Letter to the Editor

The Effect of Beta-2 Adrenergic Receptor Genetic Variants on Vasopressor Requirements in Surgery Patients: A Meta-analysis

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Spinal anesthesia is a common technique which can significantly alleviate surgery patients' anguish, and can avoid the risks associated with general anesthesia. However, spinal anesthesia is associated with some other risks. The most common adverse event is hypotension resulting from a near complete sympathetic block. Nearly 1/3 of non-obstetric patients experience spinal anesthesia-induced hypotension. Moreover, in obstetric patients without pharmacological prophylaxis, the incidence rate of spinal anesthesia-induced hypotension can reach up to 70%-80%[1].

Surgery patients with spinal anesthesia-induced hypotension are often accompanied by nausea and vomiting, and preoperative hypovolemia, which may severely compromise patients' health, and induce cardiovascular collapse, put patients in danger. Therefore, it will be of great significance to prevent and treat spinal anesthesia-induced hypotension to ensure patients' safety and raise the success chances of the operation.

Studies have shown that patients' cardiac output, heart rate and stroke volume increased in the first 15 min following the initiation of spinal anesthesia[2], in addition, the systemic vascular resistance decreased significantly. These results highlight the fact that loss of arteriolar tone is the main mechanism of spinal anesthesia-induced hypotension. Therefore, vasopressors, such as ephedrine and phenylephrine, are currently identified as the mainstay of therapy for spinal-induced hypotension. In the past decades, ephedrine has been used as the drug of choice to treat spinal-induced hypotension.

The severity of hypotension and the response to vasopressors varies from patients to patients. Studies have proved that genetic factors are involved in the pathogenesis of the response to vasopressors, but the genetic basis remains poorly understood[3]. Identifying the genetic variants underlying the response to vasopressors is very helpful for prevention and treatment of spinal anesthesia-induced hypotension.

The beta-2 adrenergic receptor (β2AR) is ubiquitous in distribution and plays an important role in cardiovascular regulation. Altered β2AR is involved in the pathogenesis of hypertension, moreover, several polymorphisms of *β2AR* have been identified. Polymorphisms of codons 16, 27, and 164 may result in significantly changed functions of this receptor. In particular, researchers have paid much more attention to codons 16 and 27. The substitution of glycine for arginine at codon 16 (Gly16) was associated with enhanced agonist-induced desensitization, and the substitution of glutamic acid for glutamine at position 27 (Glu27) was associated with resistance to desensitization, in contrast to the responses associated with the products of wild-type alleles (Arg16 and Gln27, respectively)[4].

A number of studies report the associations between genetic variants of codons 16 and 27 of *β2AR* with vasopressor requirements. However, the results of the different studies are inconsistent. Almustafa et al. and Magalhães et al. found that patients with the Gly16 or Glu27 alleles need more ephedrine during the surgery than other patients[5,6]. While Smiley et al. reported that Gly16 and/or Glu27 resulted in lower vasopressor requirements[7]; Landau and Nielsen revealed that *β2AR* genotype did not affect ephedrine requirements[8,9].

Currently, there is no systematic assessment to explore the effect of these variants on vasopressor ephedrine requirements in surgery patients. Therefore, the present work was designed to perform a meta-analysis on the overall association

doi: 10.3967/bes2019.031

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between the polymorphisms of *β2AR* gene and ephedrine requirements based on the information collected from literature search.

All the studies on the association of β2AR gene polymorphisms with vasopressor requirements that were published before December 31, 2018 were retrieved from the PubMed, CNKI, Web of Science, Embase, ScienceDirect databases, and Cochrane Library. The key words used for literature search were: Beta-2 adrenergic receptor, genetic variants, single nucleotide polymorphism (SNP), vasopressor, ephedrine. Cross- references and citations in review articles were searched. Only the papers published in English and Chinese were assessed in this study.

The papers which include the following contents were selected, 1) the association between *β2AR* polymorphisms and vasopressor requirements in surgery patients; 2) genetic variants of codons 16 and 27; 3) ephedrine used as the vasopressor. The study design was not limited. Studies did not report genotypic frequencies were excluded. If more than one paper was published from the same sample sets, the one with the highest number of subjects was selected only.

Genotype frequencies of codons 16 and 27 on *β2AR* gene and the dose of ephedrine used in the surgery were independently extracted using a standardized, structured form including first author's name and year of publication from all selected studies.

The effect size of two genetic variants codons 16 (Arg16Gly) and 27 (Glu27Gln) on vasopressor ephedrine requirements in surgery patients was assessed based on the weighted mean difference (WMD) with calculation of 95% confidence interval (95% *CI*). Homogeneity among studies was tested based on the I^2 value. If the I^2 test *P* value was < 0.05, a random-effect model was applied. Otherwise, a fixed-effect model was applied. Meta-analysis was performed using the Review Manager 5.0 program and results were shown as forest plots. Begg's rank correlation was applied to investigate publication bias with STATA 12, in which a *P* value of less than 0.05 was considered to indicate significant potential publication bias.

A total of 49 papers hit literature search, 5 papers satisfying the criteria were analyzed. Twenty-six articles were included in different databases; fourteen researches were excluded as their subjects were not surgery patients; 3 were excluded as they used different drugs as vasopressor and 1 was excluded as its result did not list the genotype variation. Of the 5 eligible papers, 5 independent studies were performed with genotyping a total of 912 surgery patients. The protocol of the process for literature identification and selection is listed in Supplementary Figure S1 (available in www.besjournal.com). Main characteristics of these studies are shown in Table 1. Two SNPs (Arg16Gly and Glu27Gln) were considered for meta-analysis.

There was heterogeneity in the association of Gly16 for *β2AR* with vasopressor requirements among the included studies. Therefore, random-effect models were applied to analyze the association. The meta-analysis results showed that there were no differences of ephedrine requirements between patients with Gly/Gly and Arg/Gly of Arg16Gly, and between patients with Gly/Gly and Arg/Arg. The weighted mean difference (WMD) between Gly/Gly and Arg/Gly of Arg16Gly was -2.78 with 95% *CI* -10.07–4.52 (*P* = 0.46); WMD between Gly/Gly and Arg/Arg was 6.45 with 95% *CI* -7.82–20.73 (*P* = 0.38). While the ephedrine requirements were different between patients with Arg/Gly and Arg/Arg. The WMD between Arg/Gly and Arg/Arg was 9.65 with 95% *CI* 1.99–17.31 (*P* = 0.01), as shown in Figure 1.

There was homogeneity for vasopressor requirements in patients with Gln/Glu and Glu/Glu polymorphisms of Glu27 for *β2AR* among the included studies. Therefore, fix-effect model was applied to analyze the association. While there was heterogeneity for the others, and random-effect models were applied. The meta-analysis results showed that there were no differences of ephedrine

Table 1. Main Characteristics of the Included Studies

First Author and Year	Surgery	Sample Size (*n*)	Population	Age (y)	Sex (M/F)
Almustafa MM, 2016[5]	Cesarean delivery	234	Arab	32.3	0/234
Landau R, 2011[8]	Cesarean delivery	104	Chinese	-	0/104
Magalhães E, 2010[6]	Cesarean delivery	50	-	24.6	0/50
Nielsen M, 2016[9]	Neurosurgery	413	Danish Caucasians	54 ± 15	284/287
Smiley RM, 2006[7]	Cesarean delivery	170	white, hispanic, and black	-	0/170

requirements among patients with different genotypes of Glu27. The WMD between Gln/Gln and Gln/Glu of Glu27Gln was -7.67 with 95% *CI* -29.46–14.12 (*P* = 0.49); WMD between Gln/Gln and Glu/Glu was -3.52 with 95% *CI* -23.78–16.75 (*P* = 0.73) and WMD between Gln/Glu and Glu/Glu was 3.24 with 95% *CI* -1.51–7.98 (*P* = 0.18). As shown in Figure 2.

No evidence of publication bias was detected with respect to DFS and OS using Begg's rank correlation (Begg's test, *P* = 0.806; Egger's test, *P* = 0.988).

Hypotension is a common complication for surgery patients undergoing spinal anesthesia. Some studies have proved that the polymorphisms of *β2AR* gene is associated with hypertension and hypotension[10]. Currently, vasopressors, such as ephedrine, are used to treat with spinal-induced hypotension[7]. But the dose varies from patients to patients. A number of studies reported the associations of *β2AR* genetic variants with vasopressor requirements with inconsistent results.

The present work showed that the WMD between Gly/Gly and Arg/Gly of Arg16Gly was -2.78 with 95% *CI* -10.07–4.52 (*P* = 0.46); WMD between Gly/Gly and Arg/Arg was 6.45 with 95% *CI* -7.82–20.73 (*P* = 0.38); while WMD between Arg/Gly and Arg/Arg was 9.65 with 95% *CI* 1.99–17.31 (*P* = 0.01). It was reported that patients with Arg/Gly genotype require 9.65 mg ephedrine more than patients with Arg/Arg genotype during a surgery. While there were no differences of ephedrine requirements between patients with Gly/Gly genotype and Arg/Gly genotype, or with Gly/Gly genotype and Arg/Arg genotype. It was suggested that Gly16, Glu27 and haplotype pairs harbouring the Gly16Glu27 haplotype were independent predictors of hypotension and vasopressor requirements. Arg16 allele might be highly linked disequilibrium with Glu27 allele. Therefore, patients with the Arg16Gly polymorphism might be the carriers with Gly16Glu27 haplotype, which had the greatest effect on vasopressor requirements.

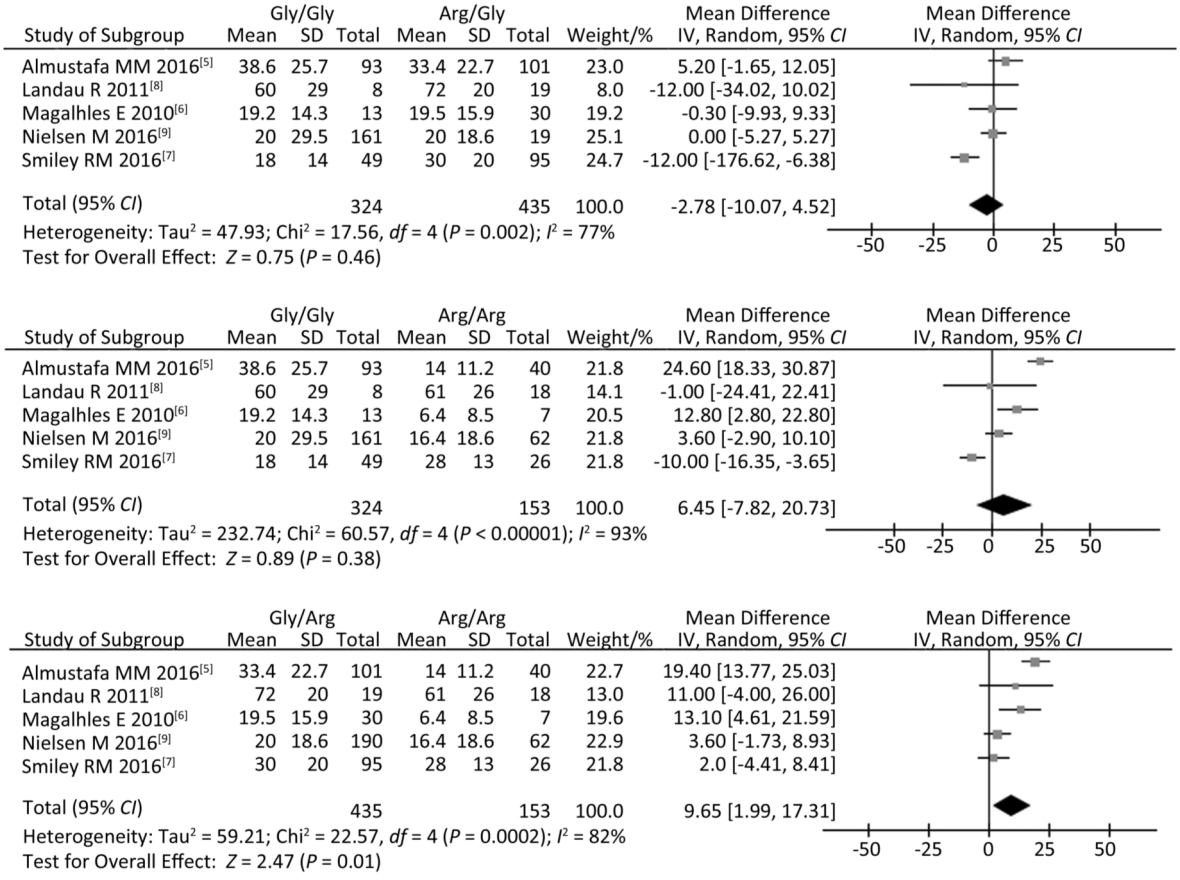

Figure 1. Meta-analysis result of the effect of Arg16Gly genetic variant on vasopressor requirements in surgery patients.

Although Almustafa MM et al. had described that the Glu27 allele carriers may need more ephedrine than Gln27 allele carriers[5], the research conducted by Smiley RM et al. showed that the Glu27 allele carriers may need the less ephedrine than Gln27 allele carriers[7], while Nielsen M et al. found that there were no differences of ephedrine requirements among patients with different genotypes of Glu27Gln[9]. The present meta-analysis found that the WMD between Gln/Gln and Gln/Glu of Glu27Gln was -7.67 with 95% *CI* -29.46–14.12 (*P* = 0.49); WMD between Gln/Gln and Glu/Glu was -3.52 with 95% *CI* -23.78–16.75 (*P* = 0.73) and WMD between Gln/Glu and Glu/Glu was 3.24 with 95% *CI* -1.51–7.98 (*P* = 0.18). There were no differences of ephedrine requirements among patients with different genotypes of Glu27Gln in the present study.

Only 3 researches exploring the relationship between the polymorphism of Glu27Gln and the ephedrine requirements are available and the number of the subjects is limited, which a limitation of the present study.

In this study, we performed a meta-analysis to clarify the effect of *β2AR* genetic variants on vasopressor requirements in surgery patients. We found that patients with the Arg16Gly polymorphism might have different vasopressor requirements from those with Arg16Gly heterozygotes in the surgery process. The results could provide a scientific basis on the clinical vasopressor dose in patients with different genotypes of Arg16Gly in *β2AR* gene.

However, it is necessary to carry out a functional study of these 2 polymorphisms on the vasopressor ephedrine requirements in surgery patients. In addition, it is also important to study the mechanism underlying in the future.

In conclusion, *Beta-2 adrenergic receptor* genetic variants codons 16 may affect the vasopressor ephedrine requirements in surgery patients. Patients with Arg16 homozygotes require less ephedrine than those with Arg16Gly heterozygotes in the surgery process.

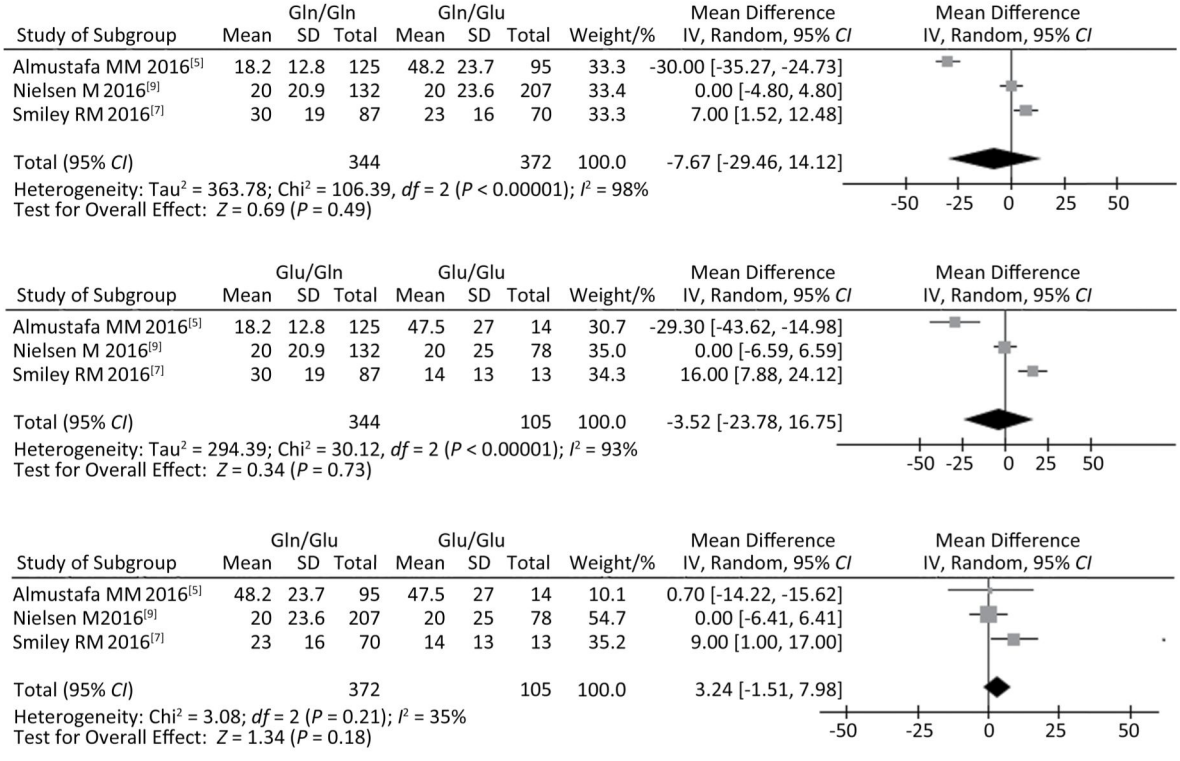

Figure 2. Meta-analysis result of the effect of Glu27Gln genetic variant on vasopressor requirements in surgery patients.

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Received: October 15, 2018;
Accepted: February 18, 2019

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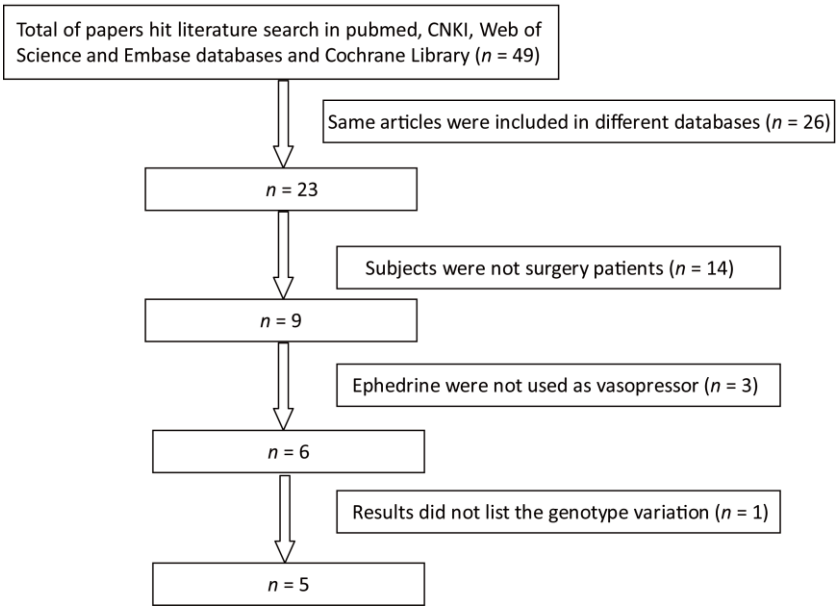

Supplementary Figure S1. Flow chart of articles screening.