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Original Contribution

Effects of intranasal dexmedetomidine premedication on hemodynamics, oxygenation and bleeding in patients undergoing total knee arthroplasty under spinal anesthesia - a secondary analysis of a prospective, double-blinded, randomized controlled trial (TKADEX)

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HIGHLIGHTS

- Intranasal dexmedetomidine can be used as premedication for patients undergoing total knee arthroplasty under spinal anesthesia.
- Intranasal dexmedetomidine is hemodynamically well tolerated in spinal anesthesia for knee arthroplasty.
- Intranasal dexmedetomidine premedication reduced intraoperative hypertension without affecting surgical bleeding.

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ABSTRACT

Background: Dexmedetomidine is a sedative adjunct with sympatholytic properties. Despite many beneficial effects, hemodynamic effects limit its use.
Methods: We performed a secondary analysis of the data from TKADEX study. This single-center, double-blind, two-arm study compared intranasal dexmedetomidine premedication (1 μg kg-1) with intranasal saline in 101 planned subjects undergoing total knee arthroplasty (TKA). We analyzed the perioperative hemodynamics, oxygenation, amount of intraoperative bleeding and perioperative change in hemoglobin and thrombocytes.
Results: Compared to baseline measurements, mean arterial pressure (MAP) decreased in the dexmedetomidine group 36.3 (1.7) mmHg (95 % CI 32.9–39.7; $p < 0.001$) and in the placebo group 26.5 (1.7) mmHg (95 % CI 23.2–29.7; $p < 0.001$), and heart rate (HR) in the dexmedetomidine group 11.6 (1.3) bpm (95 % CI 9.1–14.1; $p < 0.001$) and in the placebo group 9.7 (1.2) bpm (95 % CI 7.3–12.2; $p < 0.001$) after induction of spinal anesthesia. Patients in the dexmedetomidine group had lower intraoperative MAP (maximal difference − 8.5 (2.5) mmHg; 95 % CI -13.5 - -3.5; $p < 0.001$) and HR (maximal difference − 6.1 (2.2) bpm; 95 % CI -10.5 - -1.7; $p = 0.007$) compared to the placebo group. There was higher incidence of intraoperative hypertension in the placebo group ($p = 0.03$). There was no difference in oxygenation, in the incidence of intraoperative bradycardia, tachycardia or hypotension, in the amount of intraoperative bleeding or in the change in perioperative blood count between the groups.
Conclusions: Intranasal dexmedetomidine appears to be hemodynamically well tolerated premedication for patients undergoing TKA under spinal anesthesia. It appears to lower the incidence of intraoperative hypertension without effects on intraoperative bleeding.

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1. Introduction

Dexmedetomidine is a potential anesthetic adjuvant, with several benefits for the perioperative period including anxiolysis, analgesia, antiemesis and delirium prevention [1–3]. However, studies indicating possible advantages have raised concerns about perioperative use of dexmedetomidine due to the increased risk of bradycardia and hypotension [4]. Overall incidence of clinically significant hemodynamic instability, defined as hypotension or bradycardia necessitating interventions, reportedly ranges from 5 % to 26 % in surgical patients [5–7].

It has been suggested that extravascular administration methods such as intranasal (IN) and subcutaneous routes may reduce dexmedetomidine's hemodynamic effects. In contrast to intravenous administration, the peak concentration of dexmedetomidine in the plasma remains lower, leading to attenuated hemodynamic effects [8–10]. However, data on hemodynamic effects after extravascular dexmedetomidine administration are sparse and mostly based on healthy volunteers [8–10].

Additional research is necessary to evaluate hemodynamic effects of extravascular dexmedetomidine administration. Moreover, dexmedetomidine has been proposed to reduce perioperative blood loss [11]. However, there are no studies on IN dexmedetomidine on this subject.

This is a secondary analysis of TKADEX study, which evaluated the effect of IN dexmedetomidine on postoperative pain, opioid requirement and patient satisfaction compared to placebo in patients undergoing total knee arthroplasty (TKA) under spinal anesthesia. The primary aim was to determine the effect of IN dexmedetomidine premedication on perioperative hemodynamics and oxygenation. Our secondary aims were effects of dexmedetomidine on intraoperative bleeding and perioperative hemoglobin and platelets.

Our hypothesis was that dexmedetomidine would decrease heart rate and blood pressure, potentially leading to reduced bleeding. We also hypothesized that dexmedetomidine use would not increase hemodynamic or respiratory adverse effects.

2. Materials and methods

This was a secondary analysis of TKADEX study [12], which evaluated the effect of IN dexmedetomidine on postoperative pain, opioid consumption and patient satisfaction. 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.

The sample size was initially calculated for the primary outcomes related to pain (NRS), and not specifically for the hemodynamic variables assessed in this secondary analysis.

2.1. Ethics approval and consent to participate

Ethical approval was received from all relevant institutional review boards (Ethics Committee of the Hospital District of Southwest Finland and by the National Agency of Medicines, Fimea), and all participants provided informed consent prior to enrolment.

2.2. Patient population

A prospective double-blind randomized controlled trial was used. Patients with ASA class I-III, aged between 35 and 80 years, weighing between 50 and 100 kg, and scheduled for elective unilateral TKA under spinal anesthesia, 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 in preoperative medical examination (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 mmHg, history of cardiac disease (valvular insufficiency, severe left ventricular dysfunction) or abnormal ECG rhythm (bradycardia <50/min, 2nd or 3rd-degree AV-block, pacemaker), the use of drugs or natural products known to induce or inhibit enzymes, as well as 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 of the approved study protocol that was likely to affect the study outcomes (e.g. postponing surgery, transition to general anesthesia or administering pain medications not included in the study protocol) were considered as protocol breaches.

2.3. Study drug administration

After giving informed consent, the patients were randomized to receive 1 μg/kg of IN dexmedetomidine (DEX-group) or an equivalent dose of IN saline (PLA-group) approximately 45 min before anticipated spinal anesthesia using an LMA MAD Nasal™ -device. A senior anesthesiologist administered the study drug to the patient in a semi-recumbent position. The amount of dexmedetomidine was rounded to the nearest ten micrograms to accommodate practical dosing. The dose used in this study was based on previous studies on the use of IN dexmedetomidine in adult patients [13,14] and practical considerations regarding volume that can be effectively administered intranasally. Randomization was performed by a biostatistician and the hospital pharmacy prepared the study drugs. Both the medical staff and patients were blinded.

2.4. Preoperative patient preparation and anesthetic management

The patients had fasted a minimum of 6 h prior to administration of the study drug and time of anticipated anesthesia/sedation. During this period only water intake in small amounts was allowed. All patients received preoperatively 1000 mg of oral paracetamol. Spinal anesthesia was performed using levobupivacaine (Bicain Pond Spinal 5 mg/ml) 2,0–2,5 ml, the amount depending on the consideration of the anesthesiologist responsible for the case. The mean arterial pressure (MAP) target was between 65 and 75 mmHg, depending on the patient's age and disease history. Peripheral oxygen saturation (SpO2) target was over 95 % and supplemental oxygen was delivered with nasal cannula if needed. If the patient requested additional intraoperative sedation, 1 mg of intravenous midazolam was given with repeated doses if necessary. If the patient requested additional pain medication, 50 μg of intravenous fentanyl was given with repeated doses if necessary. All patients received 1000 mg of intravenous tranexamic acid.

2.5. Intraoperative vital measurements and definition of intraoperative hemodynamic instability

Heart rate (HR), noninvasive arterial pressure including diastolic (DAP), mean (MAP) and systolic arterial pressure (SAP), and peripheral arterial oxygen saturation (SpO2) were monitored and recorded at baseline (before the administration of dexmedetomidine or placebo). These vitals were measured at 5-min intervals throughout the operation and at 15-min intervals in the postoperative care unit.

Intraoperative hypotension was defined as systolic blood pressure < 90 mmHg, hypertension as systolic blood pressure > 150 mmHg, tachycardia as HR > 100 bpm, bradycardia as HR < 50 bpm and severe bradycardia as HR < 40 bpm. The cutoffs were chosen based on our local practices and supported by previous studies evaluating blood pressure thresholds that may warrant intervention [15]. Intraoperative phase included time from incision to wound closure.

2.6. Other perioperative measurements

Cumulative consumption of atropine, ephedrine, noradrenaline and labetalol were recorded. Hemoglobin level (Hb) and platelet level before and after surgery (first postoperative day) were recorded. Blood loss was estimated based on a combination of suction canister volume (after accounting for irrigation fluids) and weighing of blood on surgical sponges and drapes.

2.7. Outcomes

Our primary outcome measures were to evaluate the perioperative changes in MAP and HR from the baseline during anesthesia induction and at 30, 60, 90, 120 and 150 min thereafter. Changes in SAP, DAP and SpO2 were considered key secondary hemodynamic outcomes. Other secondary outcomes were the amount of intraoperative bleeding, change in perioperative hemoglobin and platelets, and incidence of intraoperative bradycardia, tachycardia, hypotension and hypertension.

2.8. Data analysis

The analyses were performed with JMP Pro 13.0 for Mac (SAS Institute Inc., Cary, NC, USA) and SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). The visual evaluation together with Shapiro-Wilks test was used to assess normality assumptions. Linear mixed models for repeated measurements were used for hemodynamics variables to study whether mean changes over time differed between DEX and PLA groups. The model included group (between-subject factor), time (within-subject factor) and group by time interaction. In addition, age and sex were included in the model. Compound symmetry covariance structure was fitted to the data. Kenward-Roger correction was used for degrees of freedom. Normality assumption was checked with studentized residuals. 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. Association between two categorical variables were tested using chi-square analysis. $P < 0.05$ (two-tailed) was considered statistically significant. Our primary outcome measures were to evaluate the perioperative changes in MAP and HR from the baseline during anesthesia induction and at 30, 60, 90, 120 and 150 min thereafter. Changes in SAP, DAP and SpO2 were considered key secondary hemodynamic outcomes. Other secondary outcomes were the amount of intraoperative bleeding, change in perioperative hemoglobin and platelets, and incidence of intraoperative bradycardia, tachycardia, hypotension and hypertension.

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. Qualitative results are expressed as numbers and frequencies.

3. Results

Altogether, 468 patients were assessed for eligibility, and a total of 110 patients were recruited for the study. Total of 101 patients were included in the final analysis: 49 patients in the dexmedetomidine (DEX) group and 52 patients in the placebo (PLA) group. There was no significant difference between the two groups regarding patients' characteristics. Patient characteristics are presented in Table 1. CONSORT flow diagram of the study is presented in Supplemental Fig. 1.

3.1. Noninvasive arterial blood pressure

Compared to baseline measurement, MAP was lower in the PLA group 30, 60, 90, 120 and 150 min after induction of spinal anesthesia, and in the DEX group during induction of spinal anesthesia and 30, 60, 90 and 120 min thereafter ($p < 0.001$ for all comparisons). Compared to PLA group, MAP was lower in the DEX group during induction of spinal anesthesia (mean difference − 6.1 (2.2) bpm; 95 % CI -10.4 - -1.7; $p = 0.007$), 60 min (mean difference − 7.5 (2.5) bpm; 95 % CI -13.5 - -3.5; $p < 0.001$), 90 min (mean difference − 7.5 (2.5) bpm; 95 % CI -13.5 - -3.5; $p < 0.001$), 120 min (mean difference − 7.5 (2.5) bpm; 95 % CI -13.5 - -3.5; $p < 0.001$) and 150 min (mean difference − 5.7 (2.6) bpm; 95 % CI -10.8 - -0.7; $p = 0.026$) (Fig. 1).

Table 1
Patient characteristics.

	All patients ($n = 101$)	DEX ($n = 49$)	PLA ($n = 52$)
Age	67.3 (7.1)	68.0 (6.0)	66.5 (7.9)
Weight (kg)	80 (73–90)	80 (73–89)	81 (71–90)
BMI (m^2 kg −1)	29.0 (3.9)	28.7 (3.6)	29.2 (4.2)
Female	80 (79 %)	39 (79 %)	41 (79 %)
ASA class			
1	13 (13 %)	5 (10 %)	8 (15 %)
2	77 (76 %)	38 (78 %)	39 (75 %)
3	11 (11 %)	6 (12 %)	5 (10 %)

Data are shown as mean (SD), interquartile ranges (IQR), or n (%). ASA, American Society of Anesthesiologists; BMI, body mass index; IN DEX, intranasal dexmedetomidine; DEX, dexmedetomidine group; PLA, control group.

Compared to baseline measurement, SAP was higher in the PLA group during induction of spinal anesthesia and lower at 30, 60, 90, 120 and 150 min after induction of spinal anesthesia and in the DEX group 30, 60, 90 and 120 min after induction of spinal anesthesia ($p < 0.001$ for all comparisons). (Fig. 1, Table 2) Compared to PLA group, SAP was lower in the DEX group during induction of spinal anesthesia (mean difference − 8.9 mmHg; 95 % CI -16.6 - -1.2; $p = 0.024$), and 60 min (mean difference − 11.6 (3.9) mmHg; 95 % CI -19.4 - -3.8; $p = 0.004$), 90 min (mean difference − 13.4 (3.9); 95 % CI –22.2 - -5.6; $p < 0.001$), 120 min (mean difference − 15.2 (4.0) mmHg; 95 % CI -23.0 - -7.4; $p < 0.001$) and 150 min (mean difference − 10.6 (4.0) mmHg; 95 % CI -18.5 - -2.7; $p = 0.009$) after induction of spinal anesthesia. For other time points, the differences were not statistically significant (Fig. 1).

Compared to baseline measurement, DAP was lower in the PLA group at 30, 60, 90, 120 and 150 min after induction of spinal anesthesia, and in the DEX group during induction of spinal anesthesia and 30, 60, 90, 120 and 150 min thereafter ($p < 0.001$ for all comparisons). Compared to the PLA group, DAP was lower in the DEX group during induction of spinal anesthesia (mean difference − 4.6 (2.0) bpm; 95 % CI -8.6 - - 0.6; $p = 0.028$), 60 min (mean difference − 5.3 (2.1) bpm; 95 % CI -9.2 - - 1.2; $p = 0.011$), 90 min (mean difference − 5.8 (2.1) bpm; 95 % CI -9.8 - -1.7; $p = 0.017$) and 120 min (mean difference − 5.0 (2.1) bpm; 95 % CI -9.0 - -0.9; $p = 0.017$) (Fig. 1).

3.2. Heart rate

Compared to baseline measurement, HR decreased in the PLA group 30, 60 and 90 min after induction of spinal anesthesia, and in the DEX group 30, 60, 90 and 120 min after induction of spinal anesthesia. For other timepoints, the decrease in HR from the baseline was not statistically significant (Fig. 2, Table 4).

Compared to the PLA group, HR was lower in the DEX group 120 min after induction of spinal anesthesia (mean difference − 6.1 (2.2) bpm; 95 % CI -10.5 - -1.7; $p = 0.007$). For other time points, the difference was not statistically significant (Fig. 2, Table 4).

3.3. Vasoactive requirement and hemodynamic adverse events

Compared to the DEX group, there was a higher incidence of intraoperative hypertension in the PLA group ($p = 0.033$). There was no difference in the incidence of bradycardia, severe bradycardia, tachycardia or hypotension, or in noradrenaline, ephedrine, or labetalol requirement between the groups. (Table 3).

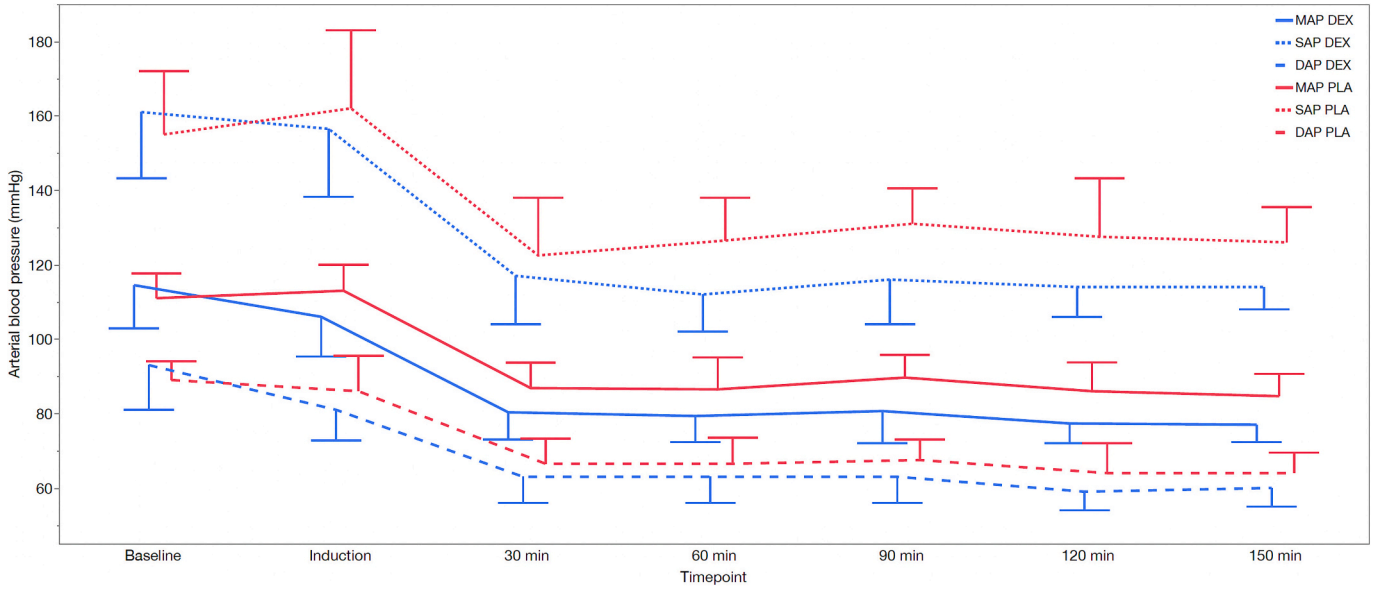

Fig. 1. Perioperative median (IQR) systolic, mean and diastolic arterial pressure. SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure, DEX, dexmedetomidine group; PLA, placebo group.

Table 2
Diastolic, mean and systolic arterial blood pressure changes from the baseline in dexmedetomidine (DEX) and placebo (PLA) groups after induction of spinal anesthesia.

DAP	MD	SE	Lower	Upper	p		MD	SE	Lower	Upper	p
DEX						PLA					
Time from induction											
0 min	−8.22	−1.55	−5.18	−11.26	< 0.001		−1.81	−1.51	1.15	−4.77	0.23
30 min	−27.6	−1.56	−24.54	−30.66	< 0.001		−23.23	−1.53	−20.22	−26.24	< 0.001
60 min	−28.49	−1.56	−25.42	−31.55	< 0.001		−21.46	−1.53	−18.45	−24.47	< 0.001
90 min	−28.43	−1.56	−25.37	−31.5	< 0.001		−20.86	−1.53	−17.84	−23.87	< 0.001
120 min	−31.48	−1.58	−28.38	−34.59	< 0.001		−24.75	−1.53	−21.74	−27.76	< 0.001
150 min	−30.17	−1.61	−27.00	−33.33	< 0.001		−25.41	−1.53	−22.40	−28.43	< 0.001
MAP	MD	SE	Lower	Upper	p		MD	SE	Lower	Upper	p
DEX						PLA					
Time from induction											
0 min	−6.7	−1.46	−3.84	−9.56	< 0.001		1.9	−1.41	4.67	−0.88	0.181
30 min	−33.34	−1.69	−30.02	−36.66	< 0.001		−26.47	−1.66	−23.21	−29.74	< 0.001
60 min	−34.36	−1.69	−31.04	−37.69	< 0.001		−24.31	−1.66	−21.05	−27.58	< 0.001
90 min	−36.34	−1.71	−32.98	−39.7	< 0.001		−25.25	−1.66	−21.99	−28.52	< 0.001
120 min	−36.34	−1.71	−32.98	−39.7	< 0.001		−25.25	−1.66	−21.99	−28.52	< 0.001
150 min	−34.4	−1.75	−30.96	−37.83	< 0.001		−26.11	−1.66	−22.85	−29.38	< 0.001
SAP	MD	SE	Lower	Upper	p		MD	SE	Lower	Upper	p
DEX						PLA					
Time from induction											
0 min	−3.66	−2.63	1.51	−8.83	0.165		9.31	−2.56	14.34	4.29	< 0.001
30 min	−44.59	−2.65	−39.38	−49.79	< 0.001		−33.13	−2.61	−28.01	−38.25	< 0.001
60 min	−45.93	−2.65	−40.73	−51.13	< 0.001		−30.22	−2.61	−25.1	−35.34	< 0.001
90 min	−43.69	−2.65	−38.48	−48.89	< 0.001		−26.21	−2.61	−21.09	−31.33	< 0.001
120 min	−45.74	−2.68	−40.47	−51.01	< 0.001		−26.47	−2.61	−21.35	−31.59	< 0.001
150 min	−42.45	−2.74	−37.06	−47.83	< 0.001		−27.73	−2.61	−22.61	−32.85	< 0.001

MD, mean difference; SE, standard error; DEX, dexmedetomidine group; PLA, control group; DAP, diastolic arterial pressure; MAP, mean arterial pressure; SAP, systolic arterial pressure.

3.4. Peripheral oxygen saturation and requirement of supplemental oxygen

Compared to baseline measurement, SpO2 was lower in both groups 30, 60, 90, 120 and 150 min after induction of spinal anesthesia, but not during the induction of spinal anesthesia. There was no statistically significant difference between the groups in SpO2 at any time points (Fig. 3, Table 4). Intraoperative median fraction of inspired oxygen was 0.28 (0.23–0.28) for DEX group and 0.28 (0.21–0.28) for PLA group ($p = 0.44$).

3.5. Intraoperative bleeding and changes in perioperative blood count

There was no difference in intraoperative blood loss ($p = 0.66$) or change in hemoglobin ($p = 0.52$) or change in thrombocytes ($p = 0.55$) between the two groups (Table 3).

3.6. Supplemental sedation and analgesia

In the dexmedetomidine group, 82 % of patients (40/49) required supplemental midazolam, while in the control group, 94 % of patients (48/51) received midazolam. The dexmedetomidine group required less

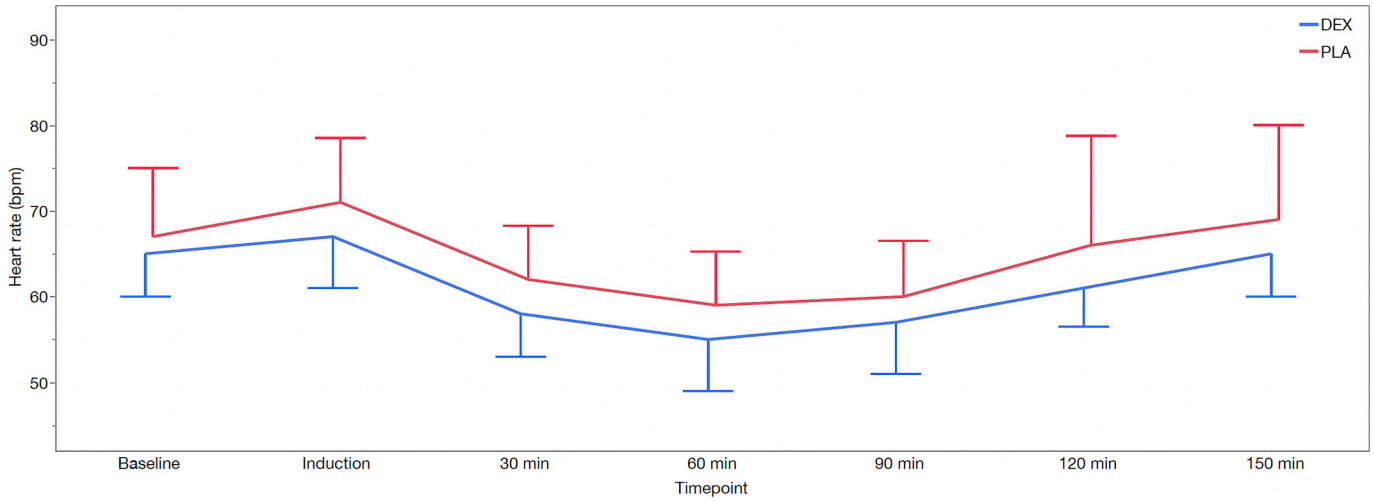

Fig. 2. Perioperative median (IQR) heart rate. HR, heart rate; DEX, dexmedetomidine group; PLA, placebo group.

Table 3
Perioperative characteristics, intraoperative hemodynamic adverse effects, intraoperative bleeding and changes in perioperative blood count.

	DEX (n = 49)	PLA (n = 52)	p
Intranasal dexmedetomidine dose (mcg)	80 (70–90)		
Intrathecal bupivacaine dose (mg)	12 (11–13)	12 (11–13)	0.65
Time from study drug to SPA (min)	40 (35–49)	45 (35–60)	0.10
Intraoperative time (min)	68 (53–76)	70 (59–75)	0.48
Bradycardia (HR <50 bpm)	14 (29 %)	9 (17 %)	0.24
Severe bradycardia (HR <40 bpm)	1 (2 %)	1 (2 %)	1.00
Tachycardia (HR >100 bpm)	0 (0 %)	1 (2 %)	0.33
Hypotension (SAP <90 mmHg)	4 (8 %)	3 (6 %)	0.71
Hypertension (SAP >150 mmHg)	4 (49 %)	13 (52 %)	*0.033**
Atropine	1 (2 %)	0 (0 %)	0.49
Ephedrine	15 (31 %)	11 (21 %)	0.36
Noradrenaline	0 (0 %)	1 (2 %)	1.00
Labetalol	0 (0 %)	2 (4 %)	0.49
Intraoperative blood loss (ml)	100 (50–150)	100 (50–137,5)	0.66
Change in Hb (Pre-op vs POD1, g/dl)	−22 (−29--16.5)	−22 (−30 --17)	0.52
Change in Trom (Pre-op vs POD1, xE9/l)	−25 (−50.5--6)	−33 (−46 --12)	0.55

Data are shown as interquartile ranges (IQR), or n (%). DEX, dexmedetomidine group; PLA, control group: SPA, spinal anesthesia; HR. heart rate; SAP, systolic arterial pressure; Trom, platelets; Pre-op, preoperative; POD1, first post-operative day.

intraoperative midazolam ($p = 0.033$). The median (IQR) dose of midazolam administered intraoperatively was 1 mg (1–2 mg) in the dexmedetomidine group, compared to 2 mg (1–3 mg) in the placebo group. Intraoperative fentanyl consumption was comparable between groups, with no statistically significant difference ($p = 0.398$).

4. Discussion

To our knowledge, the present study is the first to examine the effects of IN dexmedetomidine on hemodynamics and bleeding in patients undergoing TKA under spinal anesthesia. Compared to placebo, IN dexmedetomidine lowers blood pressure and heart rate, but the effects are small and generally do not require treatment. Patients that received IN dexmedetomidine had less intraoperative hypertension, but dexmedetomidine was found to have no effect on the amount of surgical bleeding or on perioperative blood count.

Dexmedetomidine has numerous characteristics, which make it an excellent choice for procedural sedation and anesthetic adjuvant. However, the wider application of its perioperative use has been limited by the fear of hemodynamic side effects. Intravenous administration of dexmedetomidine causes a biphasic blood pressure response, with an initial phase of transient hypertension, followed by dose-dependent bradycardia and hypotension. [16] In healthy volunteers, HR typically decreases by 15–20 % from the baseline and MAP by about 10–20 %. [4,16] Although the hemodynamic alterations are often well tolerated in healthy volunteers, patients with comorbidities may be negatively impacted by the hemodynamic effects of dexmedetomidine. Our findings on ASA 1–3 patients support the hypothesis that the IN route, which provides a slower and lower peak plasma concentration, may mitigate the hemodynamic impact commonly seen with intravenous administration in patients undergoing surgery [5–7].

Older age, lower baseline blood pressure, obesity, and female sex have all been identified as risk factors for hemodynamic instability linked to dexmedetomidine [6,17]. This is relevant for TKA patients, who are often old, have a high BMI, and are mostly female—all of which are associated with severe knee osteoarthritis [18]. Despite the high prevalence of these risk factors in our study population, IN dexmedetomidine was well-tolerated.

Blood pressure and HR decreased significantly in both groups after induction of spinal anesthesia. The extent of the observed hemodynamic alterations cannot be interpreted as clinically important, despite their statistical significance. The slight hemodynamic changes that intranasal dexmedetomidine causes are unlikely to affect standard anesthetic care, which supports its practicality. It is difficult to isolate the effect of IN dexmedetomidine on blood pressure and HR, since spinal anesthesia alone may cause hemodynamic instability [19]. However, since there was no significant difference in the incidence of perioperative hemodynamic adverse events between the groups, hemodynamic changes appear to be mostly attributable to spinal anesthesia and surgery. Notably, our patients were not given propofol for sedation, which is often linked with even higher intraoperative hemodynamic instability than after dexmedetomidine [20]. Avoiding propofol helped to limit possible overlap in sedation-induced hypotension and bradycardia, making it easier to identify the effects of IN dexmedetomidine.

Usually anesthesiologists battle with hypotension after anesthesia induction, but too high blood pressure can also be problematic. Dexmedetomidine may stabilize hemodynamics and decrease the antihypertensive requirements, but on the other hand intravenous dexmedetomidine is associated with transient hypertension [21]. We found that compared to the placebo group, the incidence of intraoperative hypertension was significantly lower in patients who had received IN dexmedetomidine. Moreover, there was a significant increase in SAP compared to baseline in the placebo group during

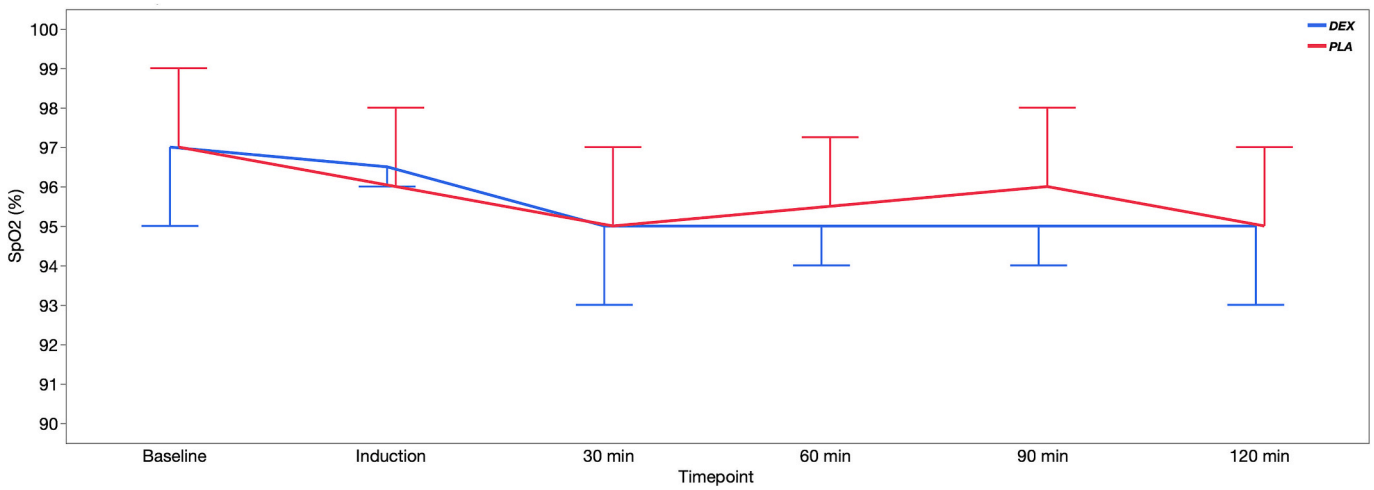

Fig. 3. Perioperative median (IQR) peripheral oxygen saturation. SpO2, peripheral oxygen saturation; DEX, dexmedetomidine group; PLA, placebo group.

Table 4
Heart rate and peripheral oxygenation changes from the baseline in dexmedetomidine (DEX) and placebo (PLA) groups after induction of spinal anesthesia.

Heart rate	MD	SE	Lower	Upper	p	MD	SE	Lower	Upper	p
	DEX					PLA				
Time from induction										
0 min	0.74	−1.25	3.2	−1.73	0.557	2.01	−1.22	4.41	−0.38	0.100
30 min	−6.8	−1.26	−4.32	−9.28	< 0.001	−5.61	−1.24	−3.17	−8.06	< 0.001
60 min	−11.62	−1.26	−9.14	−14.1	< 0.001	−9.74	−1.24	−7.3	−12.18	< 0.001
90 min	−10.11	−1.26	−7.62	−12.59	< 0.001	−8.00	−1.24	−5.56	−10.45	< 0.001
120 min	−4.00	−1.28	−1.48	−6.51	0.002	0.28	−1.24	2.73	−2.16	0.819
150 min	−1.44	−1.31	1.12	−4.01	0.270	2.52	−1.24	4.96	0.08	0.043
SpO2	MD	SE	Lower	Upper	p	MD	SE	Lower	Upper	p
	DEX					PLA				
Time from induction										
0 min	0.07	0.36	−0.78	0.645	0.852	−0.31	0.35	−0.39	1.002	0.383
30 min	−1.86	0.37	1.14	2.585	< 0.001	−1.74	0.36	1.03	2.442	< 0.001
60 min	−1.29	0.37	0.57	2.016	< 0.001	−0.96	0.36	0.25	1.67	0.008
90 min	−1.22	0.37	0.51	1.941	< 0.001	−0.96	0.36	0.25	1.661	0.008
120 min	−1.49	0.37	0.76	2.218	< 0.001	−1.50	0.36	0.8	2.209	< 0.001
150 min	−1.79	0.38	1.04	2.536	< 0.001	−2.15	0.36	1.44	2.854	< 0.001

MD, mean difference; SE, standard error; DEX, dexmedetomidine group; PLA, control group; SpO2, peripheral oxygen saturation.

induction of spinal anesthesia. Transient hypertensive effects after administration of IN administration are mild, because plasma concentrations remain lower. We did not find any significant difference in labetalol requirement. Only two patients in the placebo group required labetalol for intraoperative blood pressure management, while none of the patients in the dexmedetomidine group received it. Due to the low number of events, meaningful statistical comparison is limited.

While earlier studies have observed reduced intraoperative bleeding with dexmedetomidine, we did not find any significant differences between the groups [11,22]. In previous literature, hypotension has been suggested as the primary mechanism for reduced bleeding, but since our patients were not hypotensive, this might account for the discrepancy. Interestingly, in one previous study, blood loss was reduced without significant hemodynamic changes, suggesting alternative mechanisms, such as dexmedetomidine's possible effects on coagulation and stress response [11,23]. α_2-adrenergic receptors are expressed on platelets, and their activation could theoretically influence platelet function or aggregation.

Although hemodynamic alterations after IN administration of dexmedetomidine may be milder than with intravenous administration, they might still be harmful for fragile patients [24]. We suggest that careful patient selection and observation of hemodynamic parameters is warranted to avoid possible complications. We excluded patients with low preoperative blood pressure or heart rate and screened electrocardiogram for conduction abnormalities.

4.1. Limitations

This secondary analysis was not powered specifically for these outcomes, which may limit statistical robustness. Without an intravenous dexmedetomidine group, direct comparisons between administration routes are not possible, making the results preliminary. Relative reductions in blood pressure and duration of hypotension were not included in the analysis, which is a limitation. Also, single-center design is a limitation of our study as it may affect the generalizability of our findings. Including a standardized sedation scale would improve the objectivity of sedation assessment in future studies. There may have been variations in the depth of sedation as dosage of midazolam was determined by clinical judgment.

4.2. Future prospects

Future research should directly compare IN and intravenous administration together with an appropriately powered study to better characterize hemodynamic responses and establish the safety and effectiveness of IN dexmedetomidine as perioperative adjunct. In future studies, it would be important to include additional hemodynamic parameters, such as the relative blood pressure reduction and the duration

of hypotensive episodes, to more comprehensively characterize intraoperative circulatory changes.

5. Conclusions

Intranasal dexmedetomidine appears to be hemodynamically well tolerated premedication for patients undergoing total knee arthroplasty under spinal anesthesia. It appears to lower the incidence of intraoperative hypertension without effects on intraoperative bleeding.

CRediT authorship contribution statement

Suvi-Maria Tiainen: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Atte Koskinen:** Writing – review & editing, Data curation. **Sanna Mäkelä:** Writing – review & editing, Data curation. **Ruut Laitio:** Writing – review & editing, Investigation. **Eliisa Löyttyniemi:** Writing – review & editing, Formal analysis. **Keijo Mäkelä:** Writing – review & editing, Investigation. **Carl-Olof Pirttikangas:** Writing – review & editing, Data curation. **Teijo I. Saari:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Panu Uusalo:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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