of similar VAS scores between groups suggests that patients were aware of their perceived pain enough to know when to use their PCA and were not too sedated to do so.

Another limitation of this study was the lack of use of local anesthetics and other non-opioid pharmacological interventions administered in the postoperative period. Future studies comparing dexmedetomidine with other modalities as well as studies including dexmedetomidine with multimodal analgesic regimens would allow us to assess whether dexmedetomidine can be used either to enhance the analgesic effects of certain techniques or to be used in lieu of other methods.

In conclusion, we found that the use of dexmedetomidine for procedural sedation in patients undergoing total knee arthroplasty reduces opioid use postoperatively in the first 24 hr. The importance of multimodal regimens in providing superior analgesia, while limiting side effects and adverse events, is highlighted in the American Society of Anesthesiologists "Practice guidelines for acute pain management in the perioperative setting".³¹ It is our view that dexmedetomidine could contribute to this goal, as it offers analgesia with the benefit of providing procedural sedation without respiratory depression. Further research is needed to evaluate whether the opioid-sparing effects observed in patients undergoing total knee arthroplasty can be replicated in other types of painful surgeries performed under spinal anesthesia as well as in chronic pain patients or in patients previously taking opioids.

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was involved in the acquisition of data. *Ian A. Chan* was involved in patient recruitment, data collection, and writing the first draft of this paper. *William P. McKay* was involved in the analysis of data. *Jurgen G. Maslany*, *Kyle J. Gorman*, *Jennifer M. O'Brien*, and *William P. McKay* were involved in revising the article.

Conflicts of interest None declared.

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