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Investigation of Beta-2 Adrenergic Receptor Gene Polymorphisms and Their Association with Maternal Hypotension During Cesarean Under Spinal Anesthesia in a Turkish Population

Spinal Anestezi Altında Sezaryen Operasyonu Geçiren Gebelerde Beta–2 Adrenoreseptör Genindeki Single Nükleotid Polimorfizm ile İntraoperatif Hipotansiyon İlişkisi

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ABSTRACT

Objective: Maternal hypotension is a common complication of spinal anesthesia for cesarean delivery, pose a risk to both mother and fetus. Prophylactic and therapeutic strategies must ensure hemodynamic stability. This prospective study examined whether single-nucleotide polymorphisms (SNPs) in codons 16 (Arg16Gly) and 27 (Gln27Glu) of the Beta-2 adrenergic receptor (β2AR) gene affect the incidence of hypotension and ephedrine requirements in Turkish women undergoing elective cesarean section under spinal anesthesia.

Methods: Five hundred and twenty term pregnant women scheduled for elective cesarean delivery were enrolled. Preoperative, all patients received 500 mL lactated Ringer's solution. Hemodynamic parameters (mean arterial pressure [MAP] and heart rate [HR] were recorded at baseline and at 5, 10, 20, 40, and 60 minutes. Ephedrine dosing followed a standardized systolic blood pressure (SBP) based protocol.

Results: Genotype distribution was 270 homozygous variants (51.9%), 230 heterozygotes (44.2%), and 20 wild types (3.9%). Hypotension occurred in 330 patients (64.7%), all treated with ephedrine. No significant differences emerged among genotypes in MAP, HR, frequency of hypotension, or total ephedrine dose (respectively *P*=.061, *P*=.054). Although homozygous mutants trended toward slightly higher cumulative ephedrine usage and wild types toward lower usage, these differences were not statistically significant. Neonatal Apgar scores at 1 and 5 minutes remained within normal limits across all groups.

Conclusion: β2AR Arg16Gly and Gln27Glu polymorphisms do not appear to influence the risk of spinal anesthesia–induced hypotension or ephedrine requirements in this cohort of Turkish parturients. These findings lay the groundwork for larger, multicenter studies spanning diverse ethnic populations.

Keywords: Inotropic agent, maternal hypotension, black sea region, beta-2 adrenoreceptor

ÖZ

Amaç: Maternal hipotansiyon sezaryen operasyonlarında spinal anestezi sırasında sık görülen bir olaydır. Fetüs ve anne iyilik halinin sürdürülebilmesi için, maternal hipotansiyonu önlemek önemlidir. Çalışmamızın amacı, 16 ve 27. kromozomda, sezaryen doğum için başvuran Türk gebelerde, spinal anesteziden sonra gelişen maternal hipotansiyon gelişim sıklığı ve efedrin tüketimi miktarı üzerindeki etkisini prospektif bir çalışmada değerlendirmektir.

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Yöntemler: ASA II-III risk sınıfında, 520 miadında gravida çalışmaya alındı. Etnik farklılığı olmayan Türkçe konuşan, Doğu Karadeniz bölgesinde ikamet eden, ek obstetrik ve medikal problemi olmayan, elektif sezeryan operasyonu planlanan gebeler çalışmaya alındı. Preoperatif tüm gebelere, bir saat önce i.v. hidrasyon sağlandı. Gebeler ameliyat masasına yatırıldığında sağ el sırtından yeni bir damaryolu açılarak, EDTA'lı tüplere genetik araştırma için kanları alındı. Standart sonrası spinal anestezileri yapıldıktan sonra, 0.dk, 5.dk, 10.dk, 20., 40., 60.dakikalarda ortalama arter basınçları (OAB) ve kalp atım hızları (KAH) ve efedrin ihtiyacı olup olmadığı ve toplamda kaç mg efedrin yapıldığı kaydedildi. Olguların DNA'ları PCR yöntemiyle amplifikasyonu sağlandı.

Bulgular: Olguların Beta -2 Adrenoreseptör gen polimorfizmi açısından 3 farklı genotipte oldukları görüldü. Homozigot mutant 270 (%51,9), heterozigot mutant 230 (%44,2), Wild tip ise 20 (%3,9) sıklıkta idi. Olguların 330'sinde (%64,7) maternal hipotansiyon gelişti ve normotansiyonu sağlamak için efedrin kullanıldı. Ölçüm yapılan tüm zaman dilimlerinde OAB, KAH değerleri ve tüketilen toplam efedrin miktarı açısından anlamlı fark saptanmadı (*P*=,061, *P*=,054, *P*=,249). Tüm olgular için inceleme yapıldığında Wild tip diğer toplumlara nazaran bizim çalışma grubumuzda daha fazla sıklıkta tespit edildi.

Sonuç: Spinal anestezi altında sezaryen seksiyo operasyonu geçiren gebelerde Beta-2 Adrenoreseptör genindeki single nükleotid polimorfizm ile intraoperatif gelişen maternal hipotansiyon ve efedrin kullanımı arasında ilişki saptanmadı. Türk kadınlarında, Beta-2 adrenoreseptör-27 gen polimorfizmi ile maternal hipotansiyon arasında ilişki yoktur diyebiliriz. Çalışmamız ilerde bu konuda yapılacak olan, çok merkezli, farklı etnik grupların da dahil edildiği, geniş popülasyonlu çalışmalara ışık tutacağı kanaatindeyiz.

Anahtar Kelimeler: İnotropik ajan, maternal hipotansiyon, karadeniz bölgesi, beta-2 adrenoreseptor

INTRODUCTION

During spinal anesthesia for cesarean section surgeries, maternal hypotension frequently occurs. Fetal distress, one of the obstetric emergencies, is caused by maternal hypotension, which also affects the fetus and interferes with uteroplacental perfusion.[1-3] Numerous accounts in the literature imply that it also affects the mother's cerebral perfusion, despite the paucity of proof. Preventing hypotension during pregnancy is crucial to preserving the health of the mother and the fetus.[4,5] Maternal hypotension remains a significant problem in obstetric anesthesia practice, despite the use of several strategies to lessen the detrimental effects of hypotension on the fetus, including placing the pregnant patient in the left lateral decubitus, using prophylactic vasopressors like ephedrine or phenylephrine, and delivering crystalloid or colloid solutions either before (preload) or during (coload) surgery.[6-10]

The control of cardiac output and blood pressure is significantly influenced by the stimulation and activity of the beta-2 adrenergic receptor (Beta-2AR). Ten distinct single-nucleotide polymorphisms (SNPs) have been found to describe the variation in genes of the human Beta-2 adrenergic receptor gene, which is located on chromosome 5.[11] The function of receptors is impacted by several of these variations. In vitro research has demonstrated that increased agonist-induced desensitization is linked to the substitution of arginine at residue 16 (Arg16Gly) for glycine. To put it another way, blood pressure and heart rate do not rise even when the Beta-2 receptor gene is active. On the other hand, resistance to desensitization is linked to the substitution of glutamine for glutamic acid at position 27 (Gln27Glu) indicating that this polymorphism causes an increased sensitivity to the activation of the Beta-2 receptor gene.[12,13]

The study was conducted in Turkey, and the study population consisted of Turkish pregnant women meeting the predefined inclusion criteria. Numerous studies from various ethnic groups and various regions have investigated the relationship between polymorphisms in the Beta-2 adrenergic receptor (Beta-2AR) gene and the requirement for vasopressor drugs during or after neuraxial anesthesia.[14-18]

This study was conducted with genetically homogeneous, native Turkish -speaking, and Turkish citizen pregnant women living in Ordu province, which lies in the Eastern Black Sea region of Turkey. The main goal is to prospective evaluate the impact of chromosome 16 and 27 polymorphisms on the incidence of maternal hypotension and the amount of ephedrine needed after spinal anesthesia during cesarean sections in pregnant Turkish women.

METHODS

Ethical approval for our study was obtained from the Ordu University Clinical Research Ethics Committee (Date: September 27, 2024, Approval No: 2024/121). All pregnant women who agreed to participate in the study signed an informed consent form. For our study, participants were selected among pregnant women who applied for cesarean delivery at Ordu University Training and Research Hospital between 01.10.2024 and 01.03.2025. Our inclusion criteria

were as follows: pregnant women in the province of Ordu who spoke Turkish, were citizens of Turkey, between the ages of 18 and 45, had singleton pregnancies, were in the ASA II–III physical risk class, had no history of bleeding diathesis, did not take acetylsalicylic acid or any other antiplatelet agents, had no history of deep vein thrombosis or varicose veins, and were operated on under elective circumstances with an 8-hour oral intake limitation. Those with severe renal, hepatic, or respiratory diseases, preeclampsia/eclampsia and/or pregnancy-induced hypertension (conditions where blood pressure regulation is impaired), pregnant women with varicose veins, pregnant women undergoing emergency cesarean sections, pregnant women with acetylsalicylic acid or other antiplatelet agents, those with placental defects in insertion that could result in bleeding beyond normal during procedure (placenta accreta, increta, or percreta), those taking antihypertensive medications, and morbidly obese pregnant women were all excluded.

An 18-gauge intravenous cannula was positioned on the dorsum of the hand, and 500 mL of lactated Ringer's solution was given to each patient an hour before the procedure to hydrate them before the procedure. The pregnant patients were monitored with noninvasive blood pressure, oxygen saturation and electrocardiograms once they entered the surgery room. The monitor was used to record the mean arterial pressure (MAP). The formula (2 times diastolic pressure plus systolic pressure) / diastolic pressure was used to get the MAP. The patient was monitored using a routine monitoring approach. Heart rate (HR), oxygen saturation, and mean arterial pressure were baseline values obtained during the 0th minute of the beginning monitoring. A basic face mask was used to provide oxygen at a rate of 4 L/min to all pregnant patients. Patients were placed in a sitting position once monitoring was finished. Using a 25 G pencil-point spinal needle implanted at the L3–L4 or L4–L5 vertebral area, 2.5 cc of 0.5% heavy bupivacaine, or 12.5 mg, was given intrathecally over a 10-second period. Patients were placed in a supine position right after the injection. In every patient, a thin lumbar pelvic cushion was positioned behind the right posterior superior iliac crest. Lactated Ringer's solution infusion was maintained at a rate of 20 mL/kg/hour following spinal anesthesia. An automated monitor for blood pressure was programmed to take readings every five minutes. A predetermined protocol was followed in order to manage hypotension: 5 mg of ephedrine was given if the systolic blood pressure (SBP) fell more than 20% from baseline or fell between ≥95 and <100 mmHg; 10 mg was given if the SBP fell between ≥90 and <95 mmHg; and 15 mg was given through a vein if the SBP fell below 90 mmHg. At five, ten, twenty, forty, and sixty minutes after spinal anesthetic was administered and the patient was placed in the supine position, the attending anesthesiologist took heart rate and mean arterial pressure readings. The amount of ephedrine given, if an antiemetic was taken, and the associated dose—if any—were also recorded at the same time points. The antiemetic medication was determined to be 8 mg of intravenous dexamethasone.

Collection of Blood Samples

Maternal venous blood samples have been obtained and placed in EDTA containers. Following the manufacturer's instructions, DNA extraction was carried out using the Puregene Blood Core Kit A (Qiagen, Maryland, USA). A spectrophotometer (Biorad, USA) was used to measure the amount and quality of DNA. Until it was used, DNA was kept at -20°C.

DNA Amplification

Genomic DNA extraction was performed using the DiaRex® Whole Blood Genomic DNA Extraction Kit (Cat. No: BLD-5295, Diagen, Ankara, Turkiye). The process involved lysis, proteinase K digestion, ethanol precipitation, and column-based purification to obtain high-quality genomic DNA. The nucleic acid concentrations of the extracted genomic DNA samples were measured using a Colibri Microvolume Spectrometer (Titertek-Berthold, Germany). Real-time PCR was used to analyze specific ADRB2 gene regions (Table 1). The primers designed to analyze the rs1042713 and rs1042714 regions of the ADRB2 gene are specified below. The primers were synthesized (Biomers, Germany) and reactions were performed using TaqProbe 2X qPCR MasterMix (Sansifast, UK). PCR amplification was carried out using a BioRad CFX-96 system.

Statistical Analysis

IBM SPSS version 23 (IBM SPSS Corp., Armonk, NY, USA) was used for data analysis. The Shapiro-Wilk test was utilized to assess the distribution's normality. Quantitative variables having a normal distribution were compared using the Independent Samples t-test, whereas statistical variables with a non-normal distribution were compared using the Mann-Whitney U test. The Kruskal-Wallis H test was used for comparisons between three or more groups having non-normal distributions. Categorical variables were represented as frequencies and percentages, while quantitative data were summarized as mean±standard deviation or median (minimum–maximum). Statistical significance was defined as a p-value of less than 0.05.

For our investigation, a power analysis was carried out. The one-way ANOVA determined that a minimum total sample size of 30 was needed based on ephedrine values, assuming a 95% confidence level (1-α), a 95% test power

Table 1. Primers for the rs1042713 and rs1042714 regions

rs1042713	Forward	GAACGGCAGCGCCTTCT
	Reverse	AGGACGATGAGAGACATGACGAT
rs1042714	Forward	CGGCAGCGCCTTCTTGCTGGCAC
	Reverse	TGCGTGACGTCGTGGTC

(1-β), and an effect size f = 0.789. The minimal sample size with 80% test power was 21; at 90% power, it was 24.[19] 520 pregnant women were included in the trial, despite the fact that 24 patients would have been enough to reach 90% power given the clinical cesarean rates during the study period.

RESULTS

The flow chart of our study is presented in Figure 1.

Descriptive statistical values of the variables are presented in Table 2.

No statistically significant differences were found in terms of descriptive statistics for all three types of polymorphism. Our descriptive statistics showed no statistically significant differences among the three polymorphism groups. We believe this is evidence that we have achieved homogenization among the groups.

The comparison of MAP and HR values is presented in Table 3.

MAP and HR values for Wild Type, Heterozygous Mutant, and Homozygous Mutant did not vary statistically significantly at any time point. No statistically significant differences were observed between heart rate and mean arterial pressure at any of the intraoperative measurement times (0 min, 5 min, 10 min, ...60 min) (*P*=.061, *P*=.054). Considering our intraoperative measurement times, we observed that hypotension developed particularly at the 5th or 10th minute. In all pregnancies secondary to spinal anesthesia, we observed the same clinical outcome for maternal hypotension, regardless of whether the patient had homozygous, heterozygous, or wild-type genetic polymorphisms. Although not statistically significant, the tendency for hypotension was minimally higher in the homozygous type. Furthermore, sympathetic block secondary to spinal anesthesia can cause bradycardia in pregnant women. In our study, there was no significant bradycardia in the pregnant women included. A decrease in heart rate of at most 20% was observed. Neither clinically nor statistically significant bradycardia was seen in any of our patients. Therefore, we can say that there is no predisposition to bradycardia in any of the three genetic polymorphism types.

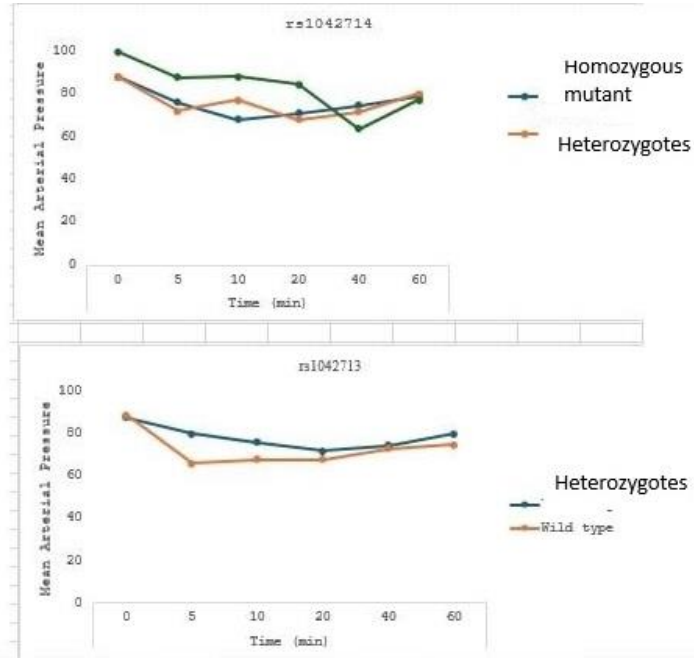

Figure 1. Flow chart of study

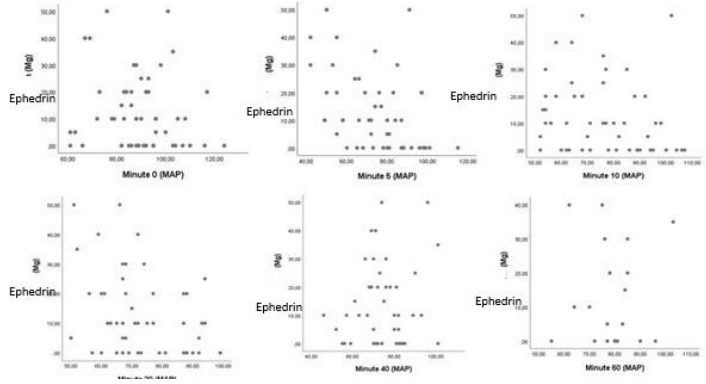

Figure 2. Graphical presentation of MAP values according to intraoperative measurement times

Figure 2 presents a graphical representation of MAP values at intraoperative measurement times for the rs1042713 and rs1042714 genes.As shown in Figure 2, hypotension occurred in all pregnant women—heterozygous, homozygous, and wild-type—within the first 5 and 10 minutes. However, hypotension persisted for a longer period in the homozygous type. In heterozygous and wild-type women, hypotension recovered much more quickly. This indicates that homozygous women are more prone to hypotension.

Figure 3 shows how frequently ephedrine was used based on the intraoperative measurement time (0.min, 5.min, 10.min .....60. min values).

As seen in Figure 3, ephedrine consumption is observed to be high at 5 and 10 minutes. Ephedrine consumption, an inotropic agent, begins to decrease from 20 minutes

Table 2. Descriptive statistics of the variables

	Mean±SD	Median (min-max)
Age (year)	29.52±5.08	29.5 (21 - 44)
Height (cm)	160.98±6.18	160 (150-178)
Weight (kg)	82.58±13.91	80 (61-117)
ASA	2.02±0.14	2 (2-3)
Sensory Block Formation Time (min.)	5.27±2.98	5 (2 - 15)
How many mg of intraoperative ephedrine was administered	12.6±13.7	10 (0 - 50)
How many mg of intraoperative antiemetic agent was administered	1.46±2.75	0 (0-12)
Postop antiemetic was administered Dexametazon 8 mg	0.23±1.23	0 (0-8)
	Frequency	**Percentage (%)**
rs1042714		
GG	270	51.9
GC	230	44.2
CC	20	3.9
rs1042714		
Homozygous Mutant	270	51.9
Heterozygous Mutant	230	44.2
Wild Type	20	3.9
rs1042714		
Glutamate	270	51.9
Glutamate/Glutamine	230	44.2
Glutamine	20	3.9
rs1042714		
GAA	270	51.9
GAA/CAA	230	44.2
CAA	20	3.9
rs1042713		
Heterozygous Mutant	330	63.5
Wild Type	190	36.5
rs1042713		
Glycine	190	36.5
Glycine/Arginine	330	63.5
rs1042713		
GGA	190	36.5
GGA/AGA	330	63.5
rs1042713		
GG	190	36.5
AG	330	63.5
General condition*		
Homozygous Mutant	270	51.9
Heterozygous Mutant	430	82.7
Wild Type	210	40.4
Was there a need for intraoperative ephedrine?		
No	180	35.3
Yes	330	64.7

*Multiple response

Table 3. Comparison of MAP and HR values

Group*	Homozygous Mutant	Heterozygous Mutant	Wild Type	*P*
MAP				
Minute 0	91.11±0.07	87.88±0.05	90.62±0.07	
Minute 5	75±0.07	73.53±0.05	71.95±0.07	
Minute 10	73.74±0.07	75±0.05	75.24±0.07	.061
Minute 20	73.3±0.07	73.53±0.05	73±0.07	
Minute 40	77.37±0.07	73.97±0.05	73.22±0.07	
Minute 60	80.17±0.07	78.82±0.05	76.33±0.07	
HR				
Minute 0	101.93±0.07	99.09±0.05	99.9±0.07	
Minute 5	97.81±0.07	93.67±0.05	96.29±0.07	
Minute 10	95.67±0.07	94.93±0.05	96.43±0.07	.054
Minute 20	98.67±0.07	94.6±0.05	97.52±0.07	
Minute 40	94.83±0.07	92.87±0.05	90.72±0.07	
Minute 60	74.86±0.07	78.16±0.05	75.1±0.07	

*Multipl Response Mean ±standart deviation

Table 4. Comparison of quantitative variables in the rs1042714 gene according to groups.

	Homozygous Mutant	Heterozygous	Wild type	Total	Test Statistics	*P*
Time of Sensory Block Onset (min)	5 (2 - 15)	5 (3 - 15)	2.5 (2 - 3)	5 (2 - 15)	4,155	,125[x]
İntraoperative ephedrin (mg)	10 (0 - 50)	5 (0 - 30)	5 (0 - 10)	10 (0 - 50)	2,779	,249[x]
İntraoperative antiemetic agent (mg)	0 (0 - 12)	0 (0 - 8)	2 (0 - 4)	0 (0 - 12)	0,566	,753[x]
Postoperative antiemetik agent (mg)	0 (0 - 4)	0 (0 - 8)	0 (0 - 0)	0 (0 - 8)	0,103	,950[x]

[x] Kruskal Wallis H test min: minute

onwards. Ephedrine consumption did not differ significantly among the three genotype groups. This proves that no genetic polymorphism is superior to another in terms of maternal hypotension development. Maternal hypotension was common across all genotype groups. Our study has once again proven the need for preventive measures such as preoperative fluid loading to prevent this clinical situation. We have once again demonstrated that intraoperative hypotension can occur in any case, regardless of the genetic polymorphism of the pregnant woman.

Ephedrine usage amount and gene polymorphism groups are presented in Table 4 and Figure 4. Ephedrine use was highest in the homozygous type and lowest in the wild type. Although there was no statistically significant difference, higher amounts of ephedrine were used in the homozygous type. In other words, a clinically significant predisposition to maternal hypotension was detected in the homozygous variant of the beta-2 adrenergic receptor

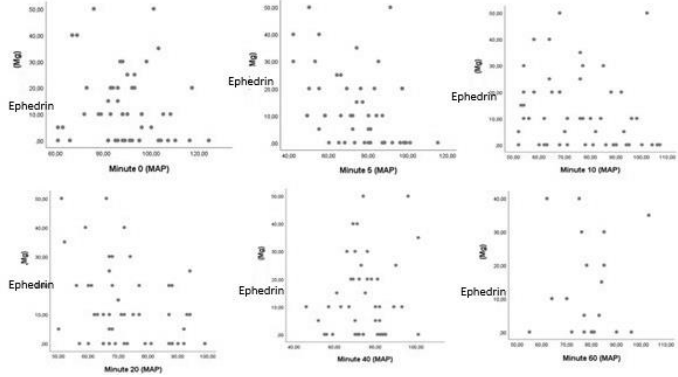

Figure 3. Frequency of Ephedrine use according to intraoperative measurement time

located on chromosome 5. As seen in Figure 4, ephedrine consumption was slightly higher in homozygous types. More precisely, hypotension showed a slightly longer, more persistent course in homozygous types. This persistent course minimally increased our ephedrine consumption in the homozygous group. Although there was a minimal difference at the clinical observation level, there was no difference at the statistical significance level.

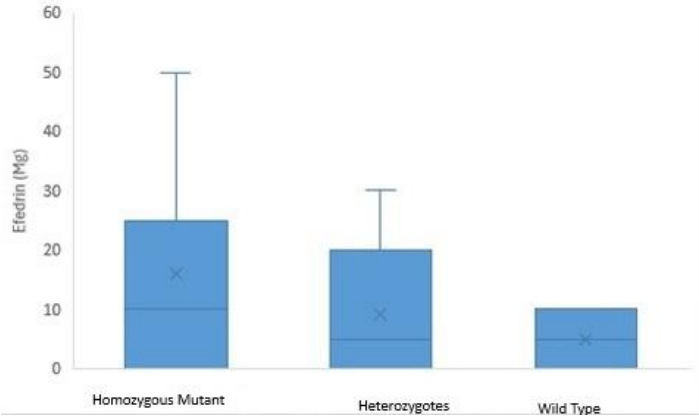

Figure 4. Ephedrine usage amount and gene polymorphism groups

Nevertheless, there was a lack of statistical significance in intraoperative ephedrine usage across subjects with wild-type, homozygous mutant, and heterozygous mutant genotypes, i.e., all three types of polymorphisms.

DISCUSSION

In terms of Beta-2 adrenergic gene polymorphism, no significant difference was found among pregnant women of Turkish ethnicity from Ordu Province in the Middle East Black Sea region.

People with the glycine allele at position 16 and/or the glutamate allele at position 27 of the Beta-2 adrenoceptor gene tended to need more ephedrine than people with homozygous arginine at position 16 and homozygous glutamine at position 27.[19] This was observed in an Arab ethnic group. 250 people made up the bigger population that was the subject of this investigation. Our smaller sample size, single-center design, and inclusion of only one ethnic group might all be contributing factors to the difference between our results and theirs.

Divergent findings were found in a North American cohort research that included several ethnic groups. During the first 15 minutes following spinal anesthesia for cesarean birth, pregnant women with homozygous Gly16 and Glu27 genotypes needed very little ephedrine, indicating that they had little intraoperative hypotension.[20] However, maternal hypotension was more common in our research, necessitating intraoperative ephedrine in 64.7% of cases.

Landau et al.[16] could not find any correlation between maternal Beta-2 adrenoceptor genotype and the need for intraoperative ephedrine after spinal anesthesia in elective cesarean sections in a Chinese sample. Our findings completely agree with those of Landau et al.[16]

Our results partially matched those of a research on adult Caucasian patients following major abdominal surgery. Carriers of the Gly16 and Glu27 alleles in the Beta-2 adrenoceptor gene needed more vasopressors to maintain intraoperative normotension after the sympathetic blockade brought on by thoracic epidural anesthesia than did carriers of the homozygous Arg16 and Gln27 alleles.[18] Although there was no statistically significant difference between the homozygous and heterozygous groups in our investigation, the intraoperative ephedrine need to maintain normotension was significantly higher in homozygous mutant individuals when all cases were taken into account. As a consequence, our findings somewhat agree with those of the Caucasian group.

One hour before to surgery, all pregnant women in our research received intravenous hydration with 500 mL of lactated Ringer's solution. As a result, all cases were handled using identical procedures and under elective settings.

Beta-2 adrenoceptor gene polymorphism was examined in the Korean population as part of a research assessing the hypertensive response brought on by the stress reaction to laryngoscopy and intubation. People with homozygous mutations in the Beta-2 adrenoceptor gene had a higher hypertensive response, according to that study. The homozygous group saw a greater rise in mean arterial pressures. The study examines the Beta-2 adrenergic response, therefore it is analogous to ours even though it concentrates on the stress reaction to intubation under general anesthesia.[20] In our investigation, the hypertensive response to stress was much more pronounced in homozygous instances, whereas the hypotensive response was more evident in those cases. The disparity in study findings raises the possibility of an ethnic component. Our work is the first to examine beta-2 adrenoceptor gene polymorphism in the Turkish population, particularly in Turkish women, in the literature.

According to certain reports, the prevalence of Beta-2-Adrenoceptor-27 polymorphisms in both normotensive and hypertensive individuals may vary by ethnicity.[21] Anderson et al.[22] found racial disparities in instances of hypertension and stress-induced cardiovascular reactivity, whereas Different studies in the literature observed racial variations in epinephrine and Beta-2 adrenoceptor responses.[23-25]

Study Limitations

Our study has several limitations. A power analysis was used to estimate the sample size. However, the primary limiting aspect in our study is the relatively small number of participants, given that there are bigger population studies in the literature. The fact that the study only covered one ethnic group and was limited to one geographic area—the Eastern Black Sea region—is the second drawback. The outcomes of a multicenter research including various ethnic groups from throughout the nation could have been different.

CONCLUSION

Single-nucleotide polymorphisms in the Beta-2 Adrenoceptor gene did not correlate with intraoperative maternal hypotension or the use of ephedrine in pregnant patients having spinal anesthesia for cesarean sections. We may conclude that there is no connection between maternal hypotension and the polymorphism of the beta-2 adrenoceptor-27 in Turkish women. We anticipate that our research will help guide future multicenter, large-population studies on this topic that involve several ethnic groups.

Etik Komite Onayı: Bu çalışma için etik kurul onayı Ordu Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (Tarih: 27 Eylül 2024, Karar No: 2024/121).
Hasta Onamı: Çalışmaya katılan tüm gebelerden bilgilendirilmiş gönüllü olur formu alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Konsept – A.K.; Tasarım – E.Ç.; Denetim – Ç.D.; Kaynaklar – Ç.D.; Malzemeler – Ç.D.; Veri Toplama ve/veya İşleme – A.K.; Analiz ve/veya Yorum – E.Ç.; Literatür Taraması – E.Ç., A.K.; Yazıyı Yazan – E.Ç.; Eleştirel İnceleme – E.Ç., Ç.D.; Diğer – A.K.
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Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Studies Ethics Committee of Ordu University Faculty of Medicine (Date: September 27, 2024, Approval Number: 2024/121).
Informed Consent: Written informed consent was obtained from all pregnant participants included in the study.
Peer-review: Externally peer-reviewed.
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