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REPORTS OF ORIGINAL INVESTIGATIONS

Association of intraoperative dexmedetomidine use with postoperative hypotension in unilateral hip and knee arthroplasties: a historical cohort study

Association entre l'utilisation peropératoire de dexmédétomidine et l'hypotension postopératoire dans les arthroplasties unilatérales de la hanche et du genou : une étude de cohorte historique

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Abstract

Purpose *Dexmedetomidine is frequently used as a sedative agent for orthopedic surgery patients undergoing total hip or knee arthroplasty. Although the benefits of dexmedetomidine are well described in the literature, there is also potential for harm, especially regarding the hemodynamic effects of dexmedetomidine in the postoperative setting.*

Methods *This historical cohort study included all primary unilateral total hip or knee arthroplasties conducted from April 2017 to February 2020 in a single, university-affiliated, tertiary care centre (Jewish General Hospital, Montreal, QC, Canada). We used multivariable logistic regression to analyze the predictors for postoperative hypotension, defined as a systolic blood pressure < 90 mm Hg or any systolic blood pressure while on a vasopressor infusion in the postanesthesia care unit. Models were validated using calibration and discrimination with bootstrapping technique.*

Results *One thousand five hundred and eighty-eight patients were included in this study. Postoperative*

Stephen Su Yang and Charles Gelinas have contributed equally to this work.

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hypotension occurred in 413 (26%) patients. Statistically significant predictors for postoperative hypotension included female sex (adjusted odds ratio [aOR], 3.24; 95% confidence interval [CI], 2.29 to 4.58), a history of transient ischemic attack or cerebrovascular accident (aOR, 1.97; 95% CI, 1.04 to 3.72), and intraoperative dexmedetomidine use (aOR, 2.61; 95% CI, 1.99 to 3.42). Moreover, the risk of postoperative hypotension was approximately two times higher than baseline, with a total intraoperative dexmedetomidine dose above 50 μg (relative risk, 1.99; 95% CI, 1.63 to 2.44; P < 0.001). A higher preoperative systolic blood pressure (aOR, 0.98; 95% CI, 0.97 to 0.99) was a protective factor for postoperative hypotension.

Conclusion *In this historical cohort study, dexmedetomidine was a strong risk factor for postoperative hypotension in total hip or knee arthroplasty patients. Dexmedetomidine, and particularly at high cumulative doses above 50 μg, should be administered judiciously in high-risk surgical patients to minimize the risk of postoperative hypotension.*

Résumé

Objectif *La dexmédétomidine est fréquemment utilisée comme agent sédatif pour les patients en chirurgie orthopédique bénéficiant d'une arthroplastie totale de la hanche ou du genou. Bien que les avantages de la dexmédétomidine soient bien décrits dans la littérature, il existe également un potentiel de préjudice, en particulier en ce qui touche aux effets hémodynamiques de la dexmédétomidine dans un contexte postopératoire.*

Méthode *Cette étude de cohorte historique comprenait toutes les arthroplasties totales unilatérales primaires de la hanche ou du genou réalisées entre avril 2017 et février 2020 dans un seul centre de soins tertiaires universitaire (Hôpital général juif, Montréal, QC, Canada). Nous avons utilisé la régression logistique multivariable pour analyser les prédicteurs d'hypotension postopératoire, définie comme une tension artérielle systolique < 90 mmHg ou toute tension artérielle systolique pendant une perfusion de vasopresseurs en salle de réveil. Les modèles ont été validés à l'aide de l'étalonnage et de la discrimination avec une technique d'auto-amorçage.*

Résultats *Mille cinq cent quatre-vingt-huit patients ont été inclus dans cette étude. Une hypotension postopératoire est survenue chez 413 (26 %) patients. Les prédicteurs statistiquement significatifs d'une hypotension postopératoire comprenaient le sexe féminin (rapport de cotes ajusté [RCA], 3,24; intervalle de confiance [IC] à 95 %, 2,29 à 4,58), des antécédents d'accident ischémique transitoire ou d'accident vasculaire cérébral (RCA, 1,97; IC 95 %, 1,04 à 3,72) et l'utilisation peropératoire de dexmédétomidine (RCA, 2,61; IC 95 %, 1,99 à 3,42). De plus, le risque d'hypotension postopératoire était environ deux fois plus élevé que la valeur initiale, avec une dose peropératoire totale de dexmédétomidine supérieure à 50 μg (risque relatif, 1,99; IC 95 %, 1,63 à 2,44; P < 0,001). Une tension artérielle systolique préopératoire plus élevée (RCA, 0,98; IC 95 %, 0,97 à 0,99) était un facteur protecteur contre l'hypotension postopératoire.*

Conclusion *Dans cette étude de cohorte historique, la dexmédétomidine était un facteur de risque important d'hypotension postopératoire chez les patients bénéficiant d'une arthroplastie totale de la hanche ou du genou. La dexmédétomidine, et en particulier à des doses cumulatives élevées supérieures à 50 μg, devrait être administrée judicieusement chez les patients chirurgicaux à haut risque afin de minimiser le risque d'hypotension postopératoire.*

Keywords adverse effects · anesthesia · arthroplasty · dexmedetomidine · hypotension · orthopedics · surgery

The optimal choice of anesthesia for total hip arthroplasty (THA) and total knee arthroplasty (TKA) remains unclear.[1] Observational data suggest better clinical outcomes with neuraxial anesthesia.[2] Intraoperative adjunctive sedation is often offered for patient comfort when neuraxial anesthesia is selected. Dexmedetomidine, a selective α_2-adrenoceptor agonist, has been shown in randomized controlled trials (RCTs) to offer significant benefits in both THAs and TKAs, including reduced opioid use,[3, 4] prolonged neuraxial analgesic effects,[5] decreased postoperative delirium,[6] and reduced incidence of nausea and shivering.[7]

Although dexmedetomidine offers significant benefits, this medication has the potential to cause harm, specifically related to its hemodynamic side effects. It can cause vasodilation and bradycardia, which is mediated by activation of central pre- and postsynaptic α_2 receptors.[8] It has a short elimination half-life of 2–3 hr.[8] However, it is unclear if dexmedetomidine is associated with the occurrence of hypotension during the postoperative period. To our knowledge, no study has examined the incidence of postoperative hypotension with the use of intraoperative dexmedetomidine in THAs and TKAs.

The current literature suggests that postoperative hypotension is linked to poor patient outcomes. The Perioperative Ischemic Evaluation Trial was a multicentre RCT examining 8,351 noncardiac surgery patients, and showed that clinically important hypotension, defined as systolic blood pressure less than 90 mm Hg that required a clinical intervention, had the highest population attributable risk (PAR) compared with all the other risk factors for death (adjusted odds ratio [aOR], 4.97; 95% confidence interval [CI], 3.62 to 6.8;

PAR, 37.3%) and stroke (aOR, 2.14; 95% CI, 1.15 to 3.96; PAR, 14.7%).[9] In the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation study, secondary analysis showed that postoperative hypotension was associated with an increased risk for major cardiovascular events (aOR, 2.14; 95% CI, 1.89 to 2.43).[10] As THAs and TKAs tend to involve older patients, major postoperative cardiovascular events are of particular concern; therefore, it is essential to establish which sedative agents are safe in this vulnerable population. We hypothesized that intraoperative dexmedetomidine is associated with an increased risk of postoperative hypotension. This study aimed to determine the predictors for postoperative hypotension in patients undergoing primary THAs and TKAs.

Methods

Study design and population

We performed a single-centre historical cohort study on all consecutive patients who underwent elective primary, unilateral THA or TKA under general and/or neuraxial anesthesia. Patients undergoing bilateral surgery or patients with missing anesthesia or postanesthesia care unit (PACU) records were excluded. The reason for excluding bilateral surgeries was that these surgeries had an average duration that was twice as long as unilateral surgeries. This has a significant impact on the choice of anesthesia as these procedures are often done under general anesthesia. Furthermore, there is an increased potential for intraoperative bleeding compared with unilateral surgery. The study was approved by the local Research Ethics Committee of *Centre Intégré Universitaire en Santé et Services Sociaux* West-Central Montreal, Jewish General Hospital (Montreal, QC, Canada). We used the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[11] and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines[12] for reporting this study.

Outcome variable

The primary outcome was the presence of postoperative hypotension in the postanesthetic recovery room. This was defined as systolic blood pressure < 90 mm Hg or any systolic blood pressure while on a vasopressor infusion. A vasopressor infusion was defined as any recorded continuous infusion of phenylephrine, norepinephrine, or vasopressin. Blood pressure measurements were obtained either invasively, using an arterial cannula, or noninvasively using an automated oscillometric blood pressure cuff at the treating physician's discretion.

Data collection

Three reviewers (C. G., E. Y., M. L.) extracted the *a priori* selected preoperative variables, which included patient characteristics, vital sign measurements, surgical and anesthetic variables, and laboratory values from the complete electronic medical records (Chartmaxx®, version 7.00, Quest Diagnostics Incorporated®, Secaucas, NJ, USA). We reviewed the data for each patient using a computerized spreadsheet. Intraoperative data were retrieved using an electronic automated anesthesia recording system (Centricity™, General Electric Company, Boston, MA, USA). The total cumulative dose of intraoperative sedation, including dexmedetomidine dose, was calculated automatically by the electronic software based on the loading dose, the rate of infusion, and the duration of administration. Furthermore, we obtained the loading dosages documented in the electronic records when available. In cases where the loading dose was unclear, we imputed the data based on the routine clinical practice of the treating anesthesiologist. To ensure inter-rater reliability, an independent reviewer (S. Y.) randomly examined 20% of all study patient files. The exposure to dexmedetomidine and the outcome of interest were adjudicated by two independent reviewers (C. G. and E. Y.). Disagreements between the reviewers were resolved through a consensus process. If the two reviewers did not agree, the final decision went to the third reviewer (S. Y.).

Statistical analyses

Stata/MP version 15 (College Station, TX, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses, with the *-rms-* package used in R.

Descriptive statistics

Continuous variables are reported using mean and standard deviation or median and interquartile range [IQR], as appropriate. We used the independent Student's *t* test to analyze the differences between intraoperative dexmedetomidine *vs* no dexmedetomidine use for continuous variables. We summarized binary or categorical variables by count and percentages and used the Chi square test to compare the differences. All tests were two-sided, and significance was defined as $P < 0.05$. Inter-rater reliability was assessed using Cohen's kappa coefficient.[13]

Development and validation of clinical prediction model

A multivariable logistic regression analysis was performed. We created a separate data set to address missing data using a single stochastic conditional imputation with logistic regression for binary variables[14] and predict mean matching for continuous variables.[15] Thirty-six independent variables were selected for entry into the model based on biological plausibility and a literature review of known associated factors. Given the expected high rate of postoperative hypotension, we performed a full model approach by including all 36 independent variables, chosen *a priori,* in the multivariable logistic regression model. This technique minimized the risk of variable selection bias.[16] Multicollinearity was tested using variance inflation factor (VIF). If two covariates were highly correlated (i.e., VIF $>$ 5), the least significant variable was dropped from the model. Univariate analysis was performed for all independent variables to illustrate their association without adjustments. A secondary model was created to determine if the surgeon was associated with the outcome of interest. The Wald Chi square test was used to determine the contribution of each independent variable to the main model.

To determine if there is a dose-dependent relationship between dexmedetomidine and the outcome of interest, we replaced the binary variable (the presence or absence of dexmedetomidine) with a categorical variable examining cumulative doses. The two threshold points were selected *a priori* based on a previously described effective dose (ED_{50}) and ED_{95} of dexmedetomidine to induce deep sedation.[17] For an average 70 kg patient, these values corresponded to approximately 50 μg and 100 μg. Given the high incidence of postoperative hypotension (i.e., $>$ 10%), modelling using Poisson regression with robust variance estimator was performed to calculate the incremental relative risk for each category compared with the baseline of no dexmedetomidine. All 36 independent variables, with the exception of dexmedetomidine, remained the same as the main model. We also performed an adjacent group contrast to determine if there was any statistical difference between adjacent categories (e.g., 1–49 μg *vs* 0 μg) with a Bonferroni-adjusted *P* value.

Internal validation was performed using calibration and discrimination. Calibration compared the proportion of observed patients with postoperative hypotension against the expected proportion of cases defined by the model. This is reported using a calibration curve. Discrimination assessed the patients who had the outcome *vs* those who did not using concordance statistics (C-statistics). Internal model validation was completed using a bootstrapping technique of 1,000 samples.[18]

Sensitivity analyses

We created a secondary model (secondary model 1) by transforming continuous variables using restricted cubic spline with three knots to allow for nonlinear relationships.[19] This transformation accounted for improved model fitting as compared with the main model. In this model, all binary or categorical variables were kept in their original format when incorporated into the multivariable logistic regression. Finally, a complete case analysis (secondary model 2) was created and compared with the main model.

Results

One thousand seven hundred and thirty-one patients underwent a primary THA or TKA under general and/or spinal anesthesia between April 2017 and February 2020, 1,588 of whom were included in the study. One hundred and twenty-eight patients who underwent bilateral surgeries were excluded. Fifteen patients were excluded because of missing anesthesia or PACU records (Fig. 1). Six hundred and one (38%) underwent TKA and 987 (62%) underwent THA. Table 1 presents the demographic and baseline patient characteristics. The mean (standard deviation [SD]) age was 69 (11) yr and 36% were male. One thousand four hundred and fifty-five (92%) patients underwent spinal anesthesia, 108 (7%) patients received general anesthesia, and 25 (2%) patients had both general and spinal anesthesia. The mean (SD) spinal dose was 13 (1) mg with bupivacaine 0.5%. As per our local hospital protocol, the majority of patients with a TKA (98%)

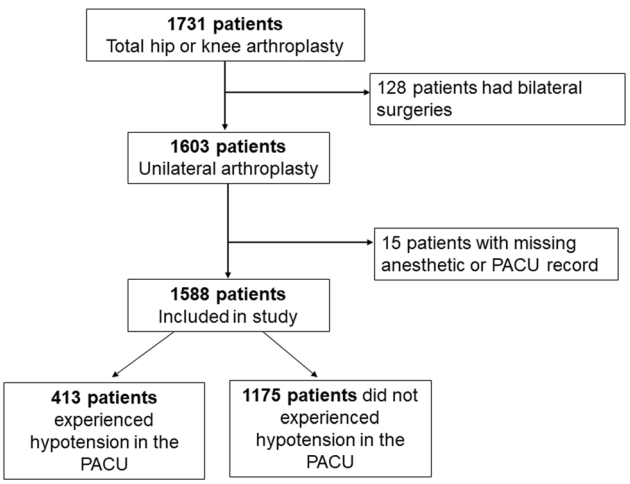

Fig. 1 Study flow diagram

Table 1 Baseline demographic and clinical characteristics of patients undergoing total hip and total knee arthroplasties

Characteristic	All patients *N* = 1,588	Dexmedetomidine *N* = 575	No dexmedetomidine *N* = 1,013	*P* value
Age (yr), mean (SD)	69 (11)	69 (10)	69 (11)	0.58
Sex (female)	1,014/1,588 (64%)	375/575 (65%)	639/1,013 (63%)	0.39
BMI ($kg \cdot m^{-2}$), mean (SD)	28.9 (5.7)	29.3 (6.1)	28.7 (5.5)	0.08
	N = 1,532	*N* = 558	*N* = 974	
Surgery				0.15
TKA	601/1,588 (38%)	231/575 (40%)	370/1,013 (37%)	
THA	987/1,588 (62%)	344/575 (60%)	643/1,013 (63%)	
Urgent surgery	36/1,588 (2%)	12/575 (2%)	24/1,013 (2%)	0.72
ASA Physical Status				0.003
I	251/1,588 (16%)	90/575 (16%)	161/1,013 (16%)	
II	895/1,588 (56%)	353/575 (61%)	542/1,013 (54%)	
III	437/1,588 (28%)	132/575 (23%)	305/1,013 (30%)	
IV	5/1,588 (0.3%)	0/575 (0%)	5/1,013 (0.5%)	
Baseline characteristics				
Hypertension	860/1,588 (54%)	320/575 (56%)	540/1,013 (53%)	0.37
Coronary artery disease	105/1,588 (7%)	33/575 (6%)	72/1,013 (7%)	0.29
Congestive heart failure	32/1,588 (2%)	5/575 (0.9%)	27/1,013 (3%)	0.01
Aortic stenosis	24/1,588 (2%)	7/575 (1%)	17/1,013 (2%)	0.47
Atrial fibrillation	97/1,588 (6%)	34/575 (6%)	63/1,013 (6%)	0.81
Pacemaker	43/1,588 (3%)	8/575 (1%)	35/1,013 (3%)	0.02
Dyslipidemia	585/1,588 (37%)	213/575 (37%)	372/1,013 (37%)	0.90
Diabetes mellitus	241/1,588 (15%)	85/575 (15%)	156/1,013 (15%)	0.74
COPD	82/1,588 (5%)	27/575 (5%)	55/1,013 (5%)	0.53
Current smoker	140/1,588 (9%)	49/575 (9%)	91/1,013 (9%)	0.76
History of DVT/PE	72/1,588 (5%)	27/575 (5%)	45/1,013 (4%)	0.82
History of TIA/CVA	62/1,588 (4%)	14/575 (2%)	48/1,013 (5%)	0.02
Hypothyroidism	257/1,588 (16%)	91/575 (16%)	166/1,013 (16%)	0.77
Chronic BP medication				
ACEI/ARB	628/1,588 (40%)	246/575 (43%)	382/1,013 (38%)	0.05
Beta blocker	260/1,588 (16%)	96/575 (17%)	164/1,013 (16%)	0.79
Calcium channel blocker	327/1,588 (21%)	125/575 (22%)	202/1,013 (20%)	0.39
Diuretic	387/1,588 (24%)	149/575 (26%)	238/1,013 (23%)	0.28
Preoperative vital signs*				
Systolic BP (mm Hg), mean (SD)	138 (18)	138 (19)	137 (18)	0.45
Diastolic BP (mm Hg), mean (SD)	81 (9)	81 (9)	80 (9)	0.15
Heart rate (min^{-1}), mean (SD)	76 (13)	77 (13)	76 (13)	0.16
Preoperative laboratory values				
Hemoglobin ($g \cdot L^{-1}$), mean (SD)	135 (14)	135 (13)	135 (14)	1.00
	n = 1,575	*n* = 573	*n* = 1,002	
Creatinine ($\mu mol \cdot L^{-1}$), mean (SD)	74 (23)	73 (22)	74 (23)	0.55
Type of anesthesia				< 0.001
Spinal	1,455/1,588 (92%)	565/575 (98%)	890/1,013 (88%)	
GA	108/1,588 (7%)	7/575 (1%)	101/1,013 (10%)	
Spinal + GA	25/1,588 (2%)	3/575 (0.5%)	22/1,013 (2%)	

Table 1 contiuned

Characteristic	All patients $N = 1,588$	Dexmedetomidine $N = 575$	No dexmedetomidine $N = 1,013$	*P* value
Bupivacaine spinal dose (mg), mean (SD)	13 (1)	13 (1)	13 (1)	0.91
	$n = 1,370$	$n = 513$	$n = 857$	
Nerve block				
Adductor canal	588/1,588 (37%)	229/575 (40%)	359/1,013 (35%)	0.01
Femoral nerve	7/1,588 (0.4%)	2/575 (0.4%)	5/1,013 (0.5%)	
ESP	1/1,588 (0.1%)	1/575 (0.2%)	0/1,013 (0%)	
Retrolaminar	5/1,588 (0.3%)	5/575 (0.9%)	0/1,013 (0%)	
Lumbar plexus	1/1,588 (0.1%)	0/575 (0%)	1/1,013 (0.1%)	
Intraoperative fluid				
Crystalloid (mL), mean (SD)	834 (378)	842 (380)	830 (377)	0.54
	$n = 1,586$	$n = 575$	$n = 1,011$	
6% hydroxyethyl starch (units)[†]	34/1,588 (2%)	9/575 (2%)	25/1,013 (2%)	0.23
Albumin (units)[‡]	0/1,588 (0%)	0/575 (0%)	0/1,013 (0%)	NA
PRBC (units)[§]	3/1,588 (0.2%)	0/575 (0%)	3/1,013 (0.3%)	0.19
Other blood products[‖]	0/1,588 (0%)	0/575 (0%)	0/1,013 (0%)	NA
Estimated blood loss (mL), mean (SD)	199 (128)	187 (124)	205 (130)	0.01
	$n = 1,377$	$n = 503$	$n = 874$	
Time in PACU (hr), median [IQR]	4.0 [3.0–6.0]	4.0 [3.0–5.5]	4.0 [3.0–6.0]	0.22

All numbers are *n*/total *N* (%) unless otherwise specified. *P* values are from the Chi square test or Student's *t* test.

* Preoperative vital signs were obtained from nursing assessment prior to surgery

† Each unit of 6% hydroxyethyl starch is 500 ml

‡ Each unit of albumin is 250 ml

§ Each unit of packed red blood cell is approximately 300 ml

‖ Other blood products include fresh frozen plasma, platelets, or cryoprecipitate.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DVT = deep vein thrombosis; ESP = erector spinae plane; GA = general anesthesia; IQR = interquartile range; PACU = postanesthesia care unit; PE = pulmonary embolism; PRBC = packed red blood cells; SD = standard deviation; THA = total hip arthroplasty; TIA = transient ischemic attack; TKA = total knee arthroplasty; VS = vital signs

received an adductor canal block with a catheter. A minority of patients with a THA (0.7%) were offered a nerve block. The median [IQR] duration of surgery was 1.2 [0.8–1.5] hr for THA and 1.3 [1.1–1.5] hr for TKA. The mean (SD) crystalloid administration was 834 (378) mL. Thirty-four (3%) patients received colloids (6% hydroxyethyl starch), with a mean (SD) volume of 520 (170) mL. Patients stayed in the PACU for a median [IQR] duration of 4[3, 4] hr.

Postoperative hypotension occurred in 413 (26%) patients in the PACU following THA or TKA with a mean (SD) systolic blood pressure of 81 (8) mm Hg. Four hundred and eleven out of four hundred and thirteen (99%) patients had a systolic blood pressure less than 90 mm Hg, and 2/413 (0.5%) patients had a vasopressor infusion in the PACU. The most common treatments for hypotension in the PACU were crystalloid boluses (79/413, 19%) or phenylephrine administration (66/413, 16%) (Electronic Supplementary Material [ESM] eAppendix 1). Among patients who received dexmedetomidine with a total mean (SD) intraoperative dose of 67 (72) μg, 214/575 (37%) developed hypotension in the PACU. No dexmedetomidine was given preoperatively or postoperatively. In patients who did not receive dexmedetomidine, 199/1,013 (20%) developed postoperative hypotension. This represents an unadjusted odds ratio (OR) of 2.42 (95% CI, 1.93 to 3.05) for postoperative hypotension (Table 2). All patients (575/575, 100%) who received dexmedetomidine had an intraoperative loading dose followed by an infusion. The median [IQR] loading dose was 28 [20–40] μg. The primary outcome was adjudicated by two reviewers and the inter-rater reliability was high, with a Cohen's kappa coefficient of 97.8% for dexmedetomidine exposure and 96.5% for postoperative hypotension.

Table 2 Univariate and multivariable logistic regression for postoperative hypotension in the PACU

Covariate	Univariate analysis		Multivariable analysis	
	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Surgery				
TKA	Reference		Reference	
THA	1.57 (1.23 to 1.99)	< 0.001	1.06 (0.72 to 1.58)	0.76
Urgent surgery	1.26 (0.61 to 2.58)	0.53	1.27 (0.53 to 3.00)	0.59
Age	0.98 (0.97 to 0.99)	0.003	0.99 (0.97 to 1.00)	0.07
Sex (Female)	2.65 (2.04 to 3.45)	< 0.001	3.24 (2.29 to 4.58)	< 0.001
Type of anesthetic				
Spinal	Reference		Reference	
GA	0.47 (0.27 to 0.81)	0.006	0.67 (0.36 to 1.26)	0.22
GA + spinal	0.37 (0.11 to 1.23)	0.11	0.34 (0.09 to 1.22)	0.10
Comorbidities				
Hypertension	0.69 (0.55 to 0.86)	0.001	0.80 (0.50 to 1.29)	0.36
Coronary artery disease	0.74 (0.46 to 1.20)	0.22	1.30 (0.73 to 2.34)	0.38
Congestive heart failure	0.40 (0.14 to 1.15)	0.09	0.62 (0.19 to 2.01)	0.43
Aortic stenosis	0.40 (0.12 to 1.36)	0.14	0.38 (0.10 to 1.40)	0.15
Atrial fibrillation	0.77 (0.47 to 1.27)	0.31	1.01 (0.55 to 1.89)	0.96
Pacemaker	1.10 (0.56 to 2.17)	0.77	1.60 (0.71 to 3.60)	0.26
Dyslipidemia	0.83 (0.65 to 1.05)	0.12	1.17 (0.87 to 1.57)	0.30
Diabetes mellitus	0.56 (0.39 to 0.79)	0.001	0.63 (0.42 to 0.96)	0.03
COPD	0.98 (0.59 to 1.63)	0.93	1.17 (0.66 to 2.07)	0.58
DVT/PE	1.18 (0.70 to 1.99)	0.53	1.30 (0.73 to 2.32)	0.37
TIA/CVA	1.08 (0.61 to 1.91)	0.80	1.97 (1.04 to 3.72)	0.04
Hypothyroidism	1.03 (0.76 to 1.39)	0.86	0.88 (0.63 to 1.24)	0.47
Preoperative medications				
ACEI/ARB	0.82 (0.65 to 1.03)	0.09	1.26 (0.83 to 1.91)	0.27
Beta blockers	0.77 (0.56 to 1.05)	0.10	1.02 (0.67 to 1.54)	0.93
Calcium channel blockers	0.64 (0.47 to 0.86)	0.003	0.80 (0.55 to 1.16)	0.24
Diuretics	0.82 (0.63 to 1.08)	0.16	1.01 (0.71 to 1.44)	0.95
Preoperative vital signs*				
Systolic BP (1 mm Hg increment)	0.98 (0.97 to 0.99)	< 0001	0.98 (0.97 to 0.99)	< 0.001
Diastolic BP (1 mm Hg increment)	0.98 (0.97 to 0.99)	0.001	1.00 (0.98 to 1.01)	0.64
Heart rate (1 beat per min increment)	1.01 (1.00 to 1.02)	0.09	1.01 (1.00 to 1.02)	0.22
Preoperative laboratory values				
Hemoglobin	0.99 (0.98 to 1.00)	0.01	1.00 (0.99 to 1.01)	0.89
Creatinine	0.99 (0.99 to 1.00)	0.003	1.00 (1.00 to 1.01)	0.47
Intraoperative sedation				
Propofol	0.69 (0.54 to 0.88)	0.004	0.75 (0.55 to 1.02)	0.07
Midazolam	1.64 (1.31 to 2.05)	< 0.001	1.66 (1.29 to 2.15)	< 0.001
Ketamine	1.00 (0.42 to 2.37)	0.99	1.02 (0.37 to 2.80)	0.98
Dexmedetomidine	2.42 (1.93 to 3.05)	< 0.001	2.61 (1.99 to 3.42)	< 0.001
Intrathecal dexmedetomidine	1.43 (0.61 to 3.37)	0.41	2.46 (0.92 to 6.6)	0.07
Gabapentin	1.18 (0.82 to 1.71)	0.37	0.88 (0.58 to 1.33)	0.55
Intraoperative fluid management				
Crystalloid administration (100 mL increments)	1.00 (0.97 to 1.03)	0.94	0.99 (0.96 to 1.02)	0.55
Intraoperative blood loss (50 mL increments)	1.10 (1.05 to 1.15)	< 0.001	1.13 (1.05 to 1.21)	0.001

Table 2 continued

Covariate	Univariate analysis		Multivariable analysis	
	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
6% hydroxyethyl starch administration	1.02 (0.47 to 2.21)	0.95	0.82 (0.35 to 1.93)	0.65

All 36 independent variables were included in the main model. Adjusted odds ratios were obtained from a multivariable logistic regression model including all independent variables listed above with a single stochastic conditional imputation

*Preoperative vital signs were obtained from nursing assessment prior to surgery

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DVT = deep vein thrombosis; GA = general anesthesia; PACU = postanesthesia care unit; PE = pulmonary embolism; THA = total hip arthroplasty; TIA = transient ischemic attack; TKA = total knee arthroplasty

Main model

A multivariable logistic regression with imputation showed several risk factors for postoperative hypotension. Female sex (aOR, 3.24; 95% CI, 2.29 to 4.58; $P < 0.001$) and a history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) (aOR, 1.97; 95% CI 1.04 to 3.72; $P = 0.04$) were patient-related risk factors for postoperative hypotension. A history of diabetes mellitus (aOR, 0.63; 95% CI, 0.42 to 0.96; $P = 0.03$) and higher preoperative systolic blood pressure (aOR, 0.98; 95% CI, 0.97 to 0.99; $P < 0.001$) were protective factors for postoperative hypotension. In terms of intraoperative sedation regimen, the use of midazolam (aOR, 1.66; 95% CI, 1.29 to 2.15; $P < 0.001$) and dexmedetomidine (aOR, 2.61; 95% CI, 1.99 to 3.42; $P < 0.001$) were significant risk factors for postoperative hypotension. Finally, higher intraoperative blood loss (aOR, 1.13; 95% CI, 1.05 to 1.21; $P = 0.001$) also increased the risk of postoperative hypotension (Table 2). Based on the Wald test, the most significant variables for postoperative hypotension were dexmedetomidine ($P < 0.001$), female sex ($P < 0.001$), and preoperative systolic blood pressure ($P < 0.001$) (ESM eAppendix 2). The sensitivity analyses using the same independent variables showed results consistent with our primary model. Predictors of postoperative hypotension included female sex (secondary model 1: aOR, 4.02; 95% CI, 2.70 to 6.0; $P < 0.001$; secondary model 2: aOR, 3.65; 95% CI, 2.50 to 5.3; $P < 0.001$) and intraoperative use of dexmedetomidine (secondary model 1: aOR, 2.79; 95% CI, 2.08 to 3.75; $P < 0.001$; secondary model 2: aOR, 2.75; 95% CI, 2.05 to 3.68; $P < 0.001$) (ESM eAppendix 3). Of the five surgeons at our institution, four used a similar surgical approach and were not significantly different when incorporated into the main multivariable regression model ($P = 0.42$ to $P = 0.95$). One surgeon used a different surgical approach for TKA and THA and had a statistically significant decrease in postoperative hypotension (aOR, 0.54; 95% CI, 0.36 to 0.79; $P = 0.001$). After incorporating this particular surgeon as an independent variable, the same covariates as the main model remained statistically significant (ESM eAppendix 4).

Dexmedetomidine dosing analysis

Intraoperative dosing of dexmedetomidine was incorporated in the prediction model as a separate variable in the analysis to determine if there was a dose-response relationship. In patients who received an intraoperative dose of 1–49 μg of dexmedetomidine, the risk of postoperative hypotension was approximately 1.5 times higher than in those who did not receive dexmedetomidine (relative risk [RR], 1.58; 95% CI, 1.26 to 1.97; $P < 0.001$). As the dose of dexmedetomidine increased to 50–99 μg, the risk of postoperative hypotension was approximately two times higher (RR, 1.99; 95% CI, 1.63 to 2.44; $P < 0.001$). At a dose ≥ 100

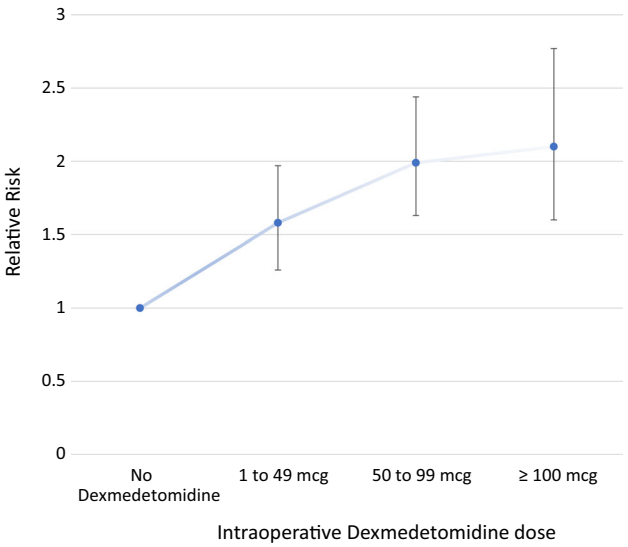

Fig. 2 All categories were compared with baseline of no dexmedetomidine. Line with marker chart of Poisson regression with robust variance estimator examining the doses of dexmedetomidine. The x-axis represents total intraoperative dexmedetomidine dose. The y-axis represents the relative risk. Error bars represents the 95% confidence interval

μg, the risk of postoperative hypotension remained elevated (RR, 2.10; 95% CI, 1.60 to 2.77; $P < 0.001$) (Fig. 2). Adjacent group contrast of dexmedetomidine dosing interval showed a statistically significant difference between 1–49 μg *vs* no dexmedetomidine (RR, 1.58; 95% CI, 1.20 to 2.07; $P < 0.001$). Nevertheless, there was no statistically significant difference between 50–99 μg *vs* 1–49 μg (RR, 1.26; 95% CI, 0.95 to 1.68; $P = 0.16$) or between ≥ 100 μg *vs* 50–99 μg (RR, 1.06; 95% CI, 0.75 to 1.49; $P = 1.00$) (ESM eAppendix 5).

Model validation

We tested the internal validity of our main model using calibration and discrimination with a bootstrapping technique of 1,000 samples by reporting a bias-corrected concordance statistic. Our calibration curve showed a well-calibrated model (ESM eAppendix 6). The ability to discriminate had a C-statistics of 0.74 and an optimism-corrected C-statistics of 0.71, indicating good model performance at predicting postoperative hypotension.

Discussion

Our results revealed that intraoperative dexmedetomidine more than doubled the risk for postoperative hypotension in patients undergoing elective primary THA and TKA. Although several other risk factors were identified in this study, the use of intraoperative dexmedetomidine was a strong modifiable risk factor. To our knowledge, this is one of the first studies to examine the hemodynamic effects of dexmedetomidine in the postoperative orthopaedic population. Similar hemodynamic effects were seen in postoperative cardiac surgery patients with dexmedetomidine infusion in the intensive care unit, where 69% of patients experienced the primary outcome of hypotension or bradycardia.[20] The mechanism of postoperative hypotension caused by dexmedetomidine is likely mediated by its α_2-adrenoceptor agonist effect. Stimulation of the α_{2A}- and α_{2C}-adrenoceptors, found in the central nervous system, may be responsible for sedation, analgesia, and sympatholytic effects, resulting in bradycardia and hypotension.[21] The sympatholytic effects of dexmedetomidine may also increase the risk of hypotension through a secondary effect of blunting homeostatic cardiovascular response. Surgical patients who undergo TKA or THA are more predisposed to postoperative hypotension given a relative hypovolemic state from surgery and the sympathectomy from spinal anesthesia.[22] During an early physiologic state of shock, the initial hemodynamic response is tachycardia to maintain cardiac output.[23] Nevertheless, patients who receive dexmedetomidine may be unable to mount such a physiologic response because of the medication's hemodynamic attenuation, namely a blunting of the compensatory tachycardia. In an RCT that compared the use of esmolol to dexmedetomidine to blunt the tachycardic response to direct laryngoscopy during intubation, the hemodynamic attenuation was similar between the two medications. After intubation, 14% of patients had an increase in heart rate with esmolol, while only 6% of patients had an increase in heart rate with dexmedetomidine.[24] A multicentre RCT examining the effect of intraoperative remifentanil *vs* dexmedetomidine was stopped prematurely because of five cases of severe bradycardia in the dexmedetomidine group, including three patients who had an asystolic cardiac arrest.[25] This hemodynamic blunting effect and minimization of tachycardia may therefore be contributing to the postoperative hypotensive episodes.

Our study found a signal for a dose-dependent relationship between postoperative hypotension and dexmedetomidine. Nevertheless, the dosing interval differences were not statistically significant and may be due to an underpowered analysis with regard to dosing. Similar hemodynamic effects of dexmedetomidine were seen intraoperatively in other studies. In a retrospective cohort study of 133 intensive care patients on dexmedetomidine infusion, hypotension was the most common adverse effect. In the low-dose dexmedetomidine group (≤ 0.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$), the incidence of hypotension was 34%, while hypotension occurred in 44% of high dose dexmedetomidine group (> 0.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$).[26] A similar dose-dependent effect was seen in studies that examined intraoperative hypotension. In a systematic review of 23 studies examining the hemodynamic effects of dexmedetomidine in noncardiac surgery patients, the pooled analysis revealed that the incidence of intraoperative hypotension was significantly higher with dexmedetomidine than with placebo (risk ratio [RR], 1.89; 95% CI, 1.1 to 3.25).[27] In the subgroup analysis, there was no statistical increase in risk of intraoperative hypotension (RR, 1.47; 95% CI, 0.5 to 4.3) when the bolus dose was < 0.5 $\mu g \cdot kg^{-1}$. Nevertheless, when the bolus dose was increased to ≥ 0.5 $\mu g \cdot kg^{-1}$, the risk of intraoperative hypotension increased significantly (RR, 2.38; 95% CI, 1.2 to 4.7).[27] This is consistent with our findings in the postoperative setting. Therefore, when an anesthesiologist decides to use intraoperative dexmedetomidine, it is important to use the minimally effective dose for patients at risk of postoperative hemodynamic changes.

Other risk factors for postoperative hypotension in our study included female sex, history of TIA/CVA, intraoperative midazolam, and increased intraoperative

blood loss. A possible explanation for the sex differences may be related to a higher incidence of a blunted cardiovagal baroreflex in females than in males.[28] Furthermore, there is a higher incidence of hypertension in males than in females.[29] Based on our study, higher preoperative blood pressure was protective against postoperative hypotension, as defined using a 90 mm Hg value; therefore, male patients with a history of hypertension may end up with fewer postoperative hypotensive events than females do. Similarly, patients with a history of TIA/CVA may have an increased risk of hypotension due to their blood pressure being tightly controlled preoperatively.[30]

Despite the generally accepted hemodynamic safety profile of midazolam, a study examining its hemodynamic effects in the emergency department as an induction medication showed significant hypotension in approximately 20% of patients.[31] This effect is especially prevalent among older individuals, which was the target population in this study.[31] Another explanation for midazolam's contribution to postoperative hypotension may be similar to that of dexmedetomidine, where the medication would unmask vulnerable patients because of sympathectomy.[32] With the introduction of an "enhanced recovery after surgery" protocol in orthopaedic patients, anesthesiologists would often minimize crystalloid administration intraoperatively as part of a fast-track pathway for surgical patients.[33] Unfortunately, for surgical patients with increased blood loss combined with minimal fluid administration, this could lead to hypotension in the postoperative setting.

The strength of our study included a large representative sample of patients who underwent primary THA or TKA. Based on previous simulation studies, to ensure the stability of the logistics regression model, at least ten events per predictor are needed.[34, 35] This requirement was met by the high event rate in our study, which minimized the risk of overfitting of the regression model to this sample. The quality of data collection was rigorous with high inter-rater reliability, and important outcomes were adjudicated. The statistical methods were rigorous and prespecified. The consistency of two additional regression models further confirmed the findings of potential risk factors. Finally, the validity of this clinical prediction model was tested using a bootstrapping technique to ensure the stability of the results.

There are some limitations to this study. The outcome of interest was based on a definition of systolic blood pressure < 90 mm Hg or on a vasopressor infusion. There is a complex relationship between blood pressure and clinical outcome, in part due to the phenomena of pressure autoregulation. At both pressure extremes (hypotension and hypertension), organ perfusion may suffer; however, in a "normal" range of blood pressure, organ perfusion remains autoregulated and optimal. The precise lower threshold for blood pressure at which limited organ dysfunction starts to appear with associated morbidities remains ill-defined.[36] There is no universal definition of intraoperative or postoperative hypotension. In a systematic review that examined the definition of hypotension in several studies, there was significant variability; however, almost all the definitions were based on either systolic blood pressure, mean arterial pressure, or a combination of both.[37] Although a definition of systolic blood pressure < 90 mm Hg would apply to most patients, there may be some patients with a history of chronic hypertension in whom relative hypotension would be underrecognized. In fact, in our study, we found that previously hypertensive patients (defined as an elevated preoperative systolic blood pressure) had less postoperative hypotension. This is likely related to how postoperative hypotension was defined. Some studies have used a relative decrease of 20% instead of an absolute blood pressure threshold, which may be more appropriate for patients with chronic hypertension.[36] In a similar fashion, underlying diabetes seems to have a protective effect against postoperative hypotension using our definition. There is significant overlap between patients with diabetes and patients with chronic hypertension.[38] Similarly, our defined threshold for hypotension may also underestimate relative hypotension in this population.

We analyzed the cumulative dose of dexmedetomidine in our study as this was the most accurate method to measure drug exposure from the electronic medical records. Moreover, based on pre-existing evidence, the overall pharmacodynamic effects of dexmedetomidine are associated with the cumulative administration dose.[39] Specific infusion rates and loading dosages may also be important, but need to be investigated in prospective RCTs.

Lastly, as this was a retrospective cohort study, there may be bias related to dexmedetomidine administration or other unknown confounders. The use of dexmedetomidine in orthopaedic patients should be studied in a prospective RCT.

Conclusion

Intraoperative dexmedetomidine was a strong risk factor for postoperative hypotension in the PACU. The hemodynamic effects of dexmedetomidine should be considered before administration, especially in high-risk surgical patients where postoperative hypotension can be deleterious. Furthermore, the appropriate dosing of dexmedetomidine should be considered, particularly when the total cumulative dose is over 50 μg, to

minimize potential hemodynamic side effects and for close postoperative monitoring. Future RCTs are needed to examine the hemodynamic effects of dexmedetomidine and the postoperative cardiovascular outcomes of these effects in this patient population.

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