Risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia
A retrospective study
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Abstract
Sedation with dexmedetomidine is needed for patients undergoing spinal anesthesia. However, dexmedetomidine sedation increases the incidence of bradycardia. We aimed to identify and to evaluate risk factors for bradycardia in patients undergoing spinal anesthesia with dexmedetomidine sedation. The records of 91 patients who underwent spinal anesthesia with sedation using dexmedetomidine were reviewed retrospectively. For this study, we identified 15 characteristics of included patients from this group who underwent lower leg surgery and had an estimated blood loss of <300mL. We collected details on potential risk factors for bradycardia from their clinical records. These factors included age, American Society of Anesthesiologists classification, height, weight, sensory level of spinal anesthesia, history of hypertension, diabetes mellitus, loading, and maintenance dose of dexmedetomidine, tourniquet time, initial diastolic and systolic blood pressure, initial heart rate (HR), and anesthesia and surgery duration. The primary endpoint of this study was the occurrence of bradycardia. We identified potential risk factors using logistic regression analysis. The incidence of bradycardia was obtained in 23 (25%) of 91 patients. Initial HR and tourniquet time were significant individual predictive factors for the occurrence of bradycardia. Logistic regression analysis showed that adjusted baseline HR and duration of tourniquet use were risk factors for bradycardia. Patients should be monitored when undergoing spinal anesthesia with sedation using dexmedetomidine for bradycardia when they have a long tourniquet time. A low initial HR could also be a predictive factor for bradycardia.

Abbreviations: AUC = area under the curve, bpm = beats per minute, CI = confidence interval, DBP = diastolic blood pressure, HR = heart rate, OR = odds ratio, ROC = receiver operating characteristic, SBP = systolic blood pressure.

Keywords: bradycardia, dexmedetomidine, sedation, spinal anesthesia

1. Introduction
Patients receiving spinal anesthesia are sedated to induce anterograde amnesia and to improve the patient’s experience, including anesthesia compliance.\textsuperscript{[1]} Intravenous midazolam, ketamine, propofol, and dexmedetomidine are commonly used sedatives during spinal anesthesia. Dexmedetomidine is a highly selective $\alpha_2$-adrenoeceptor agonist with anxiolytic, analgesic, sedative, and sympatholytic effects.\textsuperscript{[2]} This sedative causes less hemodynamic instability and no or minimal respiratory depression.\textsuperscript{[3]} Intraoperative administration of dexmedetomidine prolongs the duration of sensory and motor blockade and reduces opioid requirement in the first 24 hours after surgery.\textsuperscript{[4]} Dexmedetomidine is also associated with a decrease in the occurrences of postoperative shivering.\textsuperscript{[5]} These advantages have led to the common use of continuous intravenous dexmedetomidine during spinal anesthesia.

However, sedation with dexmedetomidine may increase the incidence of bradycardia and hypotension, requiring treatment.\textsuperscript{[6]} Dexmedetomidine has a sympatholytic action that can exacerbate hypotension and bradycardia resulting from spinal anesthesia.\textsuperscript{[7]} Intraoperative hypotension is associated with postoperative mortality and organ damage, such as acute kidney injury, myocardial injury, ischemic stroke, and delirium.\textsuperscript{[8]} It is important to prevent the occurrence of hypotension and bradycardia during spinal anesthesia to reduce postoperative complications. Therefore, we aimed to identify the risk factors for dexmedetomidine-associated hemodynamic instability during spinal anesthesia. This is the first study to identify these risk factors.
2. Methods
This retrospective study identified 91 adult patients who underwent lower extremity orthopedic surgery under spinal anesthesia combined with sedation by intravenous dexmedetomidine at a university hospital between May 2015 and December 2016. This study was approved by the Institutional Review Board of Seoul Paik Hospital, Inje University (2019-07-005-003). The requirement for informed consent was waived by the Institutional Review Board of Seoul Paik Hospital, Inje University since we used de-identified administrative claims data. All methods were performed in accordance with the relevant guidelines and regulations.

Patients who were aged <20 years or whose estimated blood loss during surgery was >300 mL were excluded. Baseline demographics abstracted from the file included age, sex, height, weight, American Society of Anesthesiologists classification, and past medical history. In addition, we recorded the sensory level of spinal anesthesia, loading and maintenance dose, tourniquet time, initial systolic and diastolic blood pressure (SBP and DBP, respectively), initial heart rate (HR), and duration of anesthesia and surgery. Vital signs were recorded on the anesthesia record every 5 minutes, although the HR at the time of the bradycardia event may not be recorded. Therefore, bradycardia was defined in this study as at least 1 episode in which the anesthesiologist administered a vasopressor or anticholinergic agent. We evaluated the HR between the start of anesthesia and tourniquet-off time to rule out tourniquet-associated hemodynamic changes. If the reading of the preoperative electrocardiogram was not normal sinus rhythm, we defined it as abnormal.

At our institution, we use a standard regimen of dexmedetomidine where the loading dose is 0.6 mcg/hours for 10 minutes, followed by the maintenance dose of 0.3 mcg/kg/hours. The dose of dexmedetomidine is adjusted as needed by the anesthesiologist in charge. The recommended maximum dose is 0.7 mcg/kg/hours, and dose titration is aimed at a Richmond stirring sedation scale level of −2. If an adequate level of sedation is not achieved with dexmedetomidine, 1 mg of intravenous midazolam is administered. Hypotension is defined as a 30% reduction in baseline SBP or an SBP of <90 mm Hg. It is treated with 5 mg of ephedrine or 50 to 100 mcg of phenylephrine intravenously. Bradycardia, defined as a 30% reduction in baseline HR or an HR of <45 beats per minute (bpm), is treated with 5 mg of ephedrine or 50 to 100 mcg of phenylephrine intravenously. Sensory block levels > T6 were identified in 22% and 12% of patients with and without bradycardia, respectively, although there was no statistical significance.

Patients with bradycardia had longer surgery and anesthesia duration than those who did not develop bradycardia; however, the difference was not statistically significant. High sensory block levels > T6 were identified in 22% and 12% of patients with and without bradycardia, respectively, although there was no statistical significance.

In this study, we aimed to identify risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia. Baseline HR and tourniquet time were independent risk factors associated with bradycardia during spinal anesthesia combined with dexmedetomidine infusion. The estimated threshold of the baseline HR predicting bradycardia was <73 bpm. An estimated tourniquet time of 72.5 minutes was a threshold for bradycardia.

Although an intravenous infusion of dexmedetomidine can induce satisfactory sedation during spinal anesthesia, hemodynamic instability, such as bradycardia, hypotension, and transient hypertension, may occur.[9] In this study, the incidence

3. Results
The baseline clinical characteristics of the patients are presented in Table 1. Twenty-three (25%) patients experienced bradycardia during their surgery using spinal anesthesia and intravenous dexmedetomidine. The remaining 68 patients were included in the comparison group.

In univariate analysis, there were no differences in sex; age; body mass index; American Society of Anesthesiologists physical status; previous medical history of hypertension, diabetes, or liver disease; electrocardiogram abnormality; baseline SBP and DBP; sensory blockade level; surgery and anesthesia duration; recovery time; and loading, maintenance, or total infused dose of dexmedetomidine between patients with and without bradycardia. A significant difference was observed in the baseline HR and tourniquet time between patients with and without bradycardia (P < .001 and P = .004, respectively; Table 1).

In addition to these 2 significant variables, 6 additional variables were identified as potential effect modifiers in a multivariable logistic regression analysis model (Table 2). Only baseline HR and tourniquet time were found to be significant independent risk factors of bradycardia during spinal anesthesia combined with dexmedetomidine infusion. The lower the baseline HR, the greater the risk of developing bradycardia (OR 0.89, 95% CI 0.82–0.96, P = .005). A longer tourniquet time was a significant risk factor for bradycardia (OR 1.06, 95% CI 1.02–1.1, P = .004).

Our study also showed a correlation between low baseline HR and bradycardia development. In terms of age, patients who developed bradycardia had a median age of 30 years, which was lower than that of patients who did not develop bradycardia; however, the difference was not statistically significant. High sensory block levels > T6 were identified in 22% and 12% of patients with and without bradycardia, respectively, although there was no statistical significance.

In this study, a long tourniquet time was demonstrated to be a significant risk factor for the development of bradycardia during spinal anesthesia combined with dexmedetomidine sedation (OR 10.6, P = .004).

We performed a ROC analysis and found that the optimal baseline HR threshold for predicting bradycardia was <73 bpm (sensitivity, 91.3%; specificity, 57.4%). The AUC for a cutoff value of 73 bpm was moderately accurate for predicting bradycardia (AUC, 0.764; 95% CI 0.663–0.865, P < .001) (Fig. 1). The tourniquet time threshold for estimating the development of bradycardia was >72.5 minutes (sensitivity 69.6%; specificity 61.8%). A cutoff value of 72.5 minutes was moderately accurate for estimating the risk of bradycardia (AUC, 0.701; 95% CI 0.577–0.826; P = .004) (Fig. 2).

4. Discussion
In this study, we aimed to identify risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia. Baseline HR and tourniquet time were independent risk factors associated with bradycardia during spinal anesthesia combined with dexmedetomidine infusion. The estimated threshold of the baseline HR predicting bradycardia was <73 bpm. An estimated tourniquet time of 72.5 minutes was a threshold for bradycardia.

Although an intravenous infusion of dexmedetomidine can induce satisfactory sedation during spinal anesthesia, hemodynamic instability, such as bradycardia, hypotension, and transient hypertension, may occur.[9] In this study, the incidence
of bradycardia was 25% in patients who underwent spinal anesthesia combined with sedation with dexmedetomidine. Bradycardia is defined as an HR of < 60 bpm, and bradycardia requiring intervention during anesthesia is generally considered to be an HR of < 50 bpm. It has been reported that bradycardia has a 13% incidence rate owing to sympathetic nerve blockade after spinal anesthesia.\[7\] Dexmedetomidine reduces blood pressure, HR, and plasma catecholamine levels in a dose-dependent manner.\[10\] The incidence of bradycardia after spinal anesthesia combined with intravenous dexmedetomidine administration has been reported to be 20% to 30%.\[11,12\] The risk factors for bradycardia in spinal anesthesia are underlying HR of < 60 bpm, male sex, age < 37 years, current treatment with beta-blockers, and sensory block level of ≥ T5.\[7,13\]

Tourniquets are commonly used in orthopedic surgery to reduce blood loss during upper or lower extremity surgeries. Hemodynamic changes associated with tourniquet inflation are described as hyperdynamic. Tourniquet inflation leads to an increase in the HR, SBP, and DBP that persists until tourniquet deflation.\[14\] A recent study reported that dexmedetomidine attenuates hyperdynamic response in patients undergoing lower extremity surgery using a tourniquet.\[15\] Therefore, the increased risk of bradycardia development with the increase in

### Table 1
Univariate analysis of baseline characteristics.

|                      | Bradycardia (n = 23) | Without bradycardia (n = 68) | P value |
|----------------------|----------------------|-------------------------------|---------|
| Sex                  |                      |                               | .56     |
| Male                 | 13 (57%)             | 45 (66%)                      |         |
| Female               | 10 (43%)             | 23 (34%)                      |         |
| Age (years)          | 30 [25;55]           | 47.5 [33;56]                  | .06     |
| BMI (kg/m²)          | 25.2 ± 3.1           | 24.9 ± 3.0                    | .65     |
| ASA PS               |                      |                               | .33     |
| 1                    | 19 (83%)             | 47 (69%)                      |         |
| 2                    | 4 (17%)              | 21 (31%)                      |         |
| Previous medical history |                    |                               |         |
| Hypertension         | 1 (4%)               | 11 (16%)                      | .27     |
| Diabetes             | 1 (4%)               | 5 (7%)                        | >.99    |
| Liver disease        | 4 (17%)              | 8 (12%)                       | .51     |
| Abnormal ECG         | 5 (22%)              | 17 (25%)                      | .97     |
| Baseline SBP (mm Hg) | 125.0 [116.5;132.5]  | 130.0 [122.9;140.0]           | .05     |
| Baseline DBP (mm Hg) | 75.0 [67.5;82.0]     | 80.0 [73.5;85.0]              | <.001   |
| Baseline HR (bpm)    | 65.0 [56.5;69.5]     | 75.0 [65.0;82.0]              |         |
| Sensory level        |                      |                               | .40     |
| >T6 level            | 5 (22%)              | 8 (12%)                       |         |
| <T7 level            | 18 (78%)             | 60 (88%)                      |         |
| Duration of surgery  | 85.0 [60.0;105.0]    | 65.0 [40.0;97.5]              | .14     |
| Duration of anesthesia | 130.0 [107.5;155.0] | 107.5 [82.5;145.0]            | .10     |
| Tourniquet time (min)| 85.0 [60.0;107.5]    | 62.0 [35.0;97.5]              | .004    |
| Recovery time (minute)| 35.0 [27.0;61.0] | 42.0 [32.0;56.0]              | .48     |
| Dexmedetomidine      |                      |                               |         |
| Loading dose (mcg/kg)| 0.7 [0.7; 0.7]       | 0.7 [0.7; 0.7]                | .72     |
| Maintenance dose (mcg/kg/h)| 0.3 [0.3; 0.3] | 0.3 [0.3; 0.3]                | .51     |
| Total infused dose (mcg/kg)| 28.6 [20.8;37.4] | 23.4 [14.7;33.0]              | .19     |

Values are presented as numbers (%), medians with [interquartile ranges], or means ± standard deviations. ASA PS = American Society of Anesthesiologists physical status, BMI = body mass index, bpm = beats per minute, DBP = diastolic blood pressure, ECG = electrocardiography, HR = heart rate, SBP = systolic blood pressure.

### Table 2
Logistic regression analysis of selected variables.

|                          | Odds ratio (95% CI) | P value |
|--------------------------|---------------------|---------|
| Age                      | 0.97 (0.92–1.00)    | .10     |
| Baseline SBP             | 0.98 (0.92–1.03)    | .39     |
| Baseline DBP             | 1.01 (0.93–1.09)    | .87     |
| Baseline HR              | 0.89 (0.82–0.96)    | .005    |
| Duration of surgery      | 1.05 (0.99–1.13)    | .12     |
| Duration of anesthesia   | 0.97 (0.94–1.00)    | .06     |
| Tourniquet time (min)    | 1.06 (1.02–1.10)    | .004    |
| Total infused dose of dexmedetomidine | 0.88 (0.75–1.04) | .12     |

CI = confidence interval, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure.

Figure 1. Receiver operating curves for baseline heart rate. The circle on the curve indicates the cutoff point for the prediction of a bradycardia event. AUC = area under the curve.
tourniquet time shown in this study can be thought of as an effect of dexmedetomidine.

Dexmedetomidine-induced hemodynamic instability is manifested as a symptom of hypotension and bradycardia, which is known to manifest itself in a dose-dependent manner.[10] Since dexmedetomidine was administered according to a prescribed loading and maintenance dose, a higher total infused dose of dexmedetomidine in patients with bradycardia could have been associated with a longer surgery and anesthesia duration.

Dexmedetomidine-induced bradycardia is associated with a high loading dose. A recent study reported that the incidence of bradycardia was significantly higher when the loading dose was 1.0 mcg/kg than when it was 0.8 mcg/kg.[16] Ko et al reported that the effective loading dose of dexmedetomidine for adequate sedation is 0.86 µg/kg; however, a dose higher than 0.5 µg/kg is associated with hemodynamic instability.[17] In our study, an average loading dose of 0.7 mcg/kg was administered with a 25% incidence of bradycardia. In patients with initial bradycardia or surgery, which is expected to have a longer tourniquet duration, the anesthesiologist can prevent bradycardia by lowering the loading dose of dexmedetomidine. In addition, anticholinergic premedication can effectively prevent bradycardia.[11] If patients cannot tolerate bradycardia, alternative drugs such as midazolam can be effective.

Our study has some limitations. First, owing to the inherent limitations of the retrospective study design, bradycardia events were indirectly measured. Since vital signs are recorded on the anesthesia record every 5 minutes, the HR at the time of the bradycardia event may not be recorded. Therefore, we defined bradycardia as when at least 1 episode of vasopressor or anticholinergic agent administration at the judgment of the anesthesiologist in charge occurred. Second, the involvement of several anesthesiologists may have resulted in inconsistencies in the management of bradycardia. However, our institution’s protocol for bradycardia management has been appropriately applied. Finally, medications or autonomic function in patients might be associated with the development of bradycardia. We could not collect data on the medications and autonomic function of the patients. Despite these limitations, our study is the first to validate the risk factors for bradycardia in spinal anesthesia combined with intravenous dexmedetomidine administration.

In conclusion, the occurrence of bradycardia should be carefully monitored in patients undergoing spinal anesthesia with sedation using dexmedetomidine. A long tourniquet time and low baseline HR could be predictive factors for bradycardia.

Author contributions
Conceptualization: EunJin Ahn.
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