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The effect of alpha-2A adrenergic receptor (ADRA2A) genetic polymorphisms on the depth of sedation of dexmedetomidine: a genetic observational pilot study

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Abstract
Background: The genetic polymorphisms of the alpha-2A adrenergic receptor (ADRA2A), which plays a significant role in sedation, anxiety relief, and antinociception, particularly in dexmedetomidine, may differ in the degree of sedation. This study aimed to investigate the effect of the genetic polymorphisms of ADRA2A (rs11195418, rs1800544, rs2484516, rs1800545, rs553668, rs3750625) on the sedative effects of dexmedetomidine.
Methods: A total of 131 patients aged 50 years or more from May 2018 to August 2019 were included in this study. The ADRA2A gene variants were evaluated using the TaqMan Assay. Dexmedetomidine diluted in normal saline to a concentration of $4\,\mu g.mL^{-1}$ was infused at a dose of $2\,\mu g.kg^{-1}$ to achieve procedural sedation (modified Ramsay sedation scale 4 [mRSS 4]).
Results: A total of 131 patients were evaluated. The genetic polymorphisms (rs11195418) of the ADRA2A receptor gene demonstrated no variation in our participants. The ADRA2A receptor gene polymorphisms (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) exhibited no differences in total dexmedetomidine doses ($p > 0.217$), bispectral index at mRSS 4 ($p > 0.620$), and time to obtain mRSS 4 ($p > 0.349$).
Conclusion: This study suggested that the genetic polymorphisms of ADRA2A did not affect the sedative efficacy of dexmedetomidine.

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Introduction

Dexmedetomidine is a selective and potent alpha-2 adrenoceptor agonist that is used for its sedative, analgesic, and anxiolytic properties. It is an effective and safe drug that is used to sedate patients during procedural sedation, regional anesthesia, and Intensive Care Unit (ICU) sedation.[1] A considerable advantage of dexmedetomidine-based sedation is that patients remain arousable. Along with minimal impact on breathing, dexmedetomidine is an interesting alternative in several procedures. Dexmedetomidine causes the activation of presynaptic and postsynaptic α_2-receptors of the locus coeruleus, resulting in an unconscious state similar to natural sleep conditions with unique aspects that allow patients to cooperate and regain consciousness with ease.[2] However, high interindividual variability in dexmedetomidine pharmacokinetics has been reported, especially in the ICU population.[3]

The causes of high interindividual variability in the pharmacokinetics of dexmedetomidine may vary but are also found to be associated with the alpha-2 adrenergic receptor. The alpha-2 adrenergic receptor has three subtypes, namely A, B, and C. Among them, the A subtype (alpha-2A adrenergic receptor [ADRA2A]) inhibits the flow of sympathetic nerves in the central nervous system and plays a major role in sedation, anxiolysis, and antinociception.

Recently, it has been reported that there may be differences in the degree of sedation of dexmedetomidine depending on the genetic polymorphism caused by ADRA2A. Yağar et al. showed that sedation requirement with dexmedetomidine was higher in patients with the G allele than in patients with the C allele of ADRA2A, C1291.[4] Particularly, ADRA2A variants with rs11195418 rs1800544, rs553668, and rs10885122 were significantly related to various sympathetic drives.[3,5] In addition, a Single Nucleotide polymorphism (SNP) (rs11195418, rs1800544, rs2484516, rs1800545, rs34303217, rs553668, and rs3750625) of ADRA2A may be associated with cardiovascular responses to dexmedetomidine.[6]

Therefore, the genetic polymorphisms of ADRA2A can affect the depth of sedation or the amount of sedative required. This study aimed to investigate the effect of the genetic polymorphisms of ADRA2A (rs11195418, rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) on the sedative effects of dexmedetomidine.

Methods

Study design

The study protocol, collection, and use of clinical data were approved by the Institutional Review Board of Pusan National University Yangsan Hospital (Yangsan, South Korea; approval nº 04-2018-010). The study was registered at the South Korean Clinical Research Information Service (trial ACTRN12616000085471). Written informed consent was obtained from all participants included in the study. Male patients with an American Society of Anesthesiologists (ASA) physical status I–III, aged over 50 years, and expected to use dexmedetomidine were recruited. Patients with psychiatric and neurological disorders and renal dysfunction or those using tranquilizers or sedatives, which may affect the sedation level, were excluded.

After patients arrived in the operating room without any premedication, oxygen was provided via a nasal cannula at 3 L/min with routine noninvasive patient monitoring (pulse oximetry, electrocardiography, noninvasive blood pressure, and Bispectral Index [BIS]). Dexmedetomidine diluted in normal saline to a concentration of $4\,\mu g.mL^{-1}$ was infused at a dose of $2\,\mu g.kg^{-1}$ to achieve procedural sedation. The sedation level was assessed with the modified Ramsay Sedation Scale (mRSS), and the target sedation level was Mrss 4 (definition: appears asleep, purposeful responses to commands but at a level that is louder than the conversational level, requiring light glabellar tap, or both) in this study, which corresponds to the moderate sedation level of the ASA continuum of sedation and modified observer's assessment of alertness/sedation scale 2 (definition: responds only after mild prodding or mild shaking). The sedation level was assessed every 30-seconds after the patient appeared asleep. When bradycardia, defined as heart rate of less than 45 beats/min, was detected, 0.5 mg of atropine was administered via intravenous infusion. The study was terminated with the event of oxygen saturation below 94%, and/or alteration of heart rate or blood pressure 20% or greater from the baseline values. A standardized, general anesthesia technique was used for all patients after the target sedation level was achieved.

DNA isolation and genotyping analysis

Ten-milliliter volume of arterial blood samples were collected from the participants of the study. Genomic DNA for genotyping was isolated from the buffy coat using the Wizard Genomic DNA Purification Kit (Promega, Madison) by an independent investigator blinded to the clinical information (Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital). The genotype was determined using polymerase chain reaction amplification, followed by restriction enzyme digestion. Validated primers were used to amplify and sequence the ADRA2A gene fragments (Macrogen, Seoul, Korea) listed in Table 1. Polymorphic changes in the ADRA2A gene were analyzed using pyrosequencing, which was performed by the PyroMark Q96 ID system (Qiagen, Korea), as described by the manufacturer.

Statistical analysis

A prior study showed that the distribution frequency of rs1800544 alleles (CC:CG:GG) was 15%, 45%, and 45%, and the total doses of dexmedetomidine were 108 ± 18.14, 90.71 ± 14.75, and $90.22 \pm 17.99\,\mu g$ in groups with CC, CG, and GG genotypes, respectively. The minimum sample size was determined to be 121 based on an alpha-value of 0.05 and a power of 0.80, calculated from the genotype distribution of the pilot data. Assuming a 10% loss to follow-up observations, 133 patients were calculated to be required.

Allele frequencies for a given variant were calculated by excluding samples with genotyping failure at the specific site. Data are expressed as mean $\pm$ SD or median and interquartile range (25th–75th percentile). Deviation of the

Table 1 Primers used for PCR amplification and pyrosequencing of regions of human ADRA2A.

SNP	Design strand	Context sequence
rs17216473	Forward	TGACCTCAGGTGATCTGCCTGCCTC[A/G]GCCTCCCACAGTTTTGTGATTATAG
rs11195418	Forward	AATAACTGTATCACTGGTGCGGGCT[A/G]TAGACATCAGCTGGGAATGAAGGTG
rs1800544	Forward	CCGTTGCGTTCTGCTCCGTCGGCCC[C/G]GAGCTGCATGGCCAACTCCCAGCAG
rs2484516	Forward	CTCACCCCGCCGCCGCCGCCGTCCC[C/G]GAGCTCCGCACAGTGTGCCCCAGCC
rs1800545	Forward	TATTAGGAGCTCGGAGCAAGAAGGC[A/G]CCCACCGAGAGCGTCTGAAGCGCGA
rs3750625	Forward	TTTAAAGAAAAATGCTAAGGGCAGC[A/C]CTGCCTGCCCTCCCCATCCCCCGCT
rs553668	Reverse	CATTCCCAACTCTCTCTCTCTTTTT[A/G]AAGAAAAATGCTAAGGGCAGCCCTG

SNP, Single-Nucleotide Polymorphism; B, Biotinylated on the 5'-end of the primer.

frequency of polymorphisms from the Hardy-Weinberg equilibrium was assessed using the Chi-Square (χ^2) test. The median differences in the total dose of dexmedetomidine, time to reach mRSS 4, and BIS value when the target sedation level was achieved with various ADRA2A polymorphisms were evaluated using the Kruskal-Wallis test. The Mann-Whitney *U* test was performed to evaluate differences between the A/A, G/A, and G/G genotypes, and *p*-values were corrected with the Bonferroni correction according to the number of comparisons.

Statistical significance was set at $p < 0.05$ for all observations. All calculations were performed with the SPSS® software, version 20.0 (SPSS Inc., Chicago, IL, USA), for IBM computers (IBM, Armonk, NY, USA). Calculations of heterozygosity and allele frequency using the Hardy-Weinberg equilibrium test were performed using the R software, version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 133 male patients of Korean nationality, aged 50 years or more, who underwent elective surgery in our institution from May 2018 to August 2019 were included in this study. A flow diagram of the progression through the study is shown in Fig. 1. The composition of body fluids, muscle mass, body fat percentage and blood volume vary depending on the sex, which was fixed to account for any variability. One female patient and one patient with missing data were excluded (n = 2). The characteristics of the patients are presented in Table 2. The total median dose of dexmedetomidine was 98.4 (82.6–123) mcg, and the median time to obtain Mrss 4 for dexmedetomidine sedation was 7.5 (6.5–9) min.

The genotype and allele frequencies of the ADRA2A gene polymorphisms are shown in Table 3. The gene polymorphisms (rs11195418) of the ADRA2A receptor gene showed no variation in our participants. The allele frequencies (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) of the genetic polymorphisms assessed in the study population were within the Hardy-Weinberg equilibrium.

Table 4 shows the total dose of dexmedetomidine, BIS at mRSS 4, and time to obtain mRSS 4 across the SNP genotypes. The ADRA2A receptor gene polymorphisms exhibited no differences in the total dexmedetomidine doses ($p > 0.217$), BIS at mRSS 4 ($p > 0.620$), or time to obtain mRSS 4 ($p > 0.349$).

Table 2 Characteristics of the patients enrolled in this study.

	Overall (n = 131)
Age	71.0 ± 7.4
Body weight (kg)	66.0 ± 9.2
Height (cm)	166.1 ± 5.4
BMI (kg m^{-2})	23.9 ± 2.9
Comorbidities	
Hypertension	92 (70.2%)
Diabetes mellitus	53 (40.5%)
Cardiovascular disease	44 (33.6%)
Respiratory disease	17 (13.0%)
Chronic kidney disease	13 (9.9%)
Cerebrovascular disease	20 (15.3%)
Others	6 (4.6%)
Total dexmedetomidine dose (mcg)	98.4 (82.6–123)
Dexmedetomidine dose (mcg. kg^{-1})	1.6 ± 0.4
BIS value at mRSS4	87 (82–91)
Time to obtain mRSS4 (min)	7.5 (6.5–9)

Values are shown as mean ± standard deviation, median (quartile) or number (%).
BMI, Body Mass Index; BIS, Bispectral Index value when target sedation level is achieved; mRSS, Modified Ramsay Sedation Scale.

Discussion

The effect of the genetic polymorphisms of the ADRA2A gene on the sedative effects of dexmedetomidine was evaluated in this study. Only male patients were enrolled because sex has been reported to affect the pharmacokinetics of dexmedetomidine. The polymorphisms of the ADRA2A gene (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) did not have any significant association with the sedative effects of dexmedetomidine.

Dexmedetomidine is highly preferred because of its combined sedation, anxiolytic, and analgesic properties with limited respiratory depression.[7] It has a high alpha-2 adrenoceptor affinity and locus coeruleus activity, which has been shown to reduce the duration of mechanical ventilation compared with midazolam and shorten the extubation time compared with propofol and midazolam.[8] Dexmedetomidine decreases analgesic and opioid requirements, does not induce clinically significant respiratory depression, and has little effect on weaning from mechanical ventilation and extubation. Patients on dexmedetomidine can be eas-
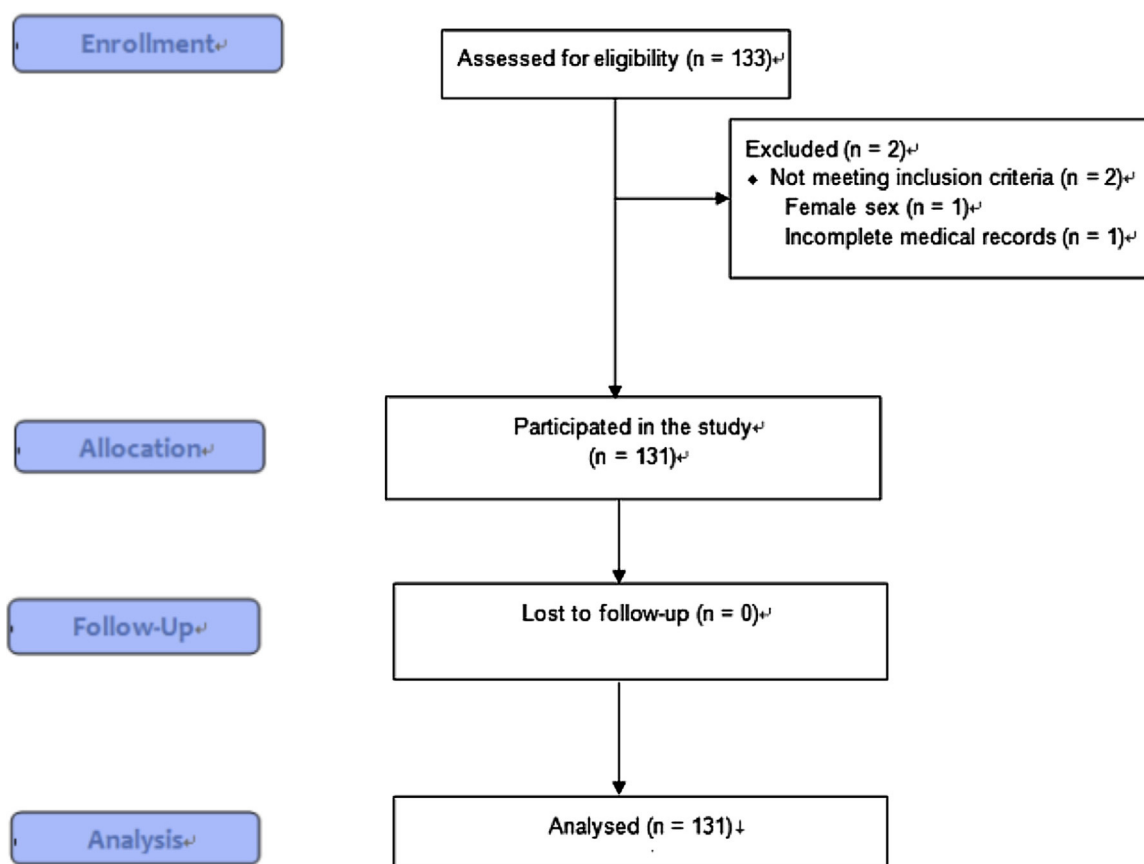
Figure 1 Flow diagram of the participants in this study.

Table 3 Genotype with allele frequencies and heterozygosity of α2-adrenergic receptor A subtype polymorphisms.

SNP	Genotype	Frequency	Allele	Frequency	p-value of Hardy-Weinberg equilibrium	Hetero-zygosity
	C/C	18 (14.06)	C	91 (35.55)	0.562	0.502
rs1800544	C/G	55 (42.97)	G	165 (64.45)		
	G/G	55 (42.97)				
	C/C	98 (74.81)	C	229 (87.40)	0.2202	0.490
rs2484516	C/G	33 (25.19)	G	33 (12.60)		
	A/A	7 (5.34)	A	45 (17.18)	0.0629	0.455
rs1800545	G/A	31 (23.66)	G	217 (82.82)		
	G/G	93 (70.99)				
	A/A	7 (5.34)	A	44 (16.79)	0.05376	0.497
rs3750625	C/A	30 (22.90)	C	218 (83.21)		
	C/C	94 (71.76)				
	A/A	26 (19.85)	A	123 (46.95)	0.3816	0.502
rs553668	G/A	71 (54.20)	G	139 (53.05)		
	G/G	34 (25.95)				

Values are described as number (%).
SNP, Single-Nucleotide Polymorphism.

ily awakened and tend to cooperate better with nursing and radiologic procedures in the ICU, which facilitates spontaneous awakening trials.[9] Based on European clinical trials), which proved the noninferiority of dexmedetomidine to propofol and midazolam in achieving the target sedation levels in mechanically ventilated patients in the ICU,

dexmedetomidine is considered as an economical option with lower ICU costs than standard sedatives.[8,10]

On the other hand, the use of dexmedetomidine alone is known to have different sedation levels among individuals using the same dose of the injected drug. In reality, the MIDEX and PRODEX clinical trials demonstrated inadequate

Table 4 Evaluation of the equivalence of the population medians of total dexmedetomidine dose, BIS at mRSS4, and time to obtain mRSS4 across the SNP genotypes using the Kruskal-Wallis test.

SNP	Geno-type	Total dose of dexmedetomidine (mcg)	p-value	BIS at mRSS4	p-value	Time to obtain mRSS4 (min)	p-value
rs1800544	C/C	108.64 ± 39.25		85.17 ± 11.94		7.64 (6.48−8.55)	
	C/G	103.60 ± 29.67	0.684	85.69 ± 7.20	0.669	7.27 (6.38−9.37)	0.967
	G/G	100.68 ± 26.50		86.85 ± 7.53		7.58 (6.54−8.38)	
rs2484516	C/C	101.83 ± 28.96		85.66 ± 8.62		7.46 (6.52−8.62)	
	C/G	108.55 ± 33.91	0.313	86.45 ± 7.63	0.620	7.68 (5.76−9.92)	0.924
	A/A	94.46 ± 25.21		87.86 ± 8.32		7.53 (6.68−8.46)	
rs1800545	A/G	97.33 ± 23.27	0.217	84.90 ± 9.48	0.702	7.49 (6.67−8.29)	0.837
	G/G	106.27 ± 32.43		86.03 ± 8.03		7.57 (6.45−9.44)	
rs3750625	A/A	94.46 ± 25.21		87.86 ± 8.32		7.53 (6.68−8.46)	
	A/C	98.64 ± 22.47	0.322	84.73 ± 9.59	0.665	7.53 (6.79−8.29)	0.950
	C/C	105.75 ± 32.63		86.07 ± 7.99		7.47 (6.34−9.40)	
rs553668	A/A	94.46 ± 25.21		87.23 ± 5.89		7.39 (6.31−7.96)	
	A/G	97.33 ± 23.27	0.544	85.68 ± 7.78	0.506	7.78 (6.54−9.45)	0.349
	G/G	106.27 ± 32.63		85.21 ± 10.91		7.31 (6.38−8.46)	

Values are shown as mean ± standard deviation.
BIS, Bispectral Index; mRSS, Modified Ramsay Sedation Scale.

sedation (undersedation) with dexmedetomidine in at least one out of eight patients.[8] Additionally, previous studies have reported a lack of efficacy as high as 21% and 50%.[11,12] In clinical practices, patients receiving sedatives frequently develop side effects that are either ineffective or difficult to tolerate. Consequently, different drugs or additional dosages are repeatedly administered until an appropriate drug or concentration is determined. This is not only inefficient, but it also poses risks to a patient's safety.

Clinically, we have observed that there is heterogeneity in the response to dexmedetomidine, for example, no sedation or excessive hypertension and severe bradycardia with the same dosage. Dexmedetomidine recipients required significantly more rescue sedation than midazolam recipients.[13] Study drug discontinuation occurred in 24% of the dexmedetomidine recipients and 20% of the midazolam recipients in MIDEX and in 28% of the dexmedetomidine recipients and 23% of the propofol recipients in PRODEX. Significantly more patients receiving dexmedetomidine versus midazolam (9% vs. 4%) or propofol (14% vs. 5%) had their treatments discontinued because of lack of efficacy in these studies.[8]

There can be several reasons why the sedative effects of dexmedetomidine differ at the same dosage. The effect of physiological factors such as age, sex, and pathological conditions can contribute to individual responses against sedative drugs. According to recent studies, the individual variability of the effectiveness of a drug can often be associated with genetically determined variations. Especially, the polymorphisms of drug metabolizing targets, carriers, and enzymes can have a significant impact on individual dose-response relationships.[14] Likewise, the genomic polymorphisms of ADRA2A can contribute to individual responses to dexmedetomidine.

In case of dexmedetomidine, the polymorphism of ADRA2A, a major implication associated with the sedative effect, may lead to differential effects on sedation levels. Previously, Yağar et al.[4] investigated the relationship between the effect of gene polymorphism of ADRA2A, C-1291 G in the promoter region of the candidate gene and the clinical characteristics of dexmedetomidine. Patients with the variant genotype demonstrated higher BIS and Ramsay sedation scores, indicating that higher drug doses were required to reach the same depth of sedation, and the use of the same dosage results in a longer duration of sleep.[4,15] Hunter et al.[16] hypothesized that the ADRA2A genes with rs1800545, rs1800035, rs1800038, rs11195418, rs1800544, rs2484516, +1483T > A, rs553668, and rs3750625 would cause different cognitive tasks and pain perceptions before and after three different dexmedetomidine doses were administered. Although the ADRA2C del322−325 variant was shown to affect pain perception, the ADRA2A gene polymorphism has not been observed to be correlated with pain perception and cognitive tasks at the three different doses.

A limitation of this study is that dexmedetomidine stimulates a spindle-type Electroencephalogram (EEG) activity, as in physiological sleep.[17] Dexmedetomidine induces sleep by activating endogenous nonrapid-eye movement sleep pathways and reduces the firing of noradrenergic locus coeruleus neurons in the brain stem.[18] Dexmedetomidine produces a state equivalent to physiological stage 2 sleep, with an abundant sleep-spindle activity corresponding to a transient EEG activation and a slight-to-moderate amount of slow-wave activity. The abundant sleep-spindle activity may be misinterpreted by the BIS algorithm as light anesthesia because spindles mimic arousal and an alpha-pattern EEG.[19] Thus, in this study, mRSS was used to assess the depth of sedation periodically.[20] The depth of sedation assessment methods, including mRSS, requires the periodical stimulation of patients, which can interfere with the depth of sedation itself.[21,22] We attempted to minimize and standardize the stimulation by providing verbal commands in a conversational level at 30-seconds intervals after the patients appeared to be asleep.

Conclusions

Based on the high interindividual variability in dexmedetomidine pharmacokinetics, this study attempted to evaluate the effect of the genetic polymorphisms of the ADRA2A on the pharmacodynamics of dexmedetomidine. The ADRA2A gene polymorphism (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) has not been observed to be correlated with the sedative effects of dexmedetomidine in this study.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

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