

# The impact of dexmedetomidine on tourniquet induced systemic effects in total knee arthroplasty under spinal anesthesia: a prospective randomized, double-blinded study.

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## Research article

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# Abstract

**Background:** Clinical studies on the impact of dexmedetomidine on tourniquet-induced systemic effects have been inconsistent. We investigated the impact of dexmedetomidine on tourniquet-induced systemic effects including pain outcomes in patients undergoing total knee arthroplasty under spinal anesthesia.

**Methods:** Eighty patients were randomly assigned to either control (CON) or dexmedetomidine (DEX) group. DEX group received an intravenous loading dose of 0.5 µg/ kg DEX over 10 minutes, followed by a continuous infusion of 0.5 µg/ kg/h from 10 minutes before the start of surgery until completion. The CON group received the same calculated volume of normal saline. Pain outcomes and metabolic and coagulative changes after tourniquet application and after tourniquet release were investigated.

**Results:** The frequency of fentanyl administration postoperatively, patient-controlled analgesia (PCA) volume at 24 hours postoperatively, total PCA volume consumed in 48 hours postoperatively, and VAS score for pain at 24 and 48 hours postoperatively were significantly lower in the DEX group than in the CON group.

Ten minutes after tourniquet release, the DEX group showed significantly higher pH and lower lactate level than those in the CON group. Antithrombin III activity and body temperature 10 minutes after tourniquet release were significantly lower in the DEX group than in the CON group.  $\text{Ca}^{2+}$ ,  $\text{K}^+$ ,  $\text{HCO}_3^-$ , base excess, and  $\text{PCO}_2$  levels 10 minutes after tourniquet release were not significantly different between the two groups.

**Conclusion:** We showed that DEX attenuated pain and hemodynamic, metabolic, and coagulative effects induced by tourniquet. However, these metabolic and coagulative changes were within normal limits. Therefore, DEX could be used as an analgesic adjuvant, but should not be considered for routine use to prevent the systemic effects induced by tourniquet use.

## Introduction

Tourniquet, which is widely used in surgeries of the extremities to induce a bloodless surgical field, can cause hemodynamic reaction, ischemia, and reperfusion injury, secondary to its inflation and deflation [1, 2]. The systemic effects associated with tourniquet depend on the tourniquet phase, duration of tourniquet application, size of the ischemic area, type of anesthesia administered, and underlying cardiovascular condition of the patient [3].

The clinical findings regarding the effects of dexmedetomidine (DEX) on tourniquet-induced systemic effects have been inconsistent [4, 5]. Clinical and experimental studies focusing on the reduction of tourniquet-induced systemic effects have shown that the use of ischemic pre-conditioning agents, anesthetic agents, various anesthetic methods, and antioxidant agents can control tissue injury [6–10].

It has been shown that alpha-2 receptor agonists, including DEX, have a preventive effect in various ischemia-reperfusion injury models; these agonists are effective in preventing hemodynamic reactions induced by tourniquet application during surgeries of the extremities by preventing the release of catecholamines [11–13]. Few studies have reported the effects of DEX on pain outcomes and metabolic, coagulative, and temperature changes by tourniquet-induced ischemia-reperfusion injury.

We hypothesized that DEX could attenuate the systemic effects induced by tourniquet use. Therefore, we investigated the impact of DEX on pain outcomes and metabolic, coagulative, temperature, and hemodynamic changes in patients undergoing total knee arthroplasty (TKA) under spinal anesthesia.

## Materials And Methods

### Study design

We obtained ethical approval for this study (Registration No. 2020 – 0224) from the institutional review board in March 2020, and informed written consent was obtained from all participants. Our study was also listed on the [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04307290) at March 13th, 2020.

### Inclusion criteria

A total of 80 patients aged between 20 and 80 years, with American Society of Anesthesiologists (ASA) physical status class I–III, who were scheduled to undergo elective TKA were enrolled in this study.

### Exclusion criteria

Patients with history of rheumatoid arthritis, diabetes mellitus, hepatic or renal disease, allergy to the drug being studied, heart block greater than first degree, left ventricular ejection fraction < 55%, or chronic administration of anti-inflammatory drugs or opioids were excluded. Patients with tourniquet duration of < 60 minutes or > 150 minutes or those with conversion to general anesthesia during surgery were also excluded.

### Randomization

Randomization sequence was created using the Stata 9.0 (Stata Corp, College Station, TX, USA) statistical software and was stratified by center with a 1:1 allocation using random block sizes of four. Assignments were concealed in sealed envelopes. Participants were randomly assigned following simple randomization procedures (computerized random numbers) to the DEX group (n = 40), which received intravenous DEX (0.5 µg/kg bolus over 10 minutes, followed by 0.5 µg/kg/h infusion from 10 minutes before the start of surgery to the end of surgery); or to the CON group (n = 40), which received an equivalent volume of normal saline bolus over 10 minutes and infusion of placebo from 10 minutes before the start of surgery until the end of the surgery.

All patients, attending anesthesiologists responsible for patient care, and nurses were blinded to the anesthetic agent during the study period.

## **Anesthesia and perioperative care**

Standard monitoring included electrocardiography, noninvasive arterial blood pressure monitoring, and pulse oximetry. All patients received spinal anesthesia administered by an attending anesthesiologist and 500 mL Ringer's lactate solution was administered to ensure hydration before spinal anesthesia.

Spinal anesthesia was induced in the lateral decubitus position. These patients received an intrathecal injection of 15 mg 0.5% bupivacaine (in 5% glucose) at the level of L4-5 via a 25-gauge needle. Patients were then turned to the supine position and the level of sensory block was evaluated by pinprick.

Peak level of sensory block, sensory dermatome at tourniquet pain, time between tourniquet application and onset of pain, and tourniquet pain were determined by an independent researcher at 5, 10, 15, and 20 minutes after the spinal injection and then at 10-minute intervals until the complete resolution of the sensory block. The affected extremity in all patients was exsanguinated with an Esmarch bandage, and a tourniquet was applied at a pressure of 300 mmHg during the surgery.

When the patient felt a poorly localized and diffuse pain after tourniquet inflation, despite adequate sensory blockade during surgery, the pain was considered to be induced by the tourniquet. Intravenous fentanyl was administered at a dose of 100  $\mu$ g as supplemental analgesia if the patients experienced tourniquet pain at any time during the procedure. General anesthesia was induced if intravenous fentanyl was ineffective. The need for supplementary intravenous fentanyl and any conversion to general anesthesia were recorded. In case of intraoperative bleeding, volume replacement with Ringer's lactate solution was performed, according to the decision of an attending anesthesiologist instead of blood products.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate (HR) were monitored every 5 minutes until the end of surgery. Hypotension was defined as a 30% reduction in basal MAP, which was treated with 5 mg intravenous ephedrine administration. When the HR was < 50 beats/min (bradycardia), 0.2 mg glycopyrrolate was injected intravenously.

Before the start of surgery, femoral nerve block was performed to reduce postoperative pain using a bolus of 20 mL 0.75% ropivacaine. Concurrently, patient-controlled analgesia (PCA) pump containing 1000  $\mu$ g fentanyl, 150 mg ketorolac, and 0.6 mg ramosetron in 150 mL saline was set to deliver a basal infusion of 2 mL/h and bolus doses of 1 mL, with a 15-minute lockout period for postoperative analgesia. PCA volume consumed at 24 and 48 hours after surgery and total PCA volume consumed in 48 hours after surgery were recorded. Postoperative pain intensity at rest was measured using a 100-mm linear visual analog scale (VAS). The VAS score for pain at rest was measured at 24 and 48 hours after surgery. Fentanyl in a dose of 100  $\mu$ g was administered for pain with VAS score  $\geq$  50 or 30 mg ketorolac was administered for pain with VAS score < 50 or on patient request.

## **Measurements of metabolic, coagulative, and temperature changes**

Arterial blood samples were obtained from the radial artery 1 minute before the start of spinal anesthesia as a baseline value and at 10 minutes after tourniquet release.

Five milliliters of blood samples were extracted through the radial artery, and 1 mL was collected in a heparinized syringe; following this, the remaining blood samples were immediately sent through the pneumatic tube system, guaranteeing their processing in the least amount of time possible, not > 5 minutes by institutional standards. The metabolic variables included pH, lactate, calcium, potassium, bicarbonate, CO<sub>2</sub>, base excess and coagulative change included antithrombin III activity.

Tympanic temperature measurements were made using the Braun Thermoscan (Thermoscan Inc., San Diego, CA) inserted into the auditory canal at 1 minute just before the start of spinal anesthesia as a baseline and at 10 minutes after tourniquet release.

### **Statistical analysis**

The sample size was calculated using the PASS 2008 (NCSS, LLC. Kaysville, Utah, USA) software. A preliminary investigation had shown that mean  $\pm$  standard deviation (SD) of the two treatment groups for total PCA volume used in 48 hours after surgery as a primary outcome were  $125.67 \pm 8.2$  and  $120.90 \pm 5.8$ , respectively. The investigation revealed that a sample size of 36 patients per group would enable the detection of a significant difference with a power of 80% and an  $\alpha$ -coefficient of 0.05. The final sample size of this study was determined to be 40 patients per group, with a dropout rate of 10%. The SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The data are presented as mean  $\pm$  SD, median (interquartile range), or number (%) of patients. The groups were compared using an independent t-test or the Mann–Whiney U test according to normality test and categorical variables with the  $\chi^2$  test or Fisher exact test as appropriate.

The group-by-time interaction assesses whether the change over time differs between groups. Repeated measure analysis of variance was used for intra-group comparisons with P values that were adjusted with the Bonferroni correction for multiple comparisons. A P value < 0.05 was considered statistically significant.

## **Results**

A total of 110 patients were assessed for eligibility and 30 were excluded, because 11 did not meet the inclusion criteria and 19 refused to participate. Eighty patients received study medication after randomization. Six patients were initially enrolled but were withdrawn due to conversion to general anesthesia, re-exploration for postoperative bleeding, or refusal for postoperative assessment (Fig. 1).

Age, sex, weight, ASA classification, duration of surgery, tourniquet time, tourniquet pain, amount of intraoperative fentanyl administration, time between tourniquet application and onset of pain, peak level of sensory block, sensory dermatome at tourniquet pain, intraoperative blood loss, intravenous fluid administered, hypotension, postoperative delirium, amount of postoperative ketorolac administration, and

PCA volume consumed at 48 hours after surgery were not significantly different between the two groups. DEX group had significantly lower postanesthetic shivering ( $P = 0.025$ ), the frequency of fentanyl administration postoperatively ( $P = 0.013$ ), PCA volume at 24 hours after surgery ( $P < 0.01$ ), total PCA volume consumed in 48 hours after surgery ( $P < 0.01$ ), and VAS score for pain at 24 hours ( $P < 0.01$ ) and 48 hours after surgery ( $P < 0.01$ ) were also significantly lower in the DEX group than the CON group (Table 1).

Table 1  
Demographic and perioperative data.

	CON group (n = 36)	DEX group (n = 38)	P- value
Age (years)	76.2 ± 7.9	75.5 ± 9.6	> 0.05
Sex (M/F)	13/23	15/23	> 0.05
Weight (kg)	65.8 ± 8.3	66.4 ± 8.0	> 0.05
ASA(I/II/III)	0/19/17	0/20/18	> 0.05
Duration of surgery (minutes)	115.0 ± 9.5	120.5 ± 18.8	> 0.05
Duration of anesthesia (minutes)	140.6 ± 14.7	141.3 ± 17.3	> 0.05
Tourniquet time (minutes)	93.5 ± 7.6	92.0 ± 6.1	> 0.05
Tourniquet pain	6 (16.7)	3 (7.9)	> 0.05
Fentanyl administered intraoperatively	4 (11.1)	2 (5.3)	> 0.05
Time between tourniquet application and onset of pain (min)	69.2 ± 5.8	78.3 ± 2.9	> 0.05
Peak level of sensory block	T9 (T7, T10)	T 9 (T7, T10)	> 0.05
Sensory dermatome at tourniquet pain	T10 (T10, T12)	T10 (T9, T11)	> 0.05
Intraoperative blood loss (ml)	366.5 ± 22.4	350.9 ± 12.1	> 0.05
Intravenous fluid administered (ml)	1550.9 ± 280.7	1640.5 ± 33	> 0.05
Hypotension	6 (16.7)	10 (26.3)	> 0.05
Bradycardia	6 (16.7)	16 (42.1)	0.017
Postoperative delirium	3 (8.3)	1 (2.6)	> 0.05
Shivering	10 (27.8)	3 (7.9)	0.025
Additional analgesic type administered postoperatively	31 (86.1)	23 (60.5)	0.013
Ketorolac	12 (33.3)	12 (31.6)	> 0.05
Fentanyl	19 (52.8)	11 (28.9)	0.037

Values are expressed as mean ± SD, median (interquartile range) or number (%) of patients

Abbreviation: PCA, patient-controlled analgesia; VAS: visual analogue scale; CON, control; DEX, dexmedetomidine; SD, standard deviation.

	<b>CON group (n = 36)</b>	<b>DEX group (n = 38)</b>	<b>P- value</b>
PCA volume consumed at 24 hours after surgery (ml) at rest	73.28 ± 4.44	56.42 ± 4.56	< 0.01
PCA volume consumed at 48 hours after surgery (ml) at rest	53.50 ± 4.09	52.42 ± 4.79	> 0.05
Total PCA volume consumed for 48 hours after surgery (ml)	126.78 ± 4.91	108.84 ± 8.59	< 0.01
VAS score for pain at 24 hours after surgery	60.56 ± 7.15	46.05 ± 9.17	< 0.01
VAS score for pain at 48 hours after surgery	41.94 ± 5.25	31.32 ± 4.75	< 0.01
Values are expressed as mean ± SD, median (interquartile range) or number (%) of patients			
Abbreviation: PCA, patient-controlled analgesia; VAS: visual analogue scale; CON, control; DEX, dexmedetomidine; SD, standard deviation.			

At 10 minutes after tourniquet release, the pH of arterial blood was significantly higher ( $P < 0.022$ ) and lactate was significantly lower ( $P < 0.014$ ) in the DEX group compared with the CON group. Antithrombin III activity ( $P < 0.01$ ) and body temperature ( $P < 0.012$ ) at 10 minutes after tourniquet release in DEX group were significantly lower than in the CON group.  $\text{Ca}^{2+}$ ,  $\text{K}^+$ ,  $\text{HCO}_3^-$ , base excess, and  $\text{PCO}_2$  at 10 minutes after tourniquet release were not significantly different between the two groups ( $P > 0.05$ ) (Table 2).

Table 2

Metabolic, coagulative, and temperature changes in arterial blood at 10 minutes after tourniquet release between groups.

	<b>CON (n = 36)</b>	<b>DEX (n = 38)</b>	<b>P- value</b>
pH at baseline	7.41 ± 0.02	7.41 ± 0.02	> 0.05
pH at 10 minutes after tourniquet release	7.38 ± 0.03	7.38 ± 0.02	0.022
Lactate at baseline (Mm/L)	0.83 ± 0.21	0.89 ± 0.18	> 0.05
Lactate at 10 minutes after tourniquet release (Mm/L)	1.89 ± 0.41	1.65 ± 0.39	0.014
Ca <sup>2+</sup> at baseline (mg/dL)	1.16 ± 0.01	1.15 ± 0.03	> 0.05
Ca <sup>2+</sup> at 10 minutes after tourniquet release (mg/dL)	1.18 ± 0.04	1.18 ± 0.04	> 0.05
K <sup>+</sup> at baseline (mEq/L)	3.89 ± 0.19	3.81 ± 0.47	> 0.05
K <sup>+</sup> at 10 minutes after tourniquet release (mEq/L)	4.22 ± 0.16	4.14 ± 0.51	> 0.05
HCO <sub>3</sub> <sup>-</sup> at baseline (Mm/L)	23.31 ± 2.37	23.76 ± 2.12	> 0.05
HCO <sub>3</sub> <sup>-</sup> at 10 minutes after tourniquet release (Mm/L)	23.83 ± 1.68	23.56 ± 1.33	> 0.05
PCO <sub>2</sub> at baseline (mmHg)	38.47 ± 2.71	39.66 ± 3.51	> 0.05
PCO <sub>2</sub> at 10 minutes after tourniquet release (mmHg)	41.00 ± 3.00	40.71 ± 2.61	> 0.05
Base Excess at baseline	0.07 ± 1.99	0.22 ± 1.87	> 0.05
Base Excess at 10 minutes after tourniquet release	-0.82 ± 1.85	-0.92 ± 1.74	> 0.05
Antithrombin III activity (%) at baseline	94.50 ± 8.71	95.89 ± 7.85	> 0.05
Antithrombin III activity (%) at 10 minutes after tourniquet release	84.47 ± 5.53	82.68 ± 6.42	< 0.01
Body temperature at baseline (°C)	36.7 ± 0.2	36.7 ± 0.3	> 0.05
Body temperature at 10 minutes after tourniquet release (°C)	36.2 ± 0.4	36.0 ± 0.2	0.012
Values are expressed as mean ± SD or number (%) of patients.			
Abbreviation: CON, control; DEX, dexmedetomidine; SD, standard deviation.			

SBP, DBP, MAP, and HR at 10 minutes after tourniquet application were not significantly different between the two groups. SBP, DBP, and MAP at 30 minutes after tourniquet application were not significantly different between the two groups, but HR was lower in the DEX group than in the CON group ( $P < 0.01$ ). SBP, DBP, MAP, and HR at 60 minutes after tourniquet application and at 10 minutes after tourniquet release were lower in the DEX group than that in the CON group ( $P < 0.05$ ) (Table 3).

Table 3  
Hemodynamic changes after tourniquet application and release between two groups

	CON (n = 36)	DEX (n = 38)	P-value
Baseline			
SBP (mmHg)	143.1 ± 9.0	146.0 ± 9.0	> 0.05
DBP (mmHg)	85.3 ± 10.4	85.5 ± 9.8	> 0.05
MAP (mmHg)	104.4 ± 9.1	107.9 ± 8.0	> 0.05
HR (beats/min)	63.8 ± 11.3	61.4 ± 6.4	> 0.05
10 minutes after tourniquet application			
SBP (mmHg)	125.9 ± 9.4	124.2 ± 6.5	> 0.05
DBP (mmHg)	77.9 ± 8.7	76.6 ± 6.2	> 0.05
MAP (mmHg)	92.6 ± 9.6	91.4 ± 9.9	> 0.05
HR (beats/min)	58.5 ± 4.2	53.0 ± 9.3	> 0.05
30 minutes after tourniquet application			
SBP (mmHg)	117.0 ± 11.5	112.5 ± 10.1	> 0.05
DBP (mmHg)	72.3 ± 10.1	68.5 ± 10.0	> 0.05
MAP (mmHg)	87.2 ± 10.4	83.1 ± 9.8	> 0.05
HR (beats/min)	53.8 ± 4.2	51.2 ± 3.3	< 0.01
60 minutes after tourniquet application			
SBP (mmHg)	128.3 ± 7.1	122.9 ± 7.9	< 0.01
DBP (mmHg)	81.2 ± 9.8	74.2 ± 11.6	< 0.01
MAP (mmHg)	96.9 ± 8.4	90.5 ± 10.1	< 0.01
HR (beats/min)	57.4 ± 4.2	54.2 ± 7.1	0.025
10 minutes after tourniquet release			
SBP (mmHg)	109.6 ± 11.2	104.4 ± 6.0	0.014
DBP (mmHg)	68.7 ± 10.2	62.6 ± 4.2	< 0.01

Values are expressed as mean ± SD or number (%) of patients.

Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; HR, heart rate; SD, standard deviation CON, control; DEX, dexmedetomidine.

	CON (n = 36)	DEX (n = 38)	P-value
MAP (mmHg)	82.4 ± 10.0	76.6 ± 4.6	< 0.01
HR (beats/min)	63.5 ± 11.1	55.9 ± 5.5	< 0.01
Values are expressed as mean ± SD or number (%) of patients.			
Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; HR, heart rate; SD, standard deviation CON, control; DEX, dexmedetomidine.			

pH, lactate, Ca<sup>2+</sup>, K<sup>+</sup>, base excess, PCO<sub>2</sub>, antithrombin III activity, and body temperature at 10 minutes after tourniquet release were significantly changed (P < 0.01) when compared to baseline values (Table 4).

Table 4.

Metabolic, coagulative, and temperature changes in arterial blood at 10 minutes after tourniquet release

	Baseline	Tourniquet Release	P value
pH	7.41 ± 0.17	7.38 ± 0.03	< 0.01
Lactate (Mm/L)	0.86 ± 0.20	1.77 ± 0.41	< 0.01
Ca <sup>2+</sup> (mg/dl)	1.16 ± 0.02	1.50 ± 1.11	< 0.01
K <sup>+</sup> (mEq/L)	3.85 ± 0.36	4.17 ± 0.38	< 0.01
HCO <sub>3</sub> <sup>-</sup> (Mm/L)	23.54 ± 2.24	23.65 ± 1.50	> 0.05
PCO <sub>2</sub> (mmHg)	38.46 ± 5.42	40.30 ± 4.7	< 0.01
Base Excess	0.15 ± 1.91	-0.87 ± 1.78	< 0.01
Antithrombin III activity (%)	91.72 ± 7.60	83.44 ± 7.05	< 0.01
Body temperature ( °C)	36.7 ± 0.2	36.1 ± 0.3	< 0.01

SBP, DBP, MAP, and HR at 10, 30, and 60 minutes after tourniquet application and at 10 minutes after tourniquet release were significantly decreased when compared to baseline values. SBP, DBP, MAP, and HR at 60 minutes after tourniquet application were significantly higher than that at 30 minutes after tourniquet application. SBP, DBP, MAP, and HR at 10 minutes after tourniquet release were significantly lower than that at 60 minutes after tourniquet application. (P < 0.01) (Table 5).

Table 5.

Hemodynamic changes after tourniquet application and release.

	Baseline	10 min after tourniquet application	30min after tourniquet application	60min after tourniquet application	10min after tourniquet release
SBP (mmHg)	144.6 ± 9.1	125.1 ± 8.0* <sup>II</sup>	114.7 ± 11.0* <sup>†II</sup>	125.6 ± 8.0* ‡ <sup>II</sup>	107.0 ± 9.2* <sup>§</sup>
DBP (mmHg)	85.4 ± 10.1	77.2 ± 7.5* <sup>II</sup>	70.3 ± 10.2* <sup>†II</sup>	77.6 ± 11.2* ‡ <sup>II</sup>	65.6 ± 8.3* <sup>§</sup>
MAP (mmHg)	106.2 ± 8.7	92.0 ± 9.7* <sup>II</sup>	85.1 ± 10.3* <sup>†II</sup>	93.6 ± 9.8* ‡ <sup>II</sup>	79.4 ± 8.2* <sup>§</sup>
HR (beats/min)	62.5 ± 9.1	55.7 ± 7.8* <sup>II</sup>	52.5 ± 3.9* <sup>†II</sup>	55.8 ± 6.1* ‡ <sup>II</sup>	59.6 ± 9.4* <sup>§</sup>

\**P* < 0.01 vs baseline, <sup>†</sup>*P* < 0.01 vs 10 min after tourniquet application, <sup>‡</sup>*P* < 0.01 vs 30min after tourniquet application, <sup>§</sup>*P* < 0.01 vs 60min after tourniquet application, Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; HR, heart rate.

## Discussion

The main findings of our study demonstrated that DEX reduced the frequency of postoperative fentanyl administration, PCA volume consumed after surgery, and VAS score for pain after surgery compared to saline. At 10 minutes after tourniquet release, the pH of arterial blood was significantly higher and lactate level was significantly lower in the DEX group than in the CON group. Antithrombin III activity and body temperature at 10 minutes after tourniquet release were significantly lower in the DEX group than in the CON group. Ca<sup>2+</sup>, K<sup>+</sup>, HCO<sub>3</sub><sup>-</sup>, base excess, and PCO<sub>2</sub> levels at 10 minutes after tourniquet release were not significantly different between the two groups. DEX attenuated pain and hemodynamic, metabolic and coagulative effects induced by tourniquet use. However, these metabolic and coagulative changes were within normal limits.

Several systemic effects, which are temporary but can be dramatic, occur with tourniquet inflation and deflation during surgeries of the extremities. These systemic effects might cause hemodynamic, central nervous system, hematologic, temperature, and metabolic changes. Several studies have been performed on the effects of patient's cardiovascular condition, various anesthetic agents, and anesthetic methods on these systemic effects induced by tourniquet-induced ischemia-reperfusion injury [3–5]. DEX reduces postoperative analgesic (fentanyl) administration, VAS pain scores at 24 and 48 hours after surgery, PCA volume consumed at 24 hours, and total PCA volume consumed in 48 hours after surgery.

Tourniquet-induced hemodynamic changes occur according to the tourniquet phases. A gradual increase in arterial pressure is frequently observed after tourniquet inflation, which increases blood volume and systemic vascular resistance. Sudden drop in central venous pressure and mean arterial pressures after tourniquet deflation are due to the combination of a shift in blood volume back into the limb and washout of metabolites from the ischemic limb into the systemic circulation. However, these changes are minimal

in healthy patients, although patients with poor cardiac function may not be able to tolerate these changes [2, 3]. Hemodynamic changes according to tourniquet use were within normal limits, although DEX in this study attenuated hemodynamic responses induced by tourniquet use when compared to saline.

Tourniquet-induced systemic changes except for postoperative pain outcomes in this study were transient but minimal, although DEX reduced these changes. These results might be due to the study design (spinal anesthesia, and good cardiovascular conditions with EF  $\geq$  55%). Koşucu et al [15] reported that total intravenous anesthesia with propofol could be better compared to inhalational anesthesia or spinal anesthesia, which were not significant. Their study with shorter duration of tourniquet application with 64–68 minutes is different from our study with 92–93 minutes of tourniquet application.

Previous studies have reported on the effects of DEX on ischemia-reperfusion injury induced by tourniquet use, focused on serum levels of proinflammatory cytokines, malondialdehyde, a biomarker of oxidative stress or hemodynamic changes [4, 5]. This study reported that DEX reduced pain outcomes, and metabolic, coagulative, temperature, and hemodynamic changes by tourniquet induced ischemia-reperfusion injury.

Tourniquet pain is characterized as a dull, aching pain occurring after spinal or epidural anesthesia, despite adequate anesthesia of the sensory dermatome underlying the tourniquet. Various interventions using adjuncts to bupivacaine such as epinephrine, clonidine and morphine, gabapentin or ketamine have been used to prevent tourniquet pain [2]. Tourniquet pain in this study occurred in 16.7% of patients in the CON group and 7.9% in the DEX group and fentanyl was administered in 11.1% of patients in the CON group and 5.3% in the DEX group. DEX decreased the frequency of tourniquet pain and fentanyl administration when compared to saline, but the difference was not significant; however, DEX did reduce pain outcomes as shown by VAS pain score intensity and PCA volume consumed after surgery. These results might be due to relatively high density of bupivacaine (15 mg) or small sample size. Administration of 15 mg hyperbaric bupivacaine to the two groups may have diluted the analgesic effect of DEX on tourniquet pain.

Postanesthetic shivering may be thermoregulatory in response to core hypothermia or due to cytokine release by the surgical procedure or non-thermoregulatory in relation with certain anesthetics or postoperative pain. Alpha2 receptor agonists including DEX are an important class of anti-shivering drugs and reduce both the vasoconstriction and shivering thresholds [16, 17]. This study showed that the DEX group had significantly lower body temperature and lower incidence of shivering than the CON group. However, several studies reported that certain patients with DEX used for sedation in the intensive care unit developed high temperatures without clear alternative causes [18, 19]. DEX-associated hyperthermia mechanisms are currently unknown. Because the temperature environment, patient conditions, or intervention applied between operating room and intensive care unit are different, further studies are required to clarify the effect of DEX on body temperature.

There were some limitations in this study. First, we took two blood samples from patients sequentially. Our institution review board recommended a maximum of two chances to draw blood due to economic and ethical issues. The arterial blood samples were obtained from the radial artery 1 minute before the start of spinal anesthesia as a baseline and at 10 minutes after tourniquet release. It was difficult to evaluate metabolic and coagulative changes induced by the tourniquet phases sequentially. Second, although sample size was determined by total PCA volume consumed in 48 hours after surgery as a primary outcome, the sample size in this study may have been inadequate to evaluate the detailed metabolic and coagulative changes. Small sample size may mislead the researcher when it comes to making clinical decisions. Further larger sample size may be needed to clarify the effect of DEX on metabolic and coagulative changes induced by tourniquet application.

## **Conclusions**

In conclusion, we report that DEX attenuated pain and hemodynamic, metabolic, and coagulative effects induced by tourniquet use. However, these hemodynamic, metabolic, and coagulative changes were within normal limits. The clinical importance of this small effect is questionable. Nevertheless, DEX could be used as an analgesic adjuvant but should not be considered for routine use to prevent the systemic effects induced by tourniquet application.

## **Declarations**

## **Conflict of Interest:**

The author declared no conflict of interest.

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## **Authors' contributions**

Cheol Lee: study design, data collection, data analysis, patient recruitment, revising the article critically for important intellectual content, and final approval of the version to be submitted.

## **Acknowledgement:**

The data used to support the findings of this study are included within the article. We can share our data, our data is also available.

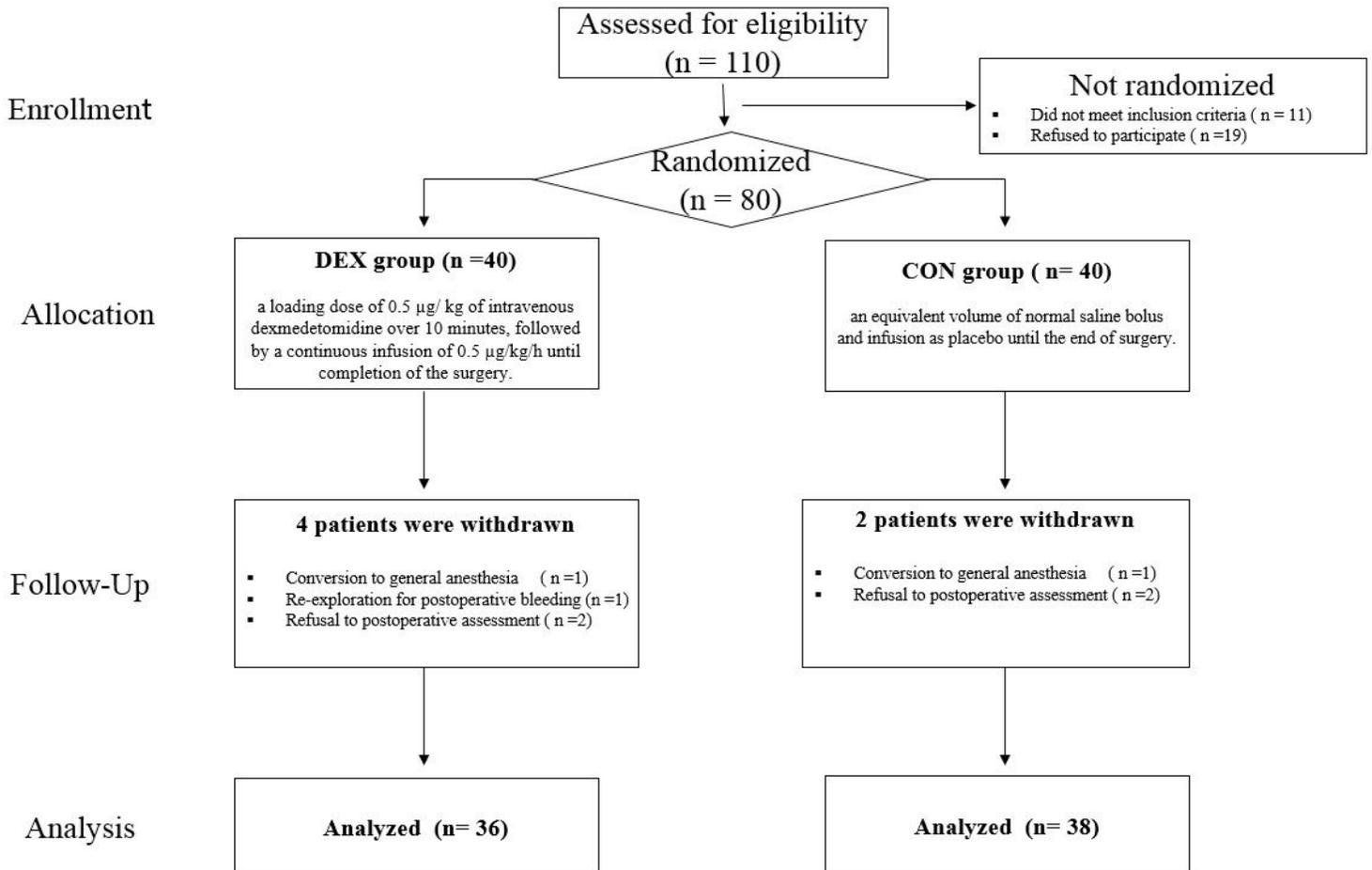
# References

1. Estebe JP, Davies JM, Richebe P. The pneumatic tourniquet: mechanical, ischaemia-reperfusion and systemic effects. *Eur J Anaesthesiol*. 2011;28:404–11.
2. Kam PC, Kavanagh R, Yoong FF. The arterial tourniquet: pathophysiological consequences and anaesthetic implications. *Anaesthesia*. 2001;56:534–45.
3. Kumar K, Railton C, Tawfic Q. Tourniquet application during anesthesia: "What we need to know?". *J Anaesthesiol Clin Pharmacol*. 2016;32:424–30.
4. Kim SH, Kim DH, Shin S, Kim SJ, Kim TL, Choi YS. Effects of dexmedetomidine on inflammatory mediators after tourniquet-induced ischemia-reperfusion injury: a randomized, double-blinded, controlled study. *Minerva Anesthesiol*. 2019;85:279–87.
5. Bostankolu E, Ayoglu H, Yurtlu S, Okyay RD, Erdogan G, Deniz Y, et al. Dexmedetomidine did not reduce the effects of tourniquet-induced ischemia-reperfusion injury during general anesthesia. *Kaohsiung J Med Sci*. 2013;29:75–8.
6. Leurcharusmee P, Sawaddiruk P, Punjasawadwong Y, Chattipakorn N, Chattipakorn SC. The Possible Pathophysiological Outcomes and Mechanisms of Tourniquet-Induced Ischemia-Reperfusion Injury during Total Knee Arthroplasty. *Oxid Med Cell Longev*. 2018;2018:8087598.
7. Halladin NL, Zahle FV, Rosenberg J, Gögenur I. Interventions to reduce tourniquet-related ischaemic damage in orthopaedic surgery: a qualitative systematic review of randomised trials. *Anaesthesia*. 2014;69:1033–50.
8. Koca K, Yurttas Y, Cayci T, Bilgic S, Kaldirim U, Durusu M, et al. The role of preconditioning and N-acetylcysteine on oxidative stress resulting from tourniquet-induced ischemia-reperfusion in arthroscopic knee surgery. *J Trauma*. 2011;70:717–23.
9. Saricaoglu F, Dal D, Salman AE, Atay OA, Doral MN, Salman MA, et al. Effects of low-dose N-acetylcysteine infusion on tourniquet-induced ischemia-reperfusion injury in arthroscopic knee surgery. *Acta Anaesthesiol Scand*. 2005;49:847–51.
10. Zalunardo MP, Serafino D, Szelloe P, Weisser F, Zollinger A, Seifert B, et al. Preoperative clonidine blunts hyperadrenergic and hyperdynamic responses to prolonged tourniquet pressure during general anesthesia. *Anesth Analg*. 2002;94:615–8.
11. Maruyama K, Takeda S, Hongo T, Kobayashi N, Kim C, Ogawa R. Oral clonidine premedication exacerbates hypotension following tourniquet deflation by inhibiting noradrenaline release. *J Nippon Med Sch*. 2004;71:44–50.
12. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg*. 2000;90:699–705.
13. Tziavrangos E, Schug SA. Regional anaesthesia and perioperative outcome. *Curr Opin Anaesthesio*. 2006;19:521–5.
14. Budić I, Pavlović D, Cvetković T, Djordjević N, Simić D, Milojević I, Stojanović M. The effects of different anesthesia techniques on free radical production after tourniquet-induced ischemia-

reperfusion injury at children's age. *Vojnosanit Pregl.* 2010;67:659–64.

15. Koşucu M, Coşkun I, Eroglu A, Kutanis D, Menteşe A, Karahan SC, et al. The effects of spinal, inhalation, and total intravenous anesthetic techniques on ischemia-reperfusion injury in arthroscopic knee surgery. *Biomed Res Int.* 2014;2014:846570.
16. Bicer C, Esmoğlu A, Akin A, Boyacı A. Dexmedetomidine and meperidine prevent postanaesthetic shivering. *Eur J Anaesthesiol.* 2006;23:149–53.
17. Elvan EG, Oç B, Uzun S, Karabulut E, Coşkun F, Aypar U. Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy. *Eur J Anaesthesiol.* 2008;25:357–64.
18. Krüger BD, Kurmann J, Corti N, Spahn DR, Bettex D, Rudiger A. Dexmedetomidine-Associated Hyperthermia: A Series of 9 Cases and a Review of the Literature. *Anesth Analg.* 2017;125:1898–906.
19. Grayson K, Tobin AE, Lim TK, Reid DE, Ghani M. Dexmedetomidine-associated hyperthermia: a retrospective cohort study of intensive care unit admissions between 2009 and 2016. *Anaesth Intensive Care.* 2017;45:727–36.

## Figures



## Figure 1

Consort flow diagram