Randomized Trial

Effects of Stellate Ganglion Block on Sedation as Assessed by Bispectral Index in Normal Healthy Volunteers

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Background: The sympathetic nervous system plays an important role in the arousal response. Recently, the stellate ganglion block (SGB) was found to effectively treat anxiety and night awakening in humans and decrease electroencephalogram (EEG) indices of arousal responses in rat. But, the role of the sympathetic block in human arousal responses has not yet been studied.

Objective: We performed this prospective, double-blinded, controlled volunteer study to investigate the sedative effects and bispectral index (BIS) changes of SGB.

Study Design: A randomized, double-blind trial.

Setting: Single academic medical center.

Methods: This study was approved by the Ethics Committee of Kyungpook National University Hospital (ref: KNUH_10-1081) and registered with CRiS (Clinical Research Information Service, http://cris.cdc.go.kr, ref: KCT0000036, 2010. 9.24). Twenty healthy volunteers were enrolled in this study. The volunteers were randomly assigned to one of 2 groups: the SGB group (n = 10) and the sham group (n =10). Volunteers in SGB group received SGB and volunteers in the sham group received a sham procedure. BIS value, heart rate, and blood pressure were measured before and 5, 10, 20, and 30 minutes after the procedure. Observer's Assessment of Alertness/Sedation (OAA/S) scores were assessed before and 10 and 30 minutes after the intervention.

Results: In the SGB group, BIS values and OAA/S scores significantly decreased after the intervention as compared to baseline ($P < 0.05$). The values were also significantly decreased in the SGB group when compared to the values in sham group after the intervention ($P < 0.05$). There was a significant change of mean blood pressure 10 to 30 minutes after SGB ($P < 0.05$). There were no differences in heart rate during study period between groups.

Limitations: This study is limited by a relatively small sample size.

Conclusions: This study showed that SGB has a sedative effect in normal healthy volunteers, as evidenced by decreased OAA/S scores and BIS values.

Key words: Stellate ganglion, sympathetic block, sedation, bisepctral index, EEG, volunteers

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Stellate ganglion blockade (SGB) is a sympathetic nerve block that produces a sympatholytic effect in the ipsilateral head, neck, and upper limb. It has been used to treat patients with various diseases including headache, angina pectoris, and complex regional pain syndrome (1). The mechanism of action of SGB involves peripheral vasodilation resulting from blocking the sympathetic ganglion (2). But, the vasomotor effect of SGB alone cannot explain various clinical efficacies of SGB. Recently, SGB has been shown to decrease anxiety symptoms and insomnia in patients with combat-related post-traumatic stress disorder (PTSD) (3) and night awakenings in breast cancer patients (4).

The bispectral index (BIS) system uses an integrated analysis of the electroencephalogram (EEG) to assess the level of consciousness during sedation with hypnotics and has been shown to be both simple and sensitive (5).

The sympathetic nervous system plays an important role in the arousal response. Adrenergic hormone agonists increase the arousal response (6,7) and beta antagonists decrease the arousal response (8). Recently, we found that SGB in rats significantly decreases EEG activities, such as spectral edge frequency 95% and median frequency, which are used to measure sedation depth (9).

We hypothesized that the sympatholytic effect of SGB might decrease the arousal response and EEG indices of arousal in humans. Therefore, we aimed to evaluate the sedative effects of SGB using BIS and Observer's Assessment of the Alertness/Sedation (OAA/S) scores (10) in healthy human volunteers (Table 1).

Methods

This study was approved by the Ethics Committee of Kyungpook National University Hospital (ref: KNUH_10-1081) and registered with CRiS (Clinical Research Information Service, http://cris.cdc.go.kr, ref: KCT0000036, 2010. 9.24). Volunteers were recruited by flyers posted at the local universities. Volunteers were excluded if they were not between the ages of 20 and 54; had a BMI < 20 or > 30kg/m^2; were taking medications which may affect BIS (α and β agonist and antagonist, hypnotic and neuroleptic agents) or coagulation (aspirin, warfarin, and heparin); if they were chronic drug or alcohol abusers; had history of liver or renal insufficiency, cardiovascular system problems, or asthma; or had a hypersensitivity to local anesthetics. Twenty healthy volunteers (10 men and 10 women) were ultimately enrolled and written informed consent was obtained from all volunteers.

All volunteers were instructed to abstain from alcoholic beverages and heavy exercise for at least 24 hours, caffeine for at least 12 hours, and food for 2 hours before the assessment. The volunteers were randomly allocated to the SGB group or the sham group using the online randomizer (Quickcals, Graphad Software, San Diego, CA, USA).

This study was performed in a quiet, light room with volunteers in the supine position and all measurements were performed between the hours of 09:00 to11:00 AM. Monitoring consisted of ECG, non-invasive blood pressure, and BIS. BIS sensor strips were applied to left side of the volunteers' foreheads and the BIS electrodes were connected to the BIS monitor (BIS Vista, Aspect Medical Systems, Newton, MA, USA). The hemodynamic and BIS monitors were located outside of the room. BIS values and hemodynamic data were electronically stored in a computer system and exported after the end of the test period in this study. BIS values were recorded before each OAA/S evaluation (Table 1) and the average BIS values were calculated for 30 second segments of continuous BIS data. Fifteen minutes were taken to obtain stable baseline BIS score, OAA/S scores, heart rate, and blood pressure. BIS and hemodynamic data were measured at 5, 10, 20, and 30 minutes after the intervention. OAA/S scores were assessed after the BIS measurement at 10 and 30 minutes after the intervention. A physician who was unaware of the volunteers' assignment groups obtained these parameters and evaluated the appearance of Horner's sign after the intervention. In the SGB group, SGB was performed by an injection of 7 mL of 1% lidocaine at the anterior aspect of the right sixth cervical transverse process with ultrasound assessment by an anesthesiologist. In the sham group, 7 mL of 1% lidocaine was injected into the subcutaneous tissue of the right side of the neck by the same anesthesiologist.

Table 1. *Observer's Assessment of Alertness/Sedation Scale (OAA/S).*

Responsiveness	Speech	Facial Expression	Eyes	Score
Responds readily to name	Normal	Normal	Clear, no ptosis	5
Lethargic response to name	Mild slowing	Mild relaxation	Glazed/mild ptosis	4
Response to name only if called repeatedly	Slurring	Marked relaxation	Glazed/marked ptosis	3
Response only after mild prodding	Not recognizable	Not recognizable	-	2
No response to prodding or shaking	-	-	-	1

OAA/S is the lowest score in any of the 4 categories.

Statistical Analysis

All parametric data are presented as mean ± standard deviation or median. Heart rate, blood pressure, and BIS values were analyzed with 2-way repeated measures analysis of variance, followed by post-hoc comparisons (Bonferroni method). OAA/S scores were analyzed with the Friedman test, followed by post-hoc comparisons (Wilcoxon signed-rank test with Bonferroni correction). Analyses were performed using the SPSS software program for Windows, version 17.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was accepted as statistically significant.

A pilot study using volunteers showed the lowest BIS value after intervention was 95 ± 4.2 in the sham group and 84 ± 9.5 in the SGB group. Based on the pilot study, we needed 7 volunteers for each group to detect a difference with a significance level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). After compensating for an assumed SGB failure rate and dropout rate, we decided to enroll 10 volunteers for each group.

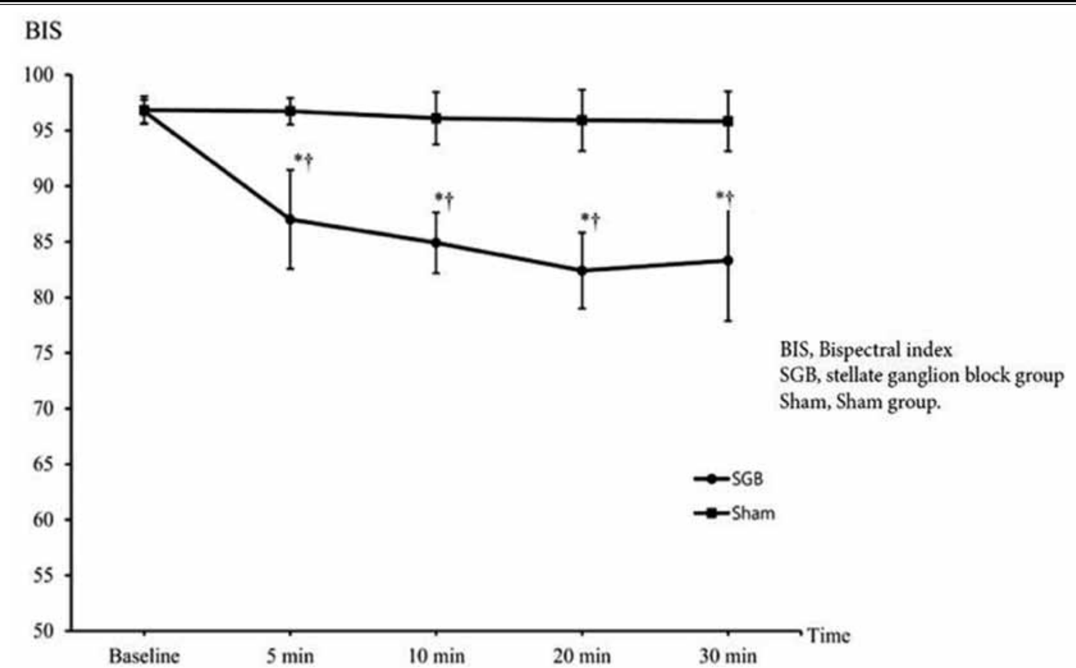
Results

Twenty healthy volunteers (10 men and 10 women) with mean age of 25.5 years (range 21 – 35 years) completed this study. There were no significant differences in age, gender, height, or weight between the 2 groups (Table 2). Within 3 minutes after the procedure, all volunteers in the SGB group showed Horner's sign. During the study period, Horner's sign was not observed in any volunteers in the sham group. The BIS values are shown in Fig 1. OAA/S scores are shown in Table 3. The BIS value and OAA/S scores before the intervention were not different between groups. The BIS values at 5, 10, 20, and 30 minutes after the intervention were significantly lower in the SGB group than in sham group ($P < 0.05$). The OAA/S scores at 10 and 30 minutes after the intervention were significantly lower in the SGB group compared to the sham group ($P < 0.05$). The median OAA/S scores in all volunteers in the SGB group was 4

Table 2. *Demographic data*.

	SGB group	Sham group
Male : Female	6:4	4:6
Height	169.0 ± 6.5	166.5 ± 10.7
Weight	63.1 ± 10.7	61.8 ± 9.0
Age	26.2 ± 4.7	24.7 ± 5.1

Values are number or mean ± standard deviation. SGB; Stellate ganglion block



*$P < 0.05$ when compared with sham group at each time.
† $P < 0.05$ when compared with baseline

Fig. 1. *Bispectral index changes*.

Table 3. *Changes of Observer's Assessment of Alertness/Sedation Scale (OAA/S).*

	OAA/S score	Baseline	10 min after intervention	30 min after intervention
SGB group (n = 10)	Median	5	4*†	4*†
	5	10	0	7
	4	0	10	0
	3	0	0	3
Sham group (n = 10)	Median	5	5	5
	5	10	9	10
	4	0	1	0
	3	0	0	0

Values are number or median. SGB; Stellate ganglion block. *$P < 0.05$ compared with sham. †$P < 0.05$ compared with baseline.

Table 4. *Changes of heart rate and mean blood pressure.*

		Baseline	5 min	10 min	20 min	30 min
SGB group (n = 10)	HR	72.2 ± 10.3	70.3 ± 10.1	70.5 ± 9.5	71.6 ± 9.4	71.1 ± 9.0
	MBP	90.7 ± 8.4	88.4 ± 12.0	78.2 ± 13.4*†	79.6 ± 13.1*†	79.7 ± 12.3*†
Sham group (n = 10)	HR	71.2 ± 8.0	70.9 ± 11.2	69.1 ± 9.7	70.2 ± 11.3	70.6 ± 9.9
	MBP	90.0 ± 9.4	85.6 ± 8.6	84.7 ± 8.4	84.5 ± 9.4	85.5 ± 9.7

Values are mean ± standard deviation. SGB; Stellate ganglion block group. *$P < 0.05$ compared with sham. †$P < 0.05$ compared with baseline.

at 10 minutes after the SGB, and 3 volunteers scored a 3 at 30 minutes after the SGB. When the OAA/S score decreased from 5 to 3, the BIS index decreased from 94.2 ± 3.3 to 78.5 ± 0.7 in the SGB group. However, there were no significant changes of BIS values and OAA/S scores in the sham group.

A significant change of mean blood pressure was shown 10 to 30 minutes after the SGB, but there were no differences in heart rate during study period between the 2 groups (Table 4).

Discussion

This study demonstrated that SGB significantly decreases the BIS value and OAA/S score in normal healthy volunteers. These results suggest that SGB may have a sedative effect.

The sympathetic nervous system plays important roles in the modulation of the central nervous system (CNS) activity. It is involved in regulating the arousal response, vigilance, and anxiety (11,12). It has been reported that the adrenergic projections, presumably from the locus ceruleus in the basal forebrain, influence EEG activity via the actions of the beta-adrenergic receptor (13). Infusion of isoproterenol, a beta-agonist, into the medial septal region of the basal forebrain suppresses REM sleep and elicits behavioral and EEG indices of waking in rats (13). Similarly in humans, it was found that the bispectral index is significantly correlated with plasma norepinephrine levels (14). Infusion of adrenergic agonists, such as isoprenaline and epinephrine, increases EEG activity and has an arousal effect in lightly anesthetized patients (6,7). Additionally, it has been reported that a significant suppression of cortical EEG activity during anesthesia is promoted by the infusion of esmolol, a beta antagonist (8).

The stellate ganglion, a sympathetic ganglion formed by the fusion of the inferior cervical ganglion and the first thoracic ganglion, supplies the head, neck, and upper extremity. It has extensive neuronal connections with various parts of the brain, such as the hypothalamus, amygdala, infralimbic, insular, and ventromedial temporal cortical regions (15). Therefore, inhibition of these complex neuronal connections between the stellate ganglion and the brain may provide the therapeutic actions of a SGB in relation to various diseases. SGB can decrease the adrenal hormone level in plasma (16) or the brain (17). The severity of PTSD symptoms is significantly correlated with norepinephrine levels in the brain (18). SGB was reported to be effective in reducing the symptoms of PTSD by inducing a prolonged reduction of nerve growth factor, which led to a decrease in brain norepinephrine levels (3). In our previous study (9), we found that SGB significantly decreases EEG indices of arousal, such as spectral edge frequency by 95%, and median frequency in rats (13).

BIS is a dimensionless variable between 0 and

100 that correlates with the degree of sedation. BIS is determined in a multivariate regression model that depends on 3 variables: burst suppression ration, relative α/β ratio, and bicoherence of the EEG. High-frequency signals from electrical devices and electrical activity of muscles potentially affect the BIS value (19). Ptosis on the ipsilateral side of the face, which is considered evidence of a successful SGB, may affect BIS value as well. Therefore, we recorded BIS on the contralateral side of the SGB.

The OAA/S scale is a reliable and sensitive method to measure the level of alertness during sedation (15). But, the OAA/S scale has potential disadvantages. For example, obtaining a score generally requires some extrinsic patient stimulation such as calling, prodding, or shaking, to evaluate the patient's neurological status. Therefore, the assessment of OAA/S itself can affect the sedative status. Consequently, we assessed the OAA/S score after measuring BIS. The median OAA/S score was significantly lower in the SGB group than in the sham group. All volunteers who received SGB showed an OAA/S score of 4 at 10 minutes after the SGB, and 3 volunteers showed a score of 3 at 20 minutes after the SGB.

Lidocaine can decrease BIS value (20), so we injected lidocaine into the subcutaneous tissue of the neck to check the systemic effect of lidocaine on BIS. In the present study, the subcutaneous injection of 7 mL of 0.1% lidocaine did not decrease the BIS value and OAA/S score when compared with the baseline value.

SGB can alter hemodynamics (21). In the present study, a significant decrease in the mean blood pressure was shown 10 to 30 minutes after the SGB, but there were no differences between the groups in the heart rate during the study period.

The small number of volunteers in this study might be a limitation of the study. A larger number of volunteers would have increased the power, but this number was sufficient to meet significant level and power by statistical analysis.

Conclusion

In conclusion, we have shown that SGB significantly decreases BIS values and OAA/S scores in healthy volunteers. These results suggest that SGB has a sedative effect.

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