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ORIGINAL RESEARCH ARTICLE

Premedication with intranasal dexmedetomidine in patients undergoing total knee arthroplasty under spinal anaesthesia (TKADEX)—a prospective, double-blinded, randomised controlled trial

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A preliminary account of the results has been given in a published abstract in the 37th SSAI Congress and *Acta Anaesthesiologica Scandinavica* (June 2024).

Abstract

Background: Previous studies have shown that perioperative use of adjuvants, such as the alpha-2 agonist dexmedetomidine, may reduce postoperative pain and opioid requirements. However, information about optimal dosing is lacking. We investigated if premedication with intranasal dexmedetomidine compared with placebo reduces postoperative pain in patients undergoing total knee arthroplasty under spinal anaesthesia.

Methods: This single-centre, double-blind, two-arm study compared premedication with intranasal dexmedetomidine (single 1 μg kg^{-1} dose) to intranasal saline in 101 consecutive elective patients undergoing total knee arthroplasty under spinal anaesthesia. The primary outcome was postoperative pain measured with the numerical rating scale during the first 24 h. Secondary outcomes were postoperative opioid requirement, perioperative haemodynamic variables, requirement of additional intraoperative sedation, incidence of postoperative nausea and vomiting, and patient satisfaction at 30 days after surgery.

Results: Patients in the dexmedetomidine group had lower numerical rating scale scores [median (interquartile range) 2.0 (0.0–3.0)] at 3 h when compared with the control group [3.0 (2.0–4.0)] (P=0.037). Cumulative 24 h opioid requirements (in morphine equivalents) did not differ between dexmedetomidine [45 mg (30–68 mg)] and control groups [53 mg (38–88 mg)] (P=0.334). More patients in the dexmedetomidine group were satisfied with pain management in the ward (P=0.0013). The groups did not differ in the incidence of postoperative nausea and vomiting (P=0.310) or haemodynamic adverse events (P>0.27 for all).

Conclusions: Our results indicate that intranasal dexmedetomidine may reduce postoperative pain and the requirement for additional sedation and increase short-term patient satisfaction in patients undergoing total knee arthroplasty.

Clinical trial registration: ClinicalTrials.gov (NCT 04859283).

Keywords: dexmedetomidine; intranasal delivery; multimodal analgesia; nonopioid analgesics; patient satisfaction; premedication

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Total knee arthroplasty (TKA) is among the most common surgical procedures and its frequency is expected to increase in the future.[1] Numerous efforts have been made to identify the ideal multimodal analgesic regimen for TKA, but postoperative pain remains a common issue. Failure to control postoperative pain adequately may result in delayed ambulation, extended hospital stay, and prolonged duration of opioid use after TKA.[2] Severe postoperative pain has been linked to inferior functional results and lower patient satisfaction in patients undergoing TKA.[3]

Several studies have concluded that the alpha-2-agonist dexmedetomidine has a synergistic effect with opioids and shown that perioperative use of dexmedetomidine may reduce postoperative opioid requirement and pain at least for 24 h.[4,5] The use of i.v. dexmedetomidine as an adjuvant for analgesia, despite its proven efficacy, has been limited because of concerns about haemodynamic adverse effects.[6] However, it has been suggested that haemodynamic alterations may be attenuated if extravascular administration routes, such as intranasal, are used instead of i.v. administration.[7] Besides haemodynamic stability, intranasal administration of dexmedetomidine may offer several other advantages over the i.v. route. Intranasal administration is simple and offers the convenience of a single dose, while bypassing hepatic first-pass metabolism and resulting in good bioavailability.[7]

It has been previously demonstrated that intranasal dexmedetomidine reduces opioid requirements in patients undergoing arthroplasty surgery under general anaesthesia.[8,9] However, no prior studies investigated the use of intranasal dexmedetomidine in patients undergoing TKA under spinal anaesthesia.

The purpose of this study was to investigate if premedication with intranasal dexmedetomidine could improve postoperative pain control after TKA under spinal anaesthesia.

Our primary hypothesis was that premedication with intranasal dexmedetomidine reduces postoperative pain levels and opioid requirements. We also hypothesised that haemodynamic variables would remain stable, there would be fewer opioid-related side-effects, and patients would be more satisfied after dexmedetomidine administration. In the PICOT format, our aims were: P (Population): patients undergoing TKA under spinal anaesthesia; I (intervention): premedication with intranasal dexmedetomidine; C (comparison): intranasal saline; and O (outcome): primary outcome is postoperative pain within the first 24 h. Secondary outcomes include postoperative opioid requirements, additional intraoperative sedation, perioperative haemodynamic stability, postoperative nausea and vomiting (PONV), and patient satisfaction. T (time): postoperative period, the first 24 h after surgery, except for patient satisfaction, 30 days.

Methods

Data were collected prospectively in TYKS ORTO Hospital (Turku University Hospital), Turku, Finland, between June 2022 and September 2023. The trial was registered on ClinicalTrials.gov (NCT 04859283). This manuscript adheres to the applicable CONSORT guidelines: CONSORT flow chart (Fig. 1), CONSORT checklist (Supplementary material).

Ethical considerations

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland on 15 March 2021 and by the National Agency of Medicines (Fimea). Written informed consent was obtained from each patient.

Patient population

A prospective double-blind, randomised, controlled trial was undertaken. Patients of ASA class 1–3, aged between 35 and 80 yr, weighing between 50 and 100 kg, and scheduled for elective unilateral TKA under spinal anaesthesia, were included in the study. Patients with a previous history of intolerance to the study drug or related compounds and additives, preoperative chronic opioid use, or other adjuvant analgesics such as ketamine, gabapentinoids, clonidine, or tricyclic antidepressants, and patients with clinically significant abnormalities at preoperative assessment (e.g. liver or kidney failure), ECG or laboratory values were excluded from the study. Exclusion criteria also included pregnancy or breastfeeding, preoperative systolic blood pressure <110 mm Hg, history of cardiac disease (valvular insufficiency, severe left ventricular dysfunction) or abnormal ECG rhythm (bradycardia <50 beats min^{-1}, second- or third-degree AV block, pacemaker), the use of drugs or natural products known to induce or inhibit enzymes, and the presence of any current or recent significant disease that could affect the absorption, distribution, metabolism, excretion, or response to the study drug. Any deviation from the approved study protocol that was likely to affect the study outcomes (e.g. postponing surgery, transition to general anaesthesia or administering pain medications not included in the study protocol) were considered as protocol breaches.

Sample size and randomisation

Based on a two-sample *t*-test power calculation, 51 patients per group and a total of 102 patients were necessary to demonstrate a 30% reduction from 5.0 to 3.5 with a standard deviation (SD) of 2.3 in numerical rating scale (NRS) ratings (a clinically significant difference) using the level of significance of $P=0.05$ and power of 90%.[10] A total of 110 patients (55 per group) were recruited and randomly assigned, allowing for eight dropouts. All patients were randomly allocated to the dexmedetomidine or control groups with an allocation ratio of 1:1. Randomisation was performed with SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) using random permuted blocks with a block size of six by a biostatistician with no clinical involvement in the trial. The hospital pharmacy prepared the study drugs according to the randomisation in identical syringes. Investigators, staff, and patients were blinded to group allocation.

Study drug administration

Depending on which group the patient was allocated to, intranasal dexmedetomidine 1 μg kg^{-1} or an equivalent volume of saline was administered approximately 45 min before anticipated spinal anaesthesia using an LMA MAD Nasal™ (Teleflex MAD Nasal; Teleflex Inc, NC, USA) device. A senior anaesthesiologist administered the study drug to the semi-recumbent patient. The amount of dexmedetomidine was rounded to the nearest 10 μg to facilitate practical dosing. The dose used in this study was based on previous studies on the use of intranasal dexmedetomidine in adult patients and practical considerations related to intranasal administration because the volume that can be administered intranasally is

limited, and exceeding this volume could compromise absorption and efficacy.[11–13]

Pharmacodynamic measurements

Heart rate, ventilatory frequency, noninvasive blood pressure, and peripheral arterial oxygen saturation (SpO2) were monitored and recorded at baseline and subsequently measured at 5-min intervals throughout the operation and at 15-min intervals in the PACU. The intraoperative period was defined as the time from skin incision to wound closure.

Anaesthetic management

Spinal anaesthesia was performed with a Whitacre spinal needle using hyperbaric levobupivacaine (5 mg ml^{-1}) 2.0–2.5 ml, the amount depending on the judgement of the anaesthesiologist responsible for the case. The mean arterial pressure target was between 65 and 75 mm Hg, depending on the patient's age and disease history. If the patient requested additional intraoperative sedation (other than the study drug), i.v. midazolam 1 mg was given with repeated doses based on the clinical judgement of the anaesthesiologist responsible for the patient. The duration of the motor block was measured starting from the spinal anaesthesia and ending when the Bromage score reached stage 4.

Pain management

All patients received oral paracetamol 1000 mg as premedication. If the patient requested additional medication for pain caused by the spinal needle, position, or tourniquet, i.v. fentanyl 50 μg was given and repeated as necessary during the surgery. Postoperative pain was assessed 1, 3, 6, 12, 18, and 24 h after wound closure using an NRS. In the PACU, patients received i.v. oxycodone 0.03–0.05 mg kg^{-1} if they reported moderate or intense pain (NRS >3) after oral oxycodone administration and the dose was repeated after 15 min until the NRS score was ≤3. The postoperative multimodal analgesia regimen in the ward consisted of oral paracetamol 1000 mg every 8 h and oral naproxen/esomeprazole 500/20 mg twice a day. Oral oxycodone was used if the patient reported moderate to intense pain (NRS >3) after these medications. The measurement of the cumulative opioid requirement was begun from the end of surgery.

Patient satisfaction

All study participants were contacted after 1 month by telephone to obtain feedback on anaesthesia and pain management. Patients were asked to rate their pain management in the PACU, postoperative ward, at home and in general on a five-point Likert scale (5=extremely satisfied, 4=somewhat satisfied, 3=neutral, 2=somewhat dissatisfied, 1=extremely dissatisfied).

Outcomes

The primary outcome was the postoperative pain NRS in the first 24 h. Secondary outcomes included opioid requirement in the first 24 h after operation, the requirement for additional intraoperative sedation, the incidence of PONV, patient satisfaction 30 days after the TKA, and intraoperative haemodynamic stability. It should be emphasised that our primary outcome measure was different than stated in our initial registration in ClinicalTrials.gov which stated: 'VAS under 30 and change in opioid consumption at 24 hours as well as intraoperative midazolam and fentanyl consumption intraoperatively'. We initially planned to use VAS and this was still the case when we registered our study in ClinicalTrials.gov.

Safety and adverse effects

Bradycardia was defined as a heart rate <50 beats min^{-1} and severe bradycardia as a heart rate <40 beats min^{-1}. Hypotension was defined as a systolic blood pressure <90 mm Hg. Hypertension was defined as a systolic blood pressure >150 mm Hg.

Data handling and statistical analysis

The Shapiro–Wilks test was used to assess normality assumptions. Student's *t*-test was used to compare the groups with normally distributed data, and Wilcoxon's rank sum test was used to test non-normally distributed data. Nominal data were tested using χ^2 analysis. To test patient satisfaction measured with the Likert scale, Fischer's exact test was used. $P<0.05$ (two-tailed) was considered statistically significant. The results are expressed as mean values with standard deviations (SD), and as medians with interquartile ranges (IQR) when the normality assumption was not met. The analyses were performed with JMP Pro 13.0 for Mac (SAS Institute Inc., Cary, NC, USA).

Results

We assessed 468 patients for eligibility, and after informed consent recruited 110 patients for the study: 55 patients in the dexmedetomidine group and 55 patients in the control group. Data were collected prospectively in TYKS ORTO Hospital (Turku University Hospital), Turku, Finland, between June 2022 and September 2023. The trial ended when the sample size goal was reached. Nine patients were excluded from the study (four because of cancelled operation, five because of breaches in the study protocol), leaving data from 101 patients to be analysed (dexmedetomidine group $n=49$, control group $n=52$). The CONSORT flow diagram of the study is presented in Fig. 1 and the CONSORT checklist is in the Supplementary material.

The patient's characteristics are shown in Table 1. The mean (SD) age of the patients was 67.3 yr (7.1 yr), and the mean BMI was 29.0 m^2 kg^{-1} (3.9 m^2 kg^{-1}). The median (IQR) dose of intranasal dexmedetomidine in the dexmedetomidine group was 80 μg (70–90 μg).

Patients in the dexmedetomidine group had lower NRS scores compared with the control group (median [IQR]: 2.0 [0.0–3.0] *vs* 3.0 [2.0–4.0], $P=0.037$), respectively, at 3 h after surgery. NRS scores at other timepoints did not differ between the groups (Fig. 2). Differences in cumulative 24-h opioid requirement (in morphine equivalents, median and IQR) did not differ between dexmedetomidine (45 mg [30–68 mg]) and control groups (53 mg [38–88 mg]) ($P=0.334$) (Fig. 3). Postoperative pain scores and opioid requirement are presented in Table 2.

Intraoperative midazolam consumption (mg) was less in the dexmedetomidine group ($P=0.033$). The median (IQR) dose in the dexmedetomidine group was 1 mg (1–2 mg), compared with 2 mg (1–3 mg) in the control group. In the control group, 94% of patients (48/51) required midazolam for sedation, while

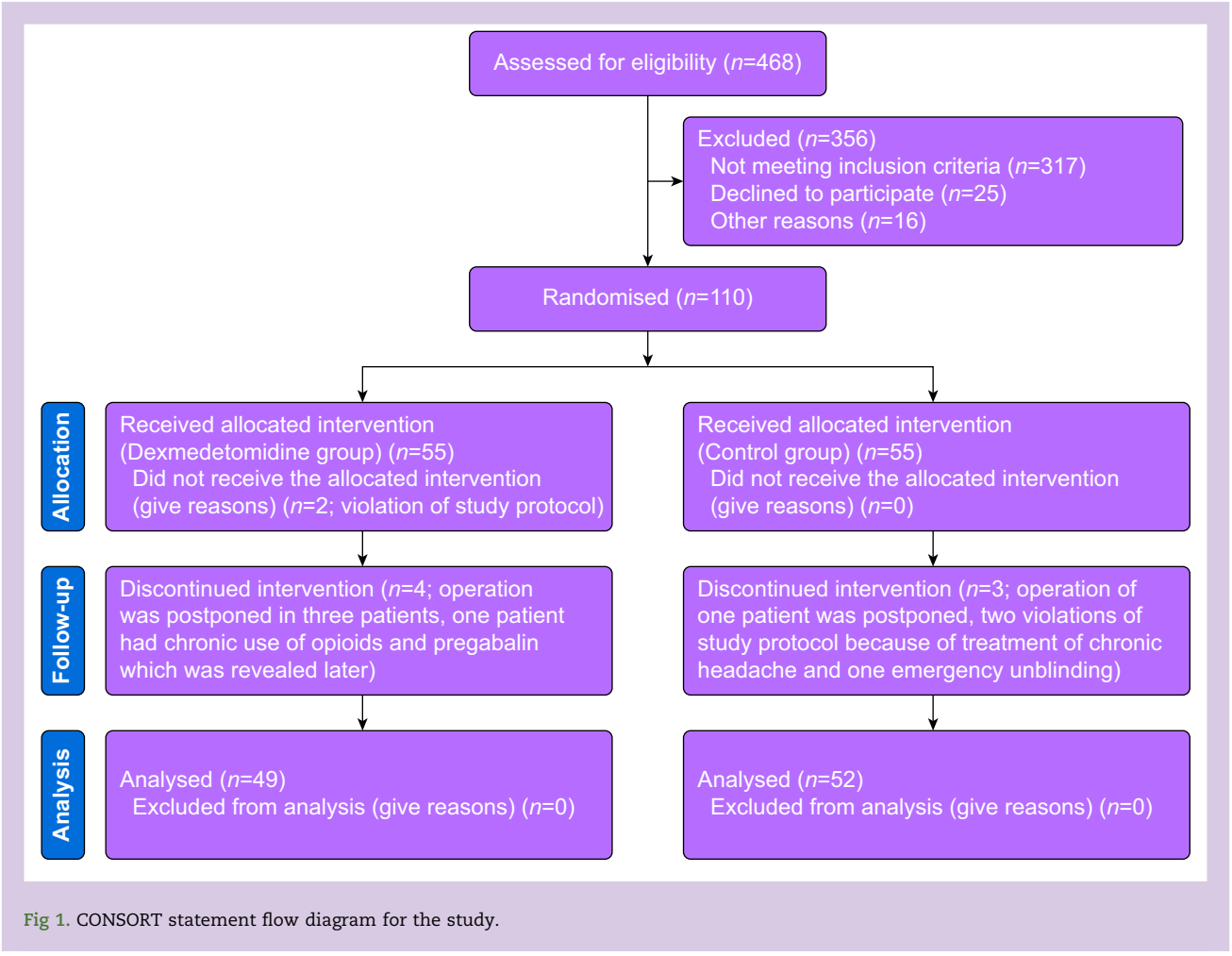

Fig 1. CONSORT statement flow diagram for the study.

82% of patients in the dexmedetomidine group (40/49) required extra sedation. There was no difference between intraoperative fentanyl use (P=0.398). The median (IQR) duration of the motor block was 172 min (138–191 min) and 159 min (135–183 min) (P=0.497 in the dexmedetomidine and control groups, respectively). There was no difference in the incidence of PONV (P=0.310) or in the length of postoperative hospital stay (P=0.861) between the two groups (Table 3).

In the 30-day questionnaire, a higher number of patients in the dexmedetomidine group were satisfied with pain management in the ward compared with the control group (P=0.0013). Other measures regarding patient satisfaction (at PACU, at home or in general) did not differ between the groups (Supplementary Table S1).

Preoperative haemodynamic variables at the beginning of spinal anaesthesia were comparable between the groups, except for diastolic blood pressure, which was lower in the dexmedetomidine group (P=0.028). The groups did not differ in the incidence of perioperative bradycardia, tachycardia, hypotension, hypertension, or vasoactive drug requirement. Perioperative haemodynamic variables and vasoactive consumption are presented in Table 4.

One patient in the control group had severe bradycardia after induction of spinal anaesthesia and was excluded from the analysis because of emergency unblinding. The patient was admitted under a cardiologist and had an uneventful recovery. Dexmedetomidine was not associated with severe adverse effects.

Discussion

Our results suggest that for patients undergoing TKA under spinal anaesthesia, intranasal dexmedetomidine is a feasible premedication. Our results show that it may provide short-term reduction in postoperative pain and enhance patient satisfaction.

Compared with earlier studies, our observed analgesic effect was somewhat less. Previous studies have shown that intraoperatively administered intranasal dexmedetomidine reduces postoperative opioid requirement in patients receiving general anaesthesia for total joint arthroplasty.[8,9] Patients having TKA under general anaesthesia might require more opioids after surgery than were needed in our study[14,15] and it is possible that the benefits of dexmedetomidine are present only with larger opioid requirements.

In the current study, the dexmedetomidine dose was lower than in some other studies, but even lower doses have been used in patients under general anaesthesia.[8] A higher dose would provide deeper sedation and possibly better analgesia, but haemodynamic side-effects could be more severe. Additionally, administering a higher dose would have required a more concentrated dexmedetomidine solution, given the

Table 1 Patient characteristics. ASA, American Society of Anesthesiologists; BMI, body mass index; CTRL, control group; DEX, dexmedetomidine group; IQR, interquartile range; SD, standard deviation.

	All patients (*n*=101)	DEX group (*n*=49)	CTRL group (*n*=52)
Age, mean (range) (yr)	67 (50–78)	68 (56–78)	66 (50–78)
Weight, median (IQR) (kg)	80 (73–90)	80 (73–89)	81 (71–90)
BMI, mean (SD) (kg m^{-2})	29.0 (3.9)	28.7 (3.6)	29.2 (4.2)
Female, *n* (%)	80 (79)	39 (79)	41 (79)
ASA class			
1, *n* (%)	13 (13)	5 (10)	8 (15)
2, *n* (%)	77 (76)	38 (78)	39 (75)
3, *n* (%)	11 (11)	6 (12)	5 (10)

limitations on the volume of liquid that can be effectively delivered intranasally.[12] The onset of action after intranasal dexmedetomidine administration is about 30–45 min.[16] In this study, the mean duration from medication administration to spinal anaesthesia was 47 min, indicating that sufficient time should have passed to observe the desired effect.

It has been suggested that the opioid-sparing effect of dexmedetomidine might be more significant in male patients.[17] Animal research shows that oestrogen may inhibit alpha-2 adrenoceptor-mediated analgesia.[18] Women were overrepresented in our study population partly because the incidence and severity of osteoarthritis vary by gender, with women experiencing higher rates of both the condition's frequency and severity.[19] Another reason for the high female-to-male ratio is that males tend to be larger than females, with many males exceeding the weight limit in our inclusion criteria. It seems unlikely that this would have affected our results, but it may affect the generalisability to other surgical populations besides TKA.

In general, patients in both groups were satisfied with pain management after surgery, but a higher number in the dexmedetomidine group were satisfied with pain management on the ward. Patient satisfaction is a multifactorial phenomenon, but residual pain and unmet patient expectations have been identified as essential factors.[20,21] The association between pain intensity scores and patient satisfaction is controversial. Increased opioid use in the PACU has been found to have a negative influence on patient satisfaction.[22] However, earlier studies showed that reported pain intensity does not correlate with satisfaction, and patients can be satisfied with pain management regardless of pain severity.[23,24] In the present study, patients were relatively satisfied even if they had experienced pain during the first postoperative days.

Patients in the dexmedetomidine group required less additional midazolam for intraoperative sedation. Besides benzodiazepines, sedation with propofol is frequently used in combination with spinal anaesthesia in total joint arthroplasty. However, respiratory depression, postoperative delirium, and paradoxical reactions (restlessness or agitation) are among the side-effects of benzodiazepines and propofol, whereas dexmedetomidine appears to have less effect on respiration.[25] Moreover, many studies have shown that intraoperative dexmedetomidine sedation lowers the incidence of postoperative delirium compared with propofol

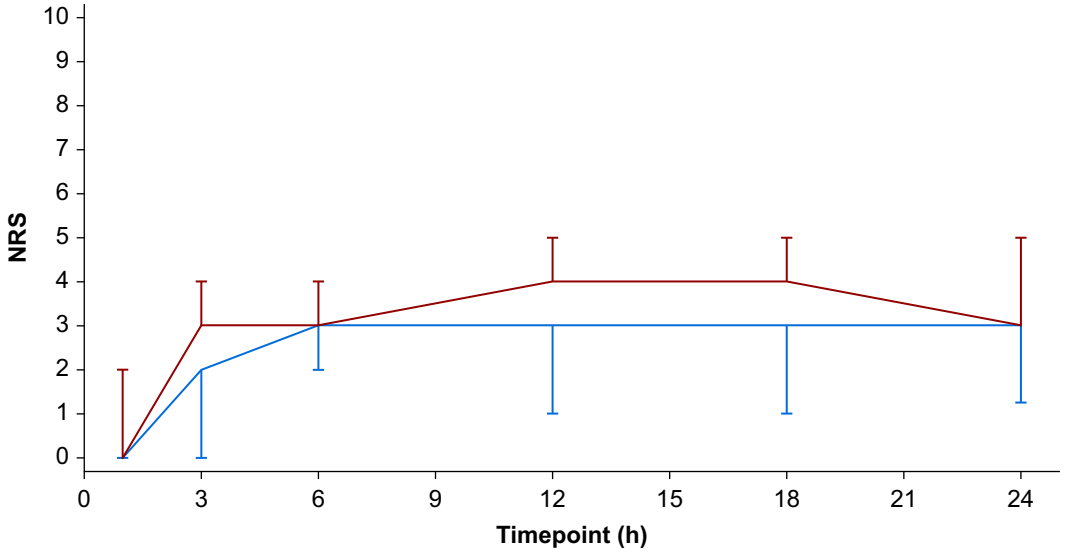

Fig 2. Postoperative NRS scores. Postoperative pain presented as NRS scores in dexmedetomidine (blue line) and control (red line) groups. Values are given as median (interquartile range). NRS, numerical rating scale.

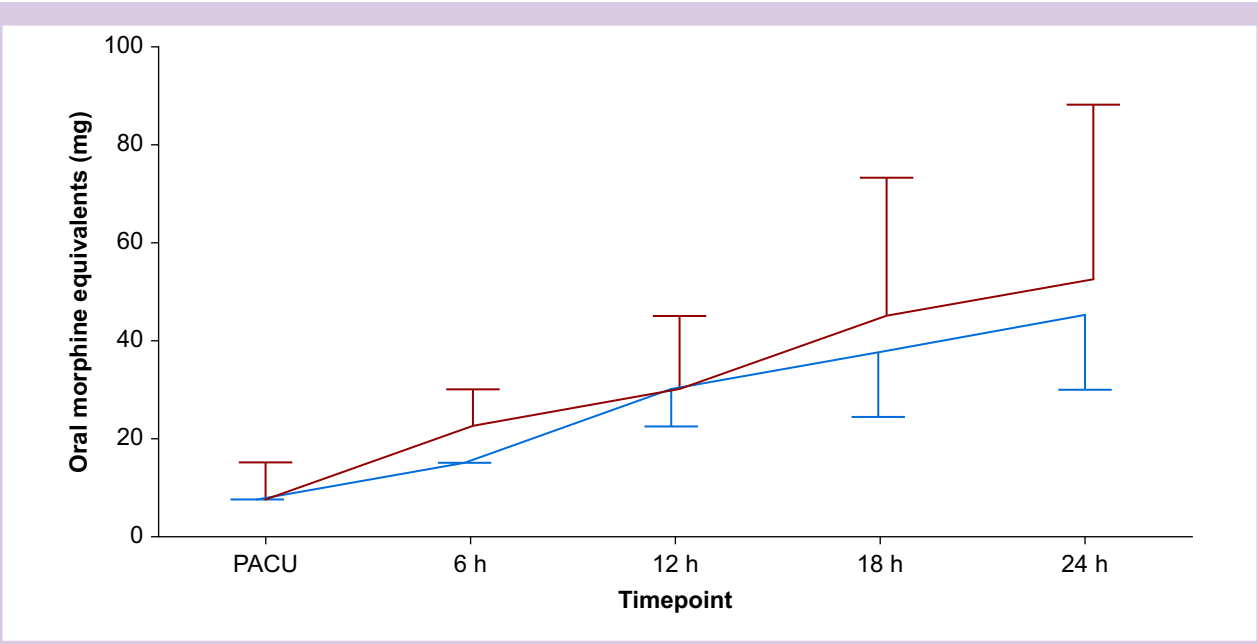

Fig 3. Opioid requirement after surgery. Cumulative opioid requirement of dexmedetomidine (blue line) and control (red line) groups, measured as oral morphine equivalents (OME). Values are given as median (interquartile range). Time zero for the measurement of cumulative opioid requirement was the end of surgery.

Table 2 Postoperative pain scores and opioid requirements. Data are shown as median and interquartile range. DEX, dexmedetomidine group; CTRL, control group; OME, oral morphine equivalent; PACU, postanaesthesia care unit; h, hour; NRS, numerical rating scale of pain.* p<0.05

	DEX group (*n*=49)	CTRL group (*n*=52)	P-value
Cumulative oxycodone consumption			
Cumulative OME in PACU (mg)	8 (8–8)	8 (8–15)	0.471
Cumulative OME at 6 h (mg)	15 (15–23)	23 (15–30)	0.101
Cumulative OME at 12 h (mg)	30 (23–43)	30 (23–45)	0.410
Cumulative OME at 18 h (mg)	38 (24–60)	45 (30–73)	0.256
Cumulative OME at 24 h (mg)	45 (30–68)	53 (38–88)	0.334
Pain scores			
Preoperative NRS (baseline)	1 (0–3)	0 (0–2)	0.231
Postoperative NRS at 1 h	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.345
Postoperative NRS at 3 h	2.0 (0.0–3.0)	3.0 (2.0–4.0)	0.037*
Postoperative NRS at 6 h	3.0 (2.0–3.8)	3.0 (2.0–4.0)	0.298
Postoperative NRS at 12 h	3.0 (1.0–4.3)	4.0 (2.0–5.0)	0.146
Postoperative NRS at 18 h	3.0 (1.0–4.8)	4.0 (2.0–5.0)	0.194
Postoperative NRS at 24 h	3.0 (1.3–5.0)	3.0 (1.0–5.0)	0.675

sedation.[26,27] Compared with sedation with midazolam, dexmedetomidine has been linked to higher levels of patient satisfaction.[28]

Given that intranasal delivery of dexmedetomidine is an off-label application, safety concerns must be addressed. The most frequent side-effects of dexmedetomidine include bradycardia and hypotension, which may restrict its perioperative use. Compared with the intravascular administration route, it has been proposed that extravascular administration of dexmedetomidine could result in cardiovascular stability.[7,29] However, in a recent study it was suggested that intranasal dexmedetomidine is unsuitable for clinical use because of haemodynamic disturbances.[30] In the current study, intranasal dexmedetomidine was well tolerated. There was no difference between the groups in the incidence of bradycardia, tachycardia, hypotension, hypertension, or vasoactive drug requirement. This study suggests that intranasal administration may be suitable because the haemodynamic changes were mild. Furthermore, the fact that intranasal dexmedetomidine did not adversely alter the length of stay or prolong spinal anaesthesia suggests that its use may be appropriate in this patient group. We suggest that while intranasal dexmedetomidine may have a role in this setting, careful patient selection is warranted.

Table 3 Dexmedetomidine dose, perioperative timings, and recovery outcomes. Data are shown as median and interquartile range or *n* (%). CTRL, control group; DEX, dexmedetomidine group; PACU, postanaesthesia care unit.* p<0.05

	DEX group (*n*=49)	CTRL group (*n*=52)	*P*-value
Intranasal dexmedetomidinedose (μg)	80 (70–90)		
Time from study drug to spinal anaesthesia (min)	40 (35–49)	45 (35–60)	0.095
Intraoperative time (min)	68 (53–76)	70 (59–75)	0.480
PACU time (min)	56 (39–91)	55 (47–70)	0.985
Postoperative hospital stay (h)	27 (24–48)	27 (24–48)	0.861
Postoperative nausea (*n*)	9 (18)	14 (27)	0.310
Intraoperative midazolam (mg)	1 (1–2)	2 (1–3)	0.033*
Intraoperative fentanyl (μg)	50 (38–50)	50 (50–50)	0.398

Table 4 Perioperative haemodynamic variables and vasoactive drug requirement. Data are shown as mean and standard deviation or *n* (%). CTRL, control group; DEX, dexmedetomidine group; MAP, mean arterial pressure; HR, heart rate.* p<0.05

	DEX group (*n*=49)	CTRL group (*n*=52)	*P*-value
Before induction of spinal anaesthesia			
Systolic blood pressure (mm Hg)	158 (24)	165 (26)	0.169
Diastolic blood pressure (mm Hg)	83 (12)	87 (12)	0.047*
MAP (mm Hg)	108 (14)	113 (15)	0.054
HR (beats min^{-1})	68 (10)	72 (12)	0.217
Perioperatively			
Bradycardia <50 beats min^{-1} (*n*)	17 (35)	12 (23)	0.271
Tachycardia >100 beats min^{-1} (*n*)	0 (0)	2 (4)	0.495
Hypotension <90 mm Hg (*n*)	4 (8)	3 (6)	0.710
Hypertension >150 mm Hg (*n*)	24 (49)	31 (60)	0.289
Atropine requirement (*n*)	1 (2)	0 (0)	0.485
Ephedrine requirement (*n*)	15 (31)	11 (21)	0.363
Norepinephrine requirement (*n*)	0 (0)	1 (2)	1.000
Labetalol requirement (*n*)	0 (0)	2 (4)	0.491

Limitations

The findings of this study must be seen in light of some limitations. The main limitation of this study is that patient-controlled analgesia could have been used in postoperative pain management, which would have enabled patients to take additional opioid doses when needed. However, the aim for our patients was that they be discharged 24 h after the operation and so it was important to establish oral dosing as soon as possible. It would have been useful also to monitor pain and opioid requirements for longer, but this was not possible because of the short duration of hospitalisation.

Another limitation of our study is the absence of a comparison group administered i.v. dexmedetomidine. As a result, direct comparisons of haemodynamic effects between the intranasal and i.v. routes could not be made. This limits our ability to draw definitive conclusions about the relative safety and efficacy of these two delivery methods.

It is possible that comparing dexmedetomidine only with placebo may have influenced the effectiveness of the study blinding. Adding a third arm with a sedative, such as intranasal midazolam, and recording a sedation score, such as Observer Assessment of Alertness/Sedation Scale (OAA/S), could have provided information and demonstrated the difficulty of distinguishing between the groups. However, previous studies comparing dexmedetomidine with placebo have demonstrated a strong placebo effect, which likely contributed to maintaining effective blinding in our study.[31]

Earlier assessment of satisfaction with pain management might have provided more accurate reflections of patient experiences. The lack of a significant link between dexmedetomidine use and higher overall satisfaction with pain management could be because pain severity evaluations made close to the time of satisfaction assessment tend to have a greater impact on patient perceptions.[24]

Lastly, the study had more dropouts than intended and the total number of patients evaluated in the intervention group was smaller than the group size needed by the power calculation. This may slightly reduce the statistical power of our findings and should be taken into account when interpreting the results.

Future prospects

Intranasally administered dexmedetomidine could provide beneficial premedication in other types of surgery besides knee arthroplasty. Further research should be conducted to find the optimal dosage.

Conclusions

Intranasal dexmedetomidine is an effective premedication that is haemodynamically well tolerated and may reduce postoperative pain and increase short-term patient satisfaction in patients undergoing TKA under spinal anaesthesia.

Authors' contributions

Study design: PU
Supervision: PU, TIS

Data collection: SMT, HH, AK, SM, RL
Figures and tables: SMT, PU
Interpretation of results: SMT, PU, TIS, EL
Writing of the manuscript: all authors

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Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2025.100382.

References

1. Shichman I, Roof M, Askew N, et al. Projections and epidemiology of primary hip and knee arthroplasty in Medicare patients to 2040-2060. *JB JS Open Access* 2023; **8**, e22.00112
2. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res* 2017; **10**: 2287–98
3. Lo LWT, Suh J, Chen JY, et al. Early postoperative pain after total knee arthroplasty is associated with subsequent poorer functional outcomes and lower satisfaction. *J Arthroplasty* 2021; **36**: 2466–72
4. Chabot-Doré AJ, Schuster DJ, Stone LS, Wilcox GL. Analgesic synergy between opioid and α2 -adrenoceptors. *Br J Pharmacol* 2015; **172**: 388–402
5. Yang Q, Ren Y, Feng B, Weng X. Pain relieving effect of dexmedetomidine in patients undergoing total knee or hip arthroplasty: a meta-analysis. *Medicine (Baltimore)* 2020; **99**, e18538
6. Colin PJ, Hannivoort LN, Eleveld DJ, et al. Dexmedetomidine pharmacodynamics in healthy volunteers: 2. Haemodynamic profile. *Br J Anaesth* 2017; **119**: 211–20
7. Iirola T, Vilo S, Manner T, et al. Bioavailability of dexmedetomidine after intranasal administration. *Eur J Clin Pharmacol* 2011; **67**: 825–31
8. Uusalo P, Jätinvuori H, Löyttyniemi E, Kosola J, Saari TI. Intranasal low-dose dexmedetomidine reduces postoperative opioid requirement in patients undergoing hip arthroplasty under general anesthesia. *J Arthroplasty* 2019; **34**: 686–692.e2
9. Seppänen SM, Kuuskoski R, Mäkelä KT, Saari TI, Uusalo P. Intranasal dexmedetomidine reduces postoperative opioid requirement in patients undergoing total knee arthroplasty under general anesthesia. *J Arthroplasty* 2021; **36**: 978–985.e1
10. Laigaard J, Pedersen C, Rønsbo TN, Mathiesen O, Karlsen APH. Minimal clinically important differences in randomised clinical trials on pain management after total hip and knee arthroplasty: a systematic review. *Br J Anaesth* 2021; **126**: 1029–37
11. Lu C, Zhang LM, Zhang Y, et al. Intranasal dexmedetomidine as a sedative premedication for patients undergoing suspension laryngoscopy: a randomized double-blind study. *PLoS One* 2016; **11**, e015419
12. Wolfe TR, Braude DA. Intranasal medication delivery for children: a brief review and update. *Pediatrics* 2010; **126**: 532–7
13. Wu X, Hang LH, Wang H, et al. Intranasally administered adjunctive dexmedetomidine reduces perioperative anesthetic requirements in general anesthesia. *Yonsei Med J* 2016; **57**: 998–1005
14. Koutp A, Hauer G, Leitner L, et al. Less induction time and postoperative pain using spinal anesthesia versus general anesthesia with or without the use of peripheral nerve blocks in total knee arthroplasty. *J Arthroplasty* 2024; **39**: 904–9
15. Yap E, Wei J, Webb C, Ng K, Behrends M. Neuraxial and general anesthesia for outpatient total joint arthroplasty result in similarly low rates of major perioperative complications: a multicentered cohort study. *Reg Anesth Pain Med* 2022; **47**: 294–300
16. Li A, Yuen VM, Goulay-Dufaÿ S, et al. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. *Br J Anaesth* 2018; **120**: 960–8
17. Li YY, Ge DJ, Li JY, Qi B. Sex differences in the morphine-sparing effects of intraoperative dexmedetomidine in patient-controlled analgesia following general anesthesia: a consort-prospective, randomized, controlled clinical trial. *Medicine* 2016; **95**: e3619
18. Thompson AD, Angelotti T, Nag S, Mokha SS. Sex-specific modulation of spinal nociception by alpha2-adrenoceptors: differential regulation by estrogen and testosterone. *Neuroscience* 2008; **153**: 1268–77
19. O'Connor MI. Osteoarthritis of the hip and knee: sex and gender differences. *Orthop Clin North Am* 2006; **37**: 559–68
20. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *Br J Anaesth* 2000; **84**: 6–10
21. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res* 2010; **468**: 57–63
22. Maher DP, Woo P, Wong W, Zhang X, Yumul R, Louy C. Perioperative factors associated with Hospital Consumer Assessment of Healthcare Providers and Systems responses of total hip arthroplasty patients. *J Clin Anesth* 2016; **34**: 232–8
23. Phillips S, Gift M, Gelot S, Duong M, Tapp H. Assessing the relationship between the level of pain control and patient satisfaction. *J Pain Res* 2013; **6**: 683–9
24. Carlson J, Youngblood R, Dalton JA, Blau W, Lindley C. Is patient satisfaction a legitimate outcome of pain management? *J Pain Symptom Manage* 2003; **25**: 264–75
25. Nolan PJ, Delgadillo JA, Youssef JM, Freeman K, Jones JL, Chehrehsa A. Dexmedetomidine provides fewer respiratory events compared with propofol and fentanyl during third molar surgery: a randomized clinical trial. *J Oral Maxillofac Surg* 2020; **78**: 1704–16
26. Shin HJ, Woo Nam S, Kim H, et al. Postoperative delirium after dexmedetomidine versus propofol sedation in healthy older adults undergoing orthopedic lower limb

surgery with spinal anesthesia: a randomized controlled trial. *Anesthesiology* 2023; **138**: 164–71
27. Liu X, Xie G, Zhang K, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: a meta-analysis with trial sequential analysis of randomized controlled trials. *J Crit Care* 2017; **38**: 190–6
28. Barends CRM, Absalom A, Van Minnen B, Vissink A, Visser A. Dexmedetomidine versus midazolam in procedural sedation. a systematic review of efficacy and safety. *PLoS One* 2017; **12**, e0169525
29. Uusalo P, Al-Ramahi D, Tilli I, Aantaa RA, Scheinin M, Saari TI. Subcutaneously administered dexmedetomidine is efficiently absorbed and is associated with attenuated cardiovascular effects in healthy volunteers. *Eur J Clin Pharmacol* 2018; **74**: 1047–54
30. Barends CRM, Driesens MK, Struys MMRF, Visser A, Absalom AR. Intranasal dexmedetomidine in elderly subjects with or without beta blockade: a randomised double-blind single-ascending-dose cohort study. *Br J Anaesth* 2020; **124**: 411–9
31. Preskorn SH, Zeller S, Citrome L, et al. Effect of sublingual dexmedetomidine vs placebo on acute agitation associated with bipolar disorder: a randomized clinical trial. *JAMA* 2022; **327**: 727–36

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