Ultrasound-guided the stellate ganglion block relieved the stress responses and improved early postoperative sleep in elderly patients after thoracoscopic surgery for lung cancer

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Research Article

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Abstract

Background: Thoracoscopic surgery is one of the main methods for the treatment of lung cancer. Most patients had severe sleep disorders after surgery, which affected the rapid recovery of patients. Postoperative sleep disturbance may be associated with strong stress responses. Our study was to evaluate the effects of stellate ganglion block (SGB) on stress responses and early postoperative sleep for the aging with lung cancer after thoracoscopic surgery.

Methods: 92 eligible elderly people were included and randomly divided into the SGB group and control group. Before anesthesia induction, The patients in SGB group were given 0.5% ropivacaine 7ml to the stellate ganglion site , while scanned the stellate ganglion block site in the control group. We needed to monitor the sleep duration, N3 sleep stage and sleep efficiency index by BIS-Vista monitor at various time points. We also needed to recorded AIS score, VAS score, the concentration of cortisol, norepinephrine and 6-HMS at various time points.

Results: Most of patients had insomnia after surgery in the both groups , but compared with the control group, patients in the SGB group showed longer sleep duration and N3 stage sleep, higher sleep efficiency index, lower AIS score, and higher concentration of 6-hydroxysulfate melatonin in urina sanguinis. In addition, the SGB treatment inhibited HPA and SAM axis, alleviated stress responses. And patients in the SGB group had lower concentration of cortisol and norepinephrine after surgery.

Conclusions: The SGB treatment relieved the stress responses and improved the early postoperative sleep of elderly patients with lung cancer after thoracoscopic surgery.

Background

Lung cancer has high rates of morbidity and mortality in the world, [1] Surgical excision under the thoracoscopic has become one of the main surgical treatment methods for lung cancer. However, it has been widely recognized that both surgical manipulation and anesthetic techniques activated the the hypothalamic-pituitary-adrenal(HPA) axis and sympathetic-adrenal-medullary(SAM) axis and generated strong stress responses,[2] and then resulted to sleep loss and sleep disruption[3,4.] Postoperative sleep disorders cause serious adverse effects, such as bad emotional , increased pain sensitivity and hypertension, Sleep loss and disruption can also lead to diminished memory consolidation,[5] weakened immune system function,[6] and declined cognitive. However, there is no good treatment for postoperative sleep disorders at present.

Many factors cause postoperative sleep disturbances. Although the mechanisms of postoperative sleep disturbance are still unclear, it may be related to autonomic system disorder, HPA and SAM axis hyperactivity. Compared with the young, the aged tends to have worse sleep quality because of the sleep structure changing, it shows frequent wake, early wake, short duration and decreased N3 sleep stage.[7] The stellate ganglion also called cervical and thoracic sympathetic ganglia, previous studies have shown

that the stellate ganglion block (SGB) is able to inhibit HPA and SAM axis overactivity.[2,8] The SGB treatment had been used more and more in perioperative period, However, the effect of the SGB on stress response and early postoperative sleep disorder in the aged undergoing thoracoscopic surgery have not been studied. Therefore, we carried out this study to investigate the effects of the SGB treatment on stress and sleep quality in the aged, providing clinical evidence for rapid recovery to the aged with lung cancer after thoracoscopic surgery.

Methods

2.1 Study design:

This is a prospective, randomized and controlled clinical trial . The study was carried out in the First Affiliated Hospital of Bengbu Medical College. The ethics was approved by The Ethic Committee of the First Affiliated Hospital of Bengbu Medical College(approval number:

2021KY063). The trail was registered in Chinese Clinical Trial Registry system on 21 November 2021 , registration number was ChiCTR2100053449 . The participants were involved from November 22, 2021 to March 20, 2022.

2.2 Participants

100 elderly patients with lung cancer who underwent thoracoscopic surgery in the First Affiliated Hospital of Bengbu Medical College were randomly divided into SGB group and control group. The Inclusion criteria include the following:(1)Age 60-80; (2)BMI between 20-27.9kg/m^2 ; (3)American Society of Anaesthesiologists (ASA) physical status I-III. The exclusion criteria include the following: (1)Inability to cooperate; (2)history of thoracic operation; (3)coagulopathy; (4)the operation transfer to thoracotomy; (5) postoperative VAS(Visual Analogu Scale) score≥4; (6)allergy to ropivacaine; (7)Liver and kidney dysfunction; (8)Bradycardia or arrhythmias; (9)Sleep apnea syndrome. (10)Serious complications:cerebral infarction ,cerebral hemorrhage or heart failure and so on.

2.3 Randomization and blinding

92 eligible patients were randomly assigned to the stellate ganglion block group (SGB group) or the control group in a 1:1 ratio. The randomization sequence was generated by an uninvolved teacher (Dr. Zhu) using SPSS package (version 25; IBM Corp, Armonk, NY, USA), and the group allocation were sealed by Dr. Zhu in identical, opaque and sequentially numbered envelopes. Envelopes were opened and revealed the allocation group when eligible patients are available in the pre-operative room. An experienced anesthesiologist (Dr. Wei) who was not involved to the study performed ultrasound-guided the stellate ganglion scanning or blocking at the C6-7 level in the pre-operative room, After that, another anesthesiologist who was not involved in the study performs routine induction and maintenance of anesthesia. All patients and data collectors were blinded.

2.4 Clinical Interventions

Before anesthesia

Once eligible patients entering to the pre-operative room, venous blood was collected 5 ml to vessels with heparin sodium after intravenous access was accessed in the pre-operative room. Dr. Wei performed the stellate ganglion scanning or blocking under the ultrasound guidance at the surgical side according to the grouping allocation after the peripheral intravenous access was secured. In supine position, patients' neck was slightly extended.The anatomy of C7 level (C7 with only one posterior tubercle) and C6 (C6 with two tubercle) level were found under the high-frequency linear array ultrasound probe with imaging depth of 4cm. At the level between C6- 7, the following anatomical structures were found under the ultrasound guidance:The common carotid artery, internal jugular vein, longus colli muscle and prevertebral fascia. The stellate ganglion located on the surface of longus colli muscle and deep prevertebral fascia.In SGB group, 7ml 0.5% ropivacaine were injected when the tip of 22-gauge needle to the stellate ganglion site in-plane approach under ultrasound guidance. After observing 20 minutes, the appearance of Horner syndrome meant that the SGB was successful.

General anesthesia

In operating room, monitoring included BIS, electrocardiography, heart rate (HR), systolic blood pressure (SP), diastolic blood pressure (DP), pulse oxygen saturation.General anesthesia induction drugs included:propofol1- 2mg/kg , sufentanil 0.5ug/kg , cis-atracuride 0.2mg/kg. 3 minutes later, the double-lumen tracheal catheter was inserted, and the correct position was adjusted through the fiber-optic bronchoscopy. Half an hour after induction, all patients were routinely given 5mg tropisetron was to prevent postoperative nausea and vomiting. The respiratory parameters was adjusted to maintain end-tidal carbon dioxide at 35-45mmHg. Anesthesia maintenance included propofol 2-3mg/kg/h, remifentanil 0.3ug/kg/min, inhalation oxygen flow 2L /min, sevoflurane 1.5%. Cis-atracuride was administered every 40-60 minutes, 10ug sufentanil was administered by 30 minutes before the end of surgery. During the operation, the BIS value was maintained at 45-60 by adjusting the infusion rate of propofol. norepinephrine and nitroglycerin were used to maintain fluctuation of blood pressure within 20% of baseline during the operation. After surgery, the patient was transferred to PACU for further observation until the patient was awake to extubation. After that, the patient was sent to the lintensive care unit of the thoracic surgery department.

Postoperative analgesia management

Postoperative analgesia pump was used in all patients to relieved pain, all patients used the same patient-controlled analgesia (PCA) . 100ug sufentanil and 10mg tropisetron diluted to 100ml in PCA.The program of the PCA system included:The bolus dose of 2mL, continuous infusion speed was 2mL /h , the single dose was 2mL, and the locking time was 30min. All patients and their families knew how to use PCA.

2.5 The study outcome

The primary outcome were sleep duration and the sleep efficiency index which were measured by BIS-Vista monitor. When the values of BIS ≤80, it means entering to the sleep state, and the values of BIS ≤40, it means entering the N3 sleep stage.[9] Sleep duration was defined as the duration of BIS ≤80 within 8 hours of monitoring time (22:00-06:00); The sleep efficiency index means that the ratio of total sleep time to the monitored 8 hours.[10] BIS-Vista monitor was used to monitor the sleep of patients on the last night before surgery (seep1), the first nights after surgery (sleep2) and the second nights after surgery (sleep3) from22:00-06:00). The secondary outcomes including: N3 stage of sleep on the last night before surgery(N3-1), the first night (N3-2) and the second night(N3-3) after surgery ,the Athens Insomnia Scale (AIS) score on the last night before surgery(AIS1), the first night (AIS2) and the second night(AIS3); the concentration of 6-hydroxysulfate melatonin (6-HMs) in urina sanguinis; the concentration of norepinephrine and cortisol in plasma; pressing the analgesic pump times within 48 hours after surgery; Visual Analogu Scale (VAS) score at 10pm of the first(VAS1) and second(VAS2) night after surgery;VAS score on the first walk after surgery.

2.7 Measurement of the stress response index and sleep hormone

5ml of venous blood was taken into a vacuum tube with heparin sodium at the following time points: before anesthesia (T1),5min after extubation (T2), at 6am on the first morning after surgery(T4). 3ml urina sanguinis into vacuum tube was collected at the following time points: at 6am in the morning of surgery(T3), at 6am on the first morning after surgery(T4), at 6am on the second morning after surgery(T5). Then the specimen was centrifuged at 3000 RPM for 30min, and the supernatant was stored in a refrigerator at -80℃. Biochemical markers of stress in plasma include norepinephrine and cortisol. The metabolite of sleep endocrine hormone - melatonin is 6-hydroxysulfate melatonin. Measurement of 6-hydroxysulfate melatonin in urine can reflect the secretion of melatonin at night. [11]Norepinephrine, cortisol and 6-hydroxysulfate melatonin were measured by enzyme-linked immunosorbent assay (ELISA).

2.8 Sample size

According to the sleep duration(mean ± standard deviation [SD]) on the first postoperative night in our Preliminary experiments(the SGB group:212.33± 125.366 min; the control group: 124.86 ±126.069 min), the sample size was 34 patients in each group with assuming a two-sided$\alpha$of 0.05 and a power of 0.80 by using https://www.cnstat.org/samplesize/7/. Considering some patients could be drop-out during the follow-up visits, we need to acquire 100 patients in each group.

2.9 Statistical analysis

SPSS(Version 25; IBM Corp, Armonk, NY, USA) software was used for statistical analysis.The categorical data were presented as percentage or frequency, and were analyzed by Chi-square test or Fisher’s exact test.Continuous data were presented as mean ±SD or median [25% percentile, 75% percentile], then used Kolmogorov-smirnov test to analyze whether the data had the normal distribution or not.The normal

distribution data were analyzed by independent T test and the non-normal distribution data were analyzed Mann-Whitney U-test. It was considered as Significant difference when P value < 0.05.

Results

3.1 Experiment design

From November 22, 2021 to March 20, 2022, a total of 100 patients were accessed eligibility, among which 2 patients refused to participate, 2 patients had sinus bradycardia, 1 patient had atrial premature beats, 1 patient had complete right bundle branch block and 2 patient had incomplete right bundle branch block, and then, 92 patients were enrolled to the study. 92 patients were randomly assigned to the SGB group or the control group(Showing in the in Fig.1). The SGB group excluded 9 participants and the control group excluded 8 participants because of BIS values collection failed or the operation transfer to thoracotomy intraoperatively or the result of the pathology weren't lung cancer. In addition, 1 participant was excluded in SGB group because the stellate ganglion block failed, In control group, 1 participant refusal to continue to participate, 1 participants were excluded because cerebral infarction2and postoperative VAS(Visual Analogu Scale) score=4.

3.2 Baseline data

The characteristics and surgical types of patients are shown in table1, there were no significant difference between the two groups in age, gender, body mass index, ASA, complications, the side and type of the operation. Compare the data during surgery(in table 2) between the two group, there were also no significant difference.

3.3 Stellate ganglion block prolong sleep duration, N3 sleep stage and improve sleep efficiency index in patients with lung cancer after thoracoscopic surgery(in table 3).

Observing the BIS monitoring data, there were no significant differences in preoperative sleep1, N3 stage sleep(N3-1) and SEI1 between the two groups. Both groups had severe sleep disorders after surgery, which were manifested as shortening sleep duration, decreasing SEI, and reducing or even lost sleep at N3 stage. However, in the SGB group, patients showed longer sleep duration on sleep2 and sleep3 (P=0.010 and 0.007, respectively) in Table3 , higher SEI2 and SEI2(Showing in the Fig.2) and less N3 stage sleep duration loss(N3-2,N3-3) than the control group(P=0.028 and 0.012, respectively) in Table3.

3.4 Stellate ganglion block improves subjective sleep quality.

In clinical practice, Athens Insomnia Scale (AIS) is used to assist in the diagnosis of insomnia and to measure the intensity of sleep difficulties[11]. AIS≥6 indicated insomnia. The scores of the AIS were remarked as AIS1, AIS2 and AIS3 on the night before surgery, the first night after surgery and the second night after surgery. According to the scores of the AIS, both groups had insomnia before surgery, and the incidence of insomnia without significant difference(51.4% and 41.7% respectively), Subjective sleep

disorder existed on the first and the second night after surgery in both groups, and the incidence of sleep disorder in stellate ganglion block group was significantly lower than the control group9(Table 3).

3.5 Stellate ganglion block improve the concentration of 6-hydroxysulfate melatonin in urina sanguinis of patients with lung cancer after thoracoscopic surgery.

Melatonin is an endocrine hormone which relate to sleep quality, the main product of melatonin metabolism by the liver was 6-hydroxysulfate melatonin. The secretion of melatonin at night was reflected by the concentration of 6-hydroxysulfate melatonin in urina sanguinis[28]. There was no significant difference at T3 on the level of 6-hydroxysulfate melatonin in urina sanguinis. The concentration of 6-hydroxysulfate melatonin decreased significantly in both groups after surgery, but the concentration in SGB group was significantly higher than the the control group(Fig.3)

3.6 Stellate ganglion block inhibit the HPA and SAM axis to reduce stress (Fig.4).

Excessive stress responses affected postoperative sleep. The levels of cortisol and norepinephrine in plasma are associated with HPA and SAM axis excitation. There was no significant difference in the plasma concentrations of cortisol and norepinephrine between the two groups at T1. The concentrations of cortisol and norepinephrine in the two groups were significantly increased at T2 and T4 , they were significantly higher in the control group than the SGB group.

3.7 Compared to the control group, the patients in the SGB group took their first steps earlier,had lower motion VAS score and fewer hospital stays. However, there were no significantly difference in postoperative extubation time, postoperative resting pain, postoperative nausea and vomiting, and The pressing the analgesic pump times between the two groups(in Table4).

Discussion

Sleep is an important process for physical and mental recovery, especially for the aging after surgery. Aging is an independent risk factor for the occurrence of sleep disorders, the incidence of insomnia up to 50% for the elderly over 65 years old.[12] In our experiment, the insomnia rate of AIS1 score was 46.6%, which may be due to the age of the patients in our study being over 60 years old. Elderly patients are often accompanied with reduction of slow wave sleep, rapid eye movement (REM) and sleep efficiency.[13] Chung et al proved that elderly patients often have lower sleep efficiency after surgery.[14] In our experiment, the insomnia rate of AIS2 score was 88.6% in the control group after thoracoscopic surgery, which was significantly higher than the SGB group. It may be related to the strong stress response of perioperative patients. It had been reported that postoperative sleep disturbances often coexisted with hypertension,[15] postoperative delirium[16] and the longer hospital stays which were against to the ERRS(Fast-track surgery or enhanced recovery after surgery) concept. Our study showed that SGB treatment improved early postoperative sleep in elderly patients undergoing thoracoscopic surgery for lung cancer and shorten their hospital stay than patients in the control group, but it may be the error caused by our small sample size.

Sleep in the healthy people was controlled by the parasympathetic nerve. However, postoperative patients always had strong stress responses[17] due to the stimulation of surgery and anesthesia. The stimulation suppressed parasympathetic nerves, excited SNS and HPA axis, which resulted in increased secretion of cortisol and norepinephrine, all of them lead to poor sleep.[18] It have been proved that sleep disturbances are often accompanied by elevated levels of cortisol [19]and catecholamines.[17] therefore, sleep disorders and stress responses form a vicious cycle. Our results showed the reduction of the sleep duration, sleep efficiency index and N3 sleep stage It was consistent with the results of Chouchou F et al.[20] In the elderly, postoperative sleep disorders are particularly obvious due to the changes in sleep structure.

In clinical, sedative-hypnotic drugs were often used to shorten the time to fall asleep, however, sedative-hypnotic drugs may cause postoperative delirium,[21] dependency, and rebound insomnia;[22] Studies have shown that dexmedetomidine improves sleep quality, however, dexmedetomidine can not only increase the incidence of hypotension[23] and other side effects,[24] but also was inconvenient to use dexmedetomidine in general wards. The sellate ganglion belongs to the cervical thoracic sympathetic ganglion. The SGB was used to treat for post-traumatic stress disorder,[25] pain syndrome in complex regional,[26] breast cancer survivors' hot flashes and sleep disturbances [27] and other painful or non-painful diseases. G. Zhu et al had confirmed that the stellate ganglion block relieved stress response and reduce cortisol and norepinephrine content of patients after colorectal cancer surgery[2,] which was also consistent with our experimental results. Our study showed that the SGB reduced the content of cortisol and norepinephrine in plasma of patients after lung cancer surgery. This may be related to the inhibition of sympathetic nerve and HPA axis excitation by the SGB.

SGB inhibited the HPA and SAM axis and reduced cortisol and norepinephrine secretion then to reduce stress responses and improve sleep quality in physiology. The ultrasound-guided nerve block achieved precise localization with few side effects and had been widely used in clinical practice. Our results showed that the ultrasound-guided SGB improved the early postoperative sleep quality of elderly patients with sleep structure changes, which was manifested by prolonged sleep duration, improved sleep efficiency, and higher subjective sleep score of AIS. The same result was Manifested by Jin Fet and Wu C. However, Jin Fet, et al choose the right side SGB to improved postoperative sleep disturbance in breast cancer patients.[28] And Wu C, et al choose the left side SGB to improved sleep quality in patients after esophageal and pulmonary surgery.[29] Both of them without further exploring the mechanism of sleep improvement by SGB . Considering that the stimulation of ipsilateral thoracoscopic surgery may be uploaded along the ipsilateral sympathetic nerve, we chose to block the stellate ganglion on the surgical side. At the same time, our results also showed that the left side or right side SGB improved the early postoperative sleep quality of elderly patients undergoing thoracoscopic surgery for lung cancer. However, due to the small number of patients undergoing thoracoscopic surgery on the left side, there may be errors.

The SGB affected peripheral and central nervous system.[30] SGB treatment inhibit sympathetic preganglion and postganglion fibers in the peripheral area to affected pain conduction in peripheral

nervous system. Our study also showed that the patients in SGB group lower motion VAS score than in the control group, but there was no significant difference in resting pain between the two groups, it may be related to the use of PCA in both group. In central nervous system, SGB treatment include regulation of autonomic nervous function,[30] immune function,[31] and neuroendocrine function.[32]

Melatonin is an important regulatory factor for human sleep.[33] It was synthesized and secreted by the pineal gland,[34] which was regulated by sympathetic nerves.[35] Dai D et al. 's animal experiments confirmed that right SGB increased serum melatonin concentration and improved sleep in rats [36.] At night, the secretion of melatonin reaches its peak at 2AM to 4AM, and it generated 6-hydroxysulfate melatonin (6-HMS) after metabolism and then excreted in the urine. The concentration of 6-HMS in urina sanguinis was closely related to the level of melatonin in serum.[37] Our results showed that the concentration of 6-HMS in urina sanguinis at T4 and T5 was lower than T3, but the concentration in the control group was lower than the SGB group. Therefore, SGB treatment improved the concentration of 6-hydroxyacid melatonin at T5 in urina sanguinis on the first and second days after thoracoscopic surgery in elderly patients with lung cancer, but the mechanism remains to be further studied due to the pineal gland was innervated by the complexity of nerves.

Several limitations were included in our study had : First, the sample size was relatively small, which was calculated by the sleep duration on the first night after surgery in the pre-test; Secondly, in order to observe the effect of SGB treatment on motor pain between two group , both of groups were not used multi-mode analgesia to relieve pain . Furthermore, we didn’t tracked the SGB treatment on the long-term sleep quality . Finally, because sleep quality was monitored by the BIS-Vista monitor , there is no good way to categorize the stages of sleeps.

Conclusions: Most elderly patients undergoing thoracoscopic surgery for lung cancer have postoperative sleep disorders, which were showed the reduction of sleep duration and sleep efficiency, reduction or deficiency of N3 sleep stage, and poor subjective sleep experience. It may be related to the strong stress response generated by the manipulation of surgery and anesthesia. The SGB treatment inhibited HPA and SAM axis, reduced stress responses, increased the concentration of 6-hydroxysulfate melatonin in urina sanguinis, and improved the early postoperative sleep of elderly patients undergoing thoracoscopic surgery for lung cancer. Compared with the control group, the patients in the SGB group had higher subjective sleep score and sleep efficiency, longer sleep duration and N3 stage sleep duration. In addition, The SGB treatment relieved the patients' motor pain and enhanced recovery after surgery.

Declarations

Ethics approval and consent to participate

The ethics was approved by The Ethic Committee of the First Affiliated Hospital of Bengbu Medical College(approval number:2021KY063). This study was registered at hinese Clinical Trial Registry system(ChiCTR2100053449, registration date: 21/11/2021; enrollment date: 22/11/2021). The study

was performed in accordance with the trail protocol. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the findings of the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

Cuifang Gu, Liu Xi and Aijun Lv designed the study. Cuifang Gu, Aijun Lv and Xiangyang Cheng conducted the study.Cuifang Gu, Liu Xi, Shasha Ma and Huan Hu collected the data. ,Xuan Li, Lu Liu and Shasha Ma analyzed the data. Cuifang Gu and Shasha Ma wrote the original draft. Xiangyang Cheng reviewed and edited it. All authors read and approved the final manuscript.

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Tables

Tables 1 to 4 are available in the Supplementary Files section

Figures

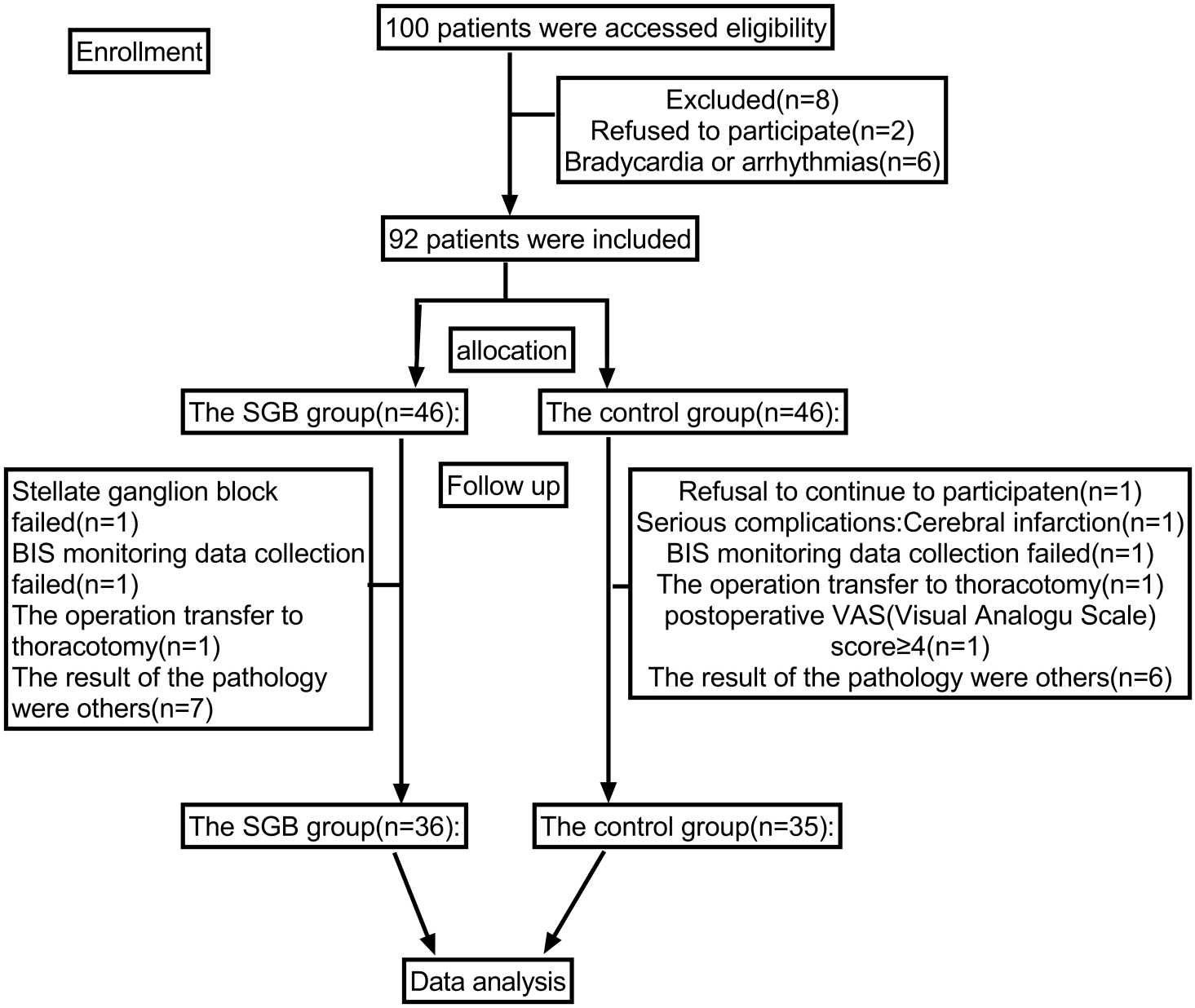

Figure 1

Flow chart

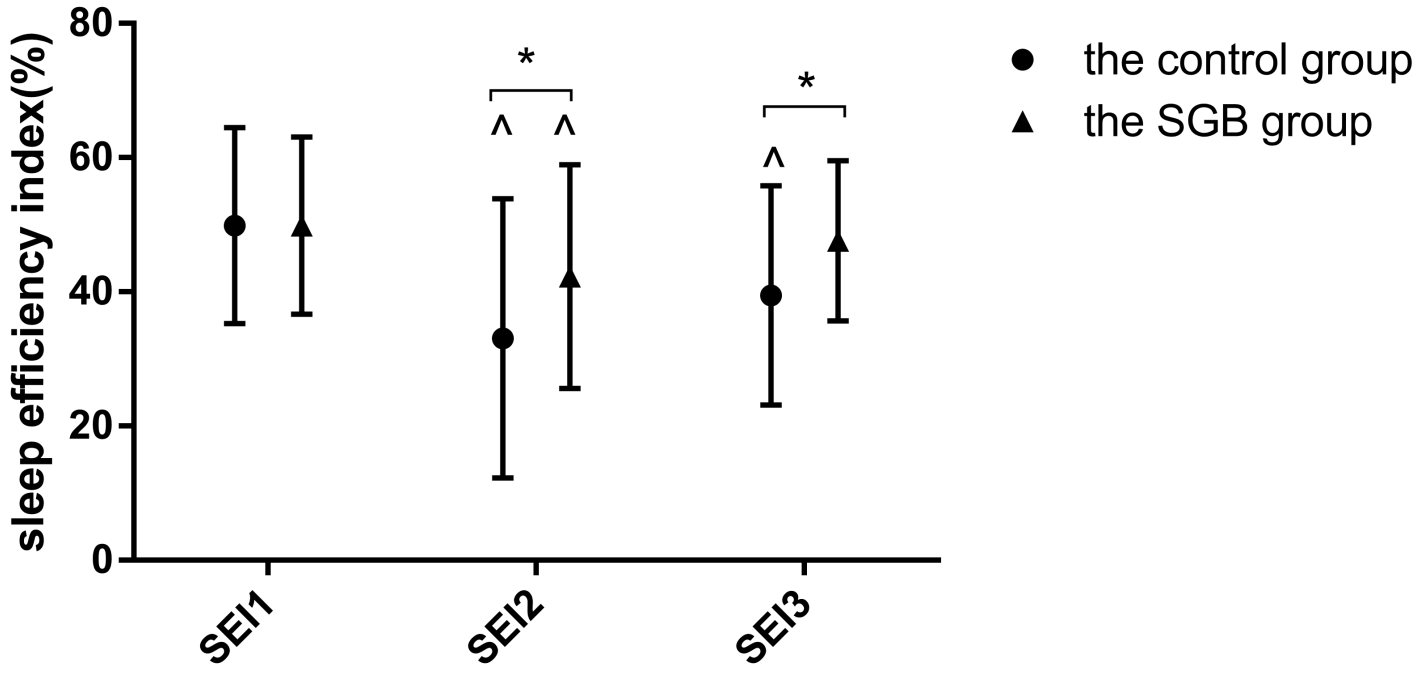

Figure 2

Comparison the sleep efficiency index between the control group and the SGB group. All data were showed as mean ± SD. sleep efficiency index: sleep duration/8*100%. SEI1:the last night before surgery.SEI2: the first night after surgery. SEI3:the second night after surgery. At the same point:*P<0.05. In the same group: comparison with SEI1, ^P<0.05.

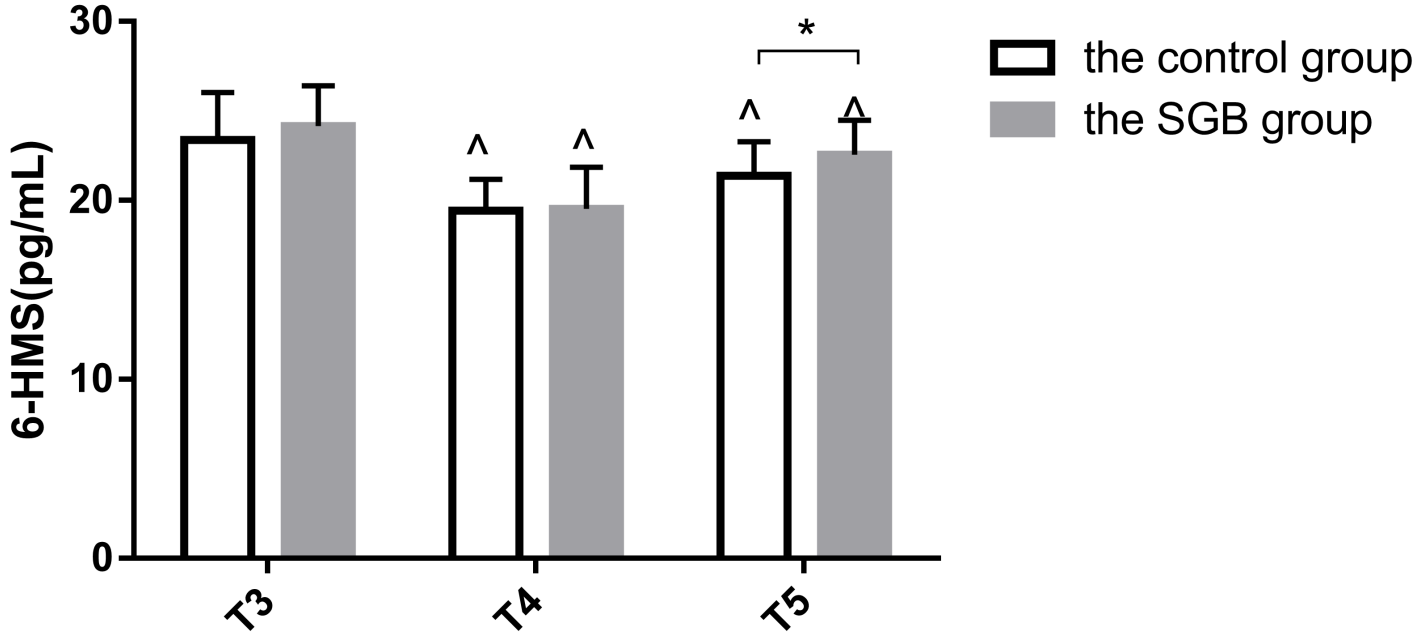

Figure 3

Comparison the concentration of 6-hydroxysulfate melatonin in urina sanguinis between the two groups. SGB:Stellate ganglion block. All data were showed as mean ± SD. T3:at 6am in the morning of surgery. T4:at 6am on the first morning after surgery. T5:at 6am on the second morning after surgery. At the same point:*P<0.05. In the same group: comparison with T3, ^P<0.05.

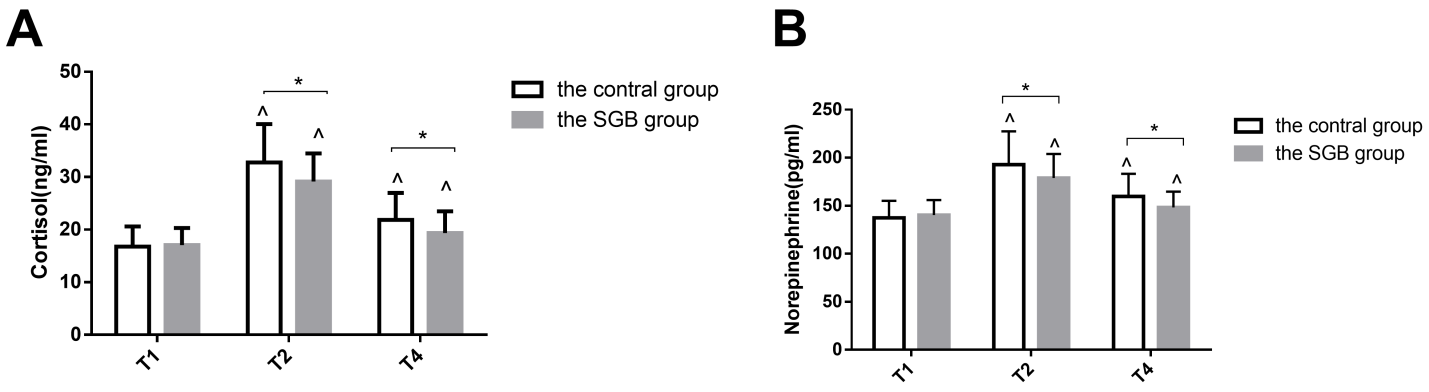

Figure 4

Comparison the concentration of the stress responses between the control group and the SGB group : cortisol (A) and norepinephrine (B). SGB:Stellate ganglion block. All data were showed as mean ± SD. T1:before anesthesia induction. T2:5min after extubation. T4:6am on the first morning after surgery. At the same point:*P<0.05. In the same group: comparison with T1, ^P<0.05.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.doc