Clinical Trial/Experimental Study

Medicine

OPEN

Comparison of the effects of cranial electrotherapy stimulation and midazolam as preoperative treatment in geriatric patients

A CONSORT-compliant randomized controlled trial

Byeong Seon Park, MD[a], Sejong Jin, MD[a,b], Woon Young Kim, MD, PhD[a,*], Da Som Kang, MD[a], Yoon Ji Choi, MD, PhD[a], Yoon Sook Lee, MD, PhD[a]

Abstract

Background: Although midazolam is widely administered as an anxiolytic premedication, it may cause over-sedation and hypoxia in geriatric patients. Cranial electrotherapy stimulation (CES) is a nonpharmacological device with anxiolytic effect. This study compared the effects of CES and midazolam as a preoperative treatment in geriatric patients.

Methods: Eighty patients, under the age of 65 to 79 years, undergoing general anesthesia were randomly assigned into midazolam premedication group (M group, n = 40) or CES pretreatment group (CES group, n = 40). The patients in the M group were intramuscularly injected with midazolam (0.07 mg/kg) 30 minutes before receiving general anesthesia. The patients in the CES group received 20 minutes of CES pretreatment on the day before and on the morning of the surgery.

Results: In the preoperative holding area, the anxiety score ($P = .02$) and the sedation score ($P < .001$) were significantly lower in the CES group compared with those in the M group. The oxygen saturations at the preoperative holding area and the operating room were significantly higher in the CES group than those in the M group ($P < .001$).

Conclusion: CES pretreatment relieved preoperative anxiety with less risk of over-sedation and respiratory depression than midazolam premedication in geriatric patients.

Abbreviations: CES = cranial electrotherapy stimulation, CES group = CES pretreatment group, HR = heart rate, M group = midazolam premedication group, OR = operating room, PHA = preoperative holding area.

Keywords: anxiety, cranial electrotherapy stimulation, geriatrics, midazolam

1. Introduction

Controlling preoperative anxiety is one of challenges that anesthesiologists face. Perks et al[1] reported that the incidence of preoperative anxiety ranges from 62% to 90% in patients scheduled for surgery. Preoperative anxiety is commonly related to the fear for general anesthesia, postoperative pain, prognosis, and death.[2] Preoperative anxiety affects patients not only psychologically but also physiologically; uncontrolled preoperative anxiety may lead to hypertension, tachycardia, sweating, and nausea.[3] It has also been identified that preoperative anxiety may manipulate neuroendocrine response in the postoperative recovery period, which may result in deleterious outcomes.[4] Moreover, a strong correlation has been observed between preoperative anxiety and prolonged hospital stay as well as the dissatisfaction of the surgical prognosis.[4,5]

Midazolam premedication is the most commonly used method to relieve preoperative anxiety.[6] Midazolam, which is a benzodiazepine derivative, rapidly crosses the blood-brain barrier at physiologic pH and acts on gamma-aminobutyric acid-A receptors,[7] producing hypnosis, amnesia, and anti-anxiety effects.[8] Midazolam is widely preferred due to its short elimination half-time and minimal hemodynamic effects in sedative dose.[8,9]

Midazolam, however, should be used with precaution, especially in elderly patients. If not used in adequate dose, midazolam may cause excessive sedative action, perioperative confusion, and delirium.[10,11] Midazolam may cause respiratory depression, as a result of undesired depressant effect on the central nervous system.[12] The administration of midazolam may also impair airway patency since it is known that midazolam may cause loss of airway muscle tone.[13] These midazolam-induced

BSP and SJ contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

[a] *Department of Anesthesiology and Pain Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Gyeonggi-do, Republic of Korea,* [b] *Department of Neuroscience, Korea University College of Medicine, Seoul, Republic of Korea.*

**Correspondence: Woon Young Kim, Department of Anesthesiology and Pain Medicine, Korea University Ansan Hospital, 516 Gojan-Dong, Danwon-Gu, Ansan city, Kyunggi-Do, 15355, Republic of Korea (e-mail: ckssis@korea.ac.kr).*

How to cite this article: Seon Park B, Jin S, Kim WY, Som Kang D, Ji Choi Y, Sook Lee Y. Comparison of the effects of cranial electrotherapy stimulation and midazolam as preoperative treatment in geriatric patients: A CONSORT-compliant randomized controlled trial. Medicine 2022;101:35(e30336).

Received: 24 January 2022 / Received in final form: 17 July 2022 / Accepted: 19 July 2022

http://dx.doi.org/10.1097/MD.0000000000030336

side effects may be highlighted in elderly patients due to their physiologically reduced organ function and modified redistribution kinetics.[10]

Cranial electrotherapy stimulation (CES) is a nondrug approach expected to have an anxiolytic effect.[14,15] CES is a noninvasive treatment by which microcurrent is delivered to the cranium through an electrode attached to the earlobe. Although the mechanism of its effect is unclear, it is assumed that by stimulating neurons in the brainstem, microcurrents increase the production of neurotransmitters, such as serotonin, and restores the brain's biochemical homeostasis disturbed by stress.[16] CES directly affects the activities of the brain's hypothalamic, limbic, and reticular activating systems.[17] It increases the alpha waves in electroencephalography, and such "alpha state" induces a relaxed mood and improves awareness and perception.[18] Due to its anxiolytic effect, CES may be applied to patients undergoing surgery for relaxation.[14] It is reported that CES may reduce preoperative anxiety in surgical patients, and therefore anesthesiologists may consider CES pretreatment as an alternative to midazolam premedication for geriatric patients who exhibit risk factors for pharmacologic sedatives.[18]

CES, unlike midazolam pretreatment, has not been reported to have deleterious side effects, such as residual sedation or respiratory depression.[19] In this study, CES pretreatment and midazolam premedication, which requires precaution in elderly patients, were applied to elderly patients to compare the anxiolytic effect and the occurrence of respiratory depression and over-sedation.

2. Patients and Methods

2.1. Patients

This study was conducted at the Department of Anesthesiology and Pain Medicine, Ansan Hospital of Korea University College of Medicine. The protocol was approved by the hospital's institutional review board (2020AS0142) and registered at the Clinical Research Information Service (KCT0006110). Written informed consent was obtained from all patients participating in this study.

Eligible patients were aged 65 to 79 years old with American Society of Anesthesiologists Physical Status Classification II or III, scheduled for elective surgery under general anesthesia. The exclusion criteria included psychiatric medications, obesity (body mass index >30 kg/m^2), chronic alcoholism, liver cirrhosis, serious renal disease, endocrine or neuromuscular disease, arrhythmia, and pacemaker or pulmonary disease. Initially, 90 patients were recruited, but 10 patients were withdrawn either spontaneously or in accordance with the exclusion criteria. In this study, 80 patients were included and randomly divided into 2 groups using a computer-generated randomization method: midazolam premedication group (M group, n = 40) and CES pretreatment group (CES group, n = 40) (Fig. 1).

2.2. Midazolam premedication and CES pretreatment

The patients in the M group were intramuscularly injected with midazolam (0.07 mg/kg) 30 minutes before receiving general anesthesia, whereas the patients in the CES group received 20 minutes of CES pretreatment on the day before and on the morning of the surgery. A microcurrent stimulator (Alpha-Stim 100; Electromedical Products International, Inc., Mineral Wells, TX) was used (Fig. 2). The electrode clips of the microcurrent stimulator were attached to the patient's earlobe, and the microcurrent was adjusted to the power of which the patient experienced light dizziness and a tingling sensation. The power of the microcurrent was limited between 200 μA and 0.5 Hz. All patients were premedicated via intramuscular injection of glycopyrrolate (0.005 mg/kg) 30 minutes before receiving general anesthesia.

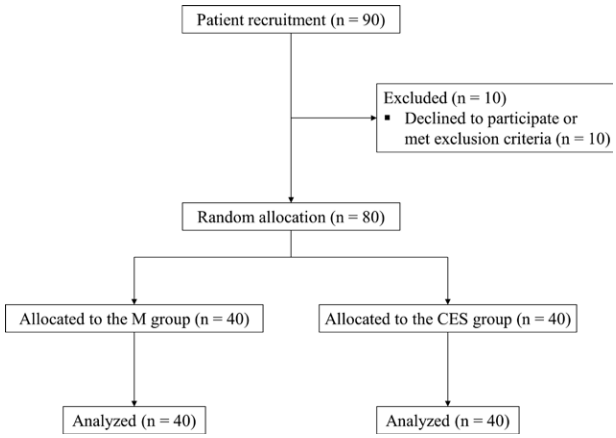

Figure 1. CONSORT flow diagram. CES group = CES pretreatment group, M group = midazolam premedication group.

Figure 2. Cranial electrotherapy stimulation unit. The Alpha-Stim 100 (Electromedical Products International Inc, Mineral Wells, TX) cranial electrotherapy stimulation unit was used in the study.

2.3. Clinical measurements and data collection

Preoperative anxiety, sedation level, and vital signs (blood pressure, heart rate [HR], and oxygen saturation) were evaluated. Preoperative anxiety was evaluated via a 5-point Likert scale: (1) not at all, (2) mild, (3) intermediate, (4) moderate, and (5) severe. The sedation score was assessed using the Ramsay sedation scale (Table 1). The anxiety score, sedation score, and vital signs (systolic and diastolic blood pressure, mean blood pressure, HR, and oxygen saturation) were assessed on the night before (baseline) and on the day of the surgery in the preoperative holding area (PHA) and in the operating room (OR) before anesthesia induction. Different investigators performed pre-anesthesia visits, assessment of preoperative anxiety scores and sedation levels, midazolam premedication, CES pretreatment, and anesthesia induction.

Anesthesia was induced with intravenous injection of propofol (2.0 mg/kg) and rocuronium (0.9 mg/kg). Three minutes of mask ventilation with sevoflurane administration (3 vol%) at an oxygenated air flow of 8 L/min and a fraction of inspired oxygen of 1.0 was performed before intubation.

2.4. Statistical analysis

The SPSS software version 25.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. All data except sex

Table 1

Assessment of sedation levels (Ramsay sedation scale).

Level	Response
1	Awake and anxious, agitated, or restless
2	Awake, cooperative accepting ventilation, oriented, tranquil
3	Awake; responds only to commands
4	Asleep; brisk response to light glabellar tap or loud noise
5	Asleep; sluggish response to light glabellar tap or loud noise stimulus but does not respond to painful response
6	Movement above shoulder, general response

were presented as the mean ± standard deviation. Demographic data were analyzed using either the Mann–Whitney *U* test, the independent *t* test, or the chi-square test. A *P* value of <.01 was considered statistically significant after Bonferroni correction. The preoperative anxiety score and sedation score were analyzed via the chi-square test. A *P* value of <.05 was considered statistically significant. Vital signs of each group on the night before surgery, on the day of the surgery in the PHA, and in the OR before anesthesia induction were analyzed via the Mann–Whitney *U* test or the independent *t* test. A *P* value of <.0033 was considered statistically significant after Bonferroni correction.

3. Results

No significant differences in age, sex, weight, height, history of previous surgery, operation time, or anesthesia time were observed between the M group and the CES group (Table 2). The anxiety scores in the PHA were significantly lower in the CES group compared with the M group (*P* = .02). No significant difference was observed in the anxiety scores in the general ward on the night before the surgery and in the OR between the 2 groups (Table 3). The sedation scores in the PHA were significantly lower in the CES group than those in the M group (*P* < .001). However, no significant difference in the sedation scores was observed in the general ward and OR between the 2 groups (Table 3).

The M group and the CES group showed no significant differences in systolic, diastolic, and mean blood pressures in the general ward on the night before surgery, in the PHA, and in the OR. No significant difference in HR was observed in the general ward on the night before surgery and in the PHA. However, HRs in the OR were significantly slower in the M group than those in the CES group (M premedication group, 69.2 ± 10.5 beats/min; CES group, 79.6 ± 15.3 beats/min) (Table 4) (*P* < .001). Finally, the M group and CES group showed no significant difference in baseline oxygen saturation in the general ward on the night before. Oxygen saturations in the PHA (M group, 94.3% ± 2.4%; CES group, 97.4% ± 1.8%) and the OR (M group, 95.9% ± 1.8%; CES group, 97.5% ± 1.6%) were significantly higher in the CES group than those in the M group (Table 4) (*P* < .001).

4. Discussion

CES pretreatment demonstrated to provide preoperative anxiolytic effect with, in comparison with the midazolam premedication, less risk of over-sedation and respiratory depression in geriatric patients.

The importance of preoperative anxiolysis in geriatric patients has been highlighted in many studies. Preoperative anxiety not only affects patients psychologically but also physiologically. Excessive anxiety activates the sympathetic nervous system and increases the level of corticosteroid, thereby causing hemodynamic instability.[20] Preoperative anxiety increases postoperative pain, demand for painkillers, and postoperative complications, along with morbidity and mortality. Geriatric patients may be more susceptible to these physiological responses. Normal aging process is accompanied by the gradual degeneration of the autonomic nervous system and reduced adaptability.[21] The homeostatic balance of aged patients is easily disturbed by exogenous stimuli.[20,22]

Preoperative anxiety manifests to various ranges depending on the patient. Many factors can contribute to preoperative anxiety level.[23] It is generally accepted that female patients tend to experience more preoperative anxiety than male patients.[24] In this study, similar results were obtained for anxiety scores in the general ward and the PHA, but not in the operation room (Table S1, Supplemental Digital Content 1, http://links.lww.com/MD/H161). Although inconsistent results were reported among studies, young age, high education level, and no experience in surgery or anesthesia are also considered potential risk factors of high preoperative anxiety.[23,25] There was no statistical difference according to the history of previous surgery in this study (Table S2, Supplemental Digital Content 2, http://links.lww.com/MD/H162). In addition to these sociodemographic factors, surgical or anesthetic factors were also considered as predictors of preoperative anxiety. The level of preoperative anxiety may vary depending on the diagnosis (cancer, etc), the invasiveness of surgery, and the purpose of surgery (diagnostic, curative, or palliative).[24] There may also be differences in preoperative anxiety depending on the type of anesthesia (general or regional).[25] It may be beneficial to detect high-risk groups of preoperative anxiety and provide appropriate interventions in advance, although the clinical benefit has not been identified clearly.

Midazolam, a potent benzodiazepine, is widely administered as an anxiolytic premedication. Anesthesiologists

Table 2

Demographic data.

	M group (n = 40)	CES group (n = 40)	*P* value
Age (yr)	70.3 ± 3.9	69.3 ± 3.6	.25
Sex (M/F)	22 (55%)/18 (45%)	21 (52.5%)/19 (47.5%)	>.99
Weight (kg)	61.8 ± 7.5	63.9 ± 9.1	.25
Height (cm)	158.7 ± 8.8	158.8 ± 6.9	.77
History of previous surgery	28 (70%)	27 (67.5%)	>.99
OP times (min)	155.5 ± 116.3	125.8 ± 97.6	.20
GA times (min)	201.5 ± 127.7	165.1 ± 104.0	.18

The values are expressed as mean ± SD. No statistical differences were observed between both groups (Mann–Whitney *U* test, independent *t* test or chi-square test).

CES group = cranial electrotherapy stimulation pretreatment group, GA times = general anesthesia time, M group = midazolam premedication group, OP times = operation time.

Table 3

Changes in anxiety and sedation score.

	Anxiety score	M group (n = 40)	CES group (n = 40)	*P* value	Ramsay sedation scale	M group (n = 40)	CES group (n = 40)	*P* value
GW	1	14 (35.0%)	10 (25.0%)	.20	1	8 (20.0%)	11 (27.5%)	.60
	2	15 (37.5%)	12 (30%)		2	32 (80.0%)	29 (72.5%)	
	3	6 (15.0%)	15 (37.5%)		3	0	0	
	4	4 (10.0%)	3 (7.5%)		4	0	0	
	5	1 (2.5%)	0		5	0	0	
					6	0	0	
PHA	1	14 (35.0%)	12 (30.0%)	.02*	1	1 (2.5%)	3 (7.5%)	<.001*
	2	14 (35.0%)	22 (55.0%)		2	22 (55.0%)	37 (92.5%)	
	3	4 (10.0%)	6 (15.0%)		3	15 (37.5%)	0	
	4	8 (20.0%)	0		4	2 (5.0%)	0	
	5	0	0		5	0	0	
					6	0	0	
OR	1	9 (22.5%)	10 (25.0%)	.05	1	1 (2.5%)	2 (5.0%)	.07
	2	16 (40.0%)	23 (57.5%)		2	33 (82.5%)	38 (95.0%)	
	3	6 (15.0%)	6 (15.0%)		3	4 (10.0%)	0	
	4	9 (22.5%)	1 (2.5%)		4	1 (2.5%)	0	
	5	0	0		5	0	0	
					6	1 (2.5%)	0	

Anxiety score was graded using a 5-point Likert scale (1 [lowest] to 5 [highest]). Sedation score was graded using the Ramsay sedation scale. The values are presented as the number of patients with percentages.

CES group = cranial electrotherapy stimulation pretreatment group, GW = general ward, M group = midazolam premedication group, OR = operating room, PHA = preoperative holding area.

*$P < .05$ compared with the M group (chi-square test).

Table 4

Comparison of blood pressure, heart rate, and SpO_2.

		M group (n = 40)	CES group (n = 40)	*P* value
SBP (mm Hg)	GW	129.7 ± 13.8	134.8 ± 17.2	.15
	PHA	140.7 ± 24.4	140.2 ± 17.4	.91
	OR	148.2 ± 24.0	152.8 ± 20.7	.37
DBP (mm Hg)	GW	74.8 ± 10.1	77.6 ± 11.1	.24
	PHA	81.7 ± 10.9	80.1 ± 9.1	.69
	OR	77.4 ± 10.3	83.4 ± 11.9	.02
MAP (mm Hg)	GW	93.9 ± 8.6	96.6 ± 11.4	.24
	PHA	103.2 ± 14.4	101.5 ± 11.6	.57
	OR	107.2 ± 15.2	112.5 ± 13.9	.10
HR (beats/m)	GW	73.2 ± 11.7	73.2 ± 13.9	.99
	PHA	70.8 ± 10.6	78.1 ± 14.5	.02
	OR	69.2 ± 10.5	79.6 ± 15.3	<.001*
SpO_2 (%)	GW	98.3 ± 1.2	97.7 ± 1.5	.08
	PHA	94.3 ± 2.4	97.4 ± 1.8	<.001*
	OR	95.9 ± 1.8	97.5 ± 1.6	<.001*

The values are expressed as mean ± SD.

CES group = cranial electrotherapy stimulation pretreatment group, DBP = diastolic blood pressure, GW = general ward, HR = heart rate, M group = midazolam premedication group, MAP = mean arterial pressure, OR = operating room, PHA = preoperative holding area, SBP = systolic blood pressure, SpO_2 = peripheral capillary oxygen saturation.

*$P < .0033$ compared with the M group (Mann–Whitney *U* test or independent *t* test with Bonferroni correction).

should be aware that midazolam may induce optimal sedation and relaxation, but with excessive dose, it may cause over-sedation, perioperative confusion, and respiratory depression.[26,27] Particularly, the respiratory depressive effect of midazolam premedication may be critical in geriatric patients since aging is associated with decreased pulmonary performance. The physiological aging of the pulmonary system is accompanied by the decrease in the elasticity of the lungs and chest wall compliance.[28] Considering the risk, in clinical situations, anesthesiologists tend to give up midazolam premedication for geriatric patients.

CES is a nonpharmacological treatment that delivers low-intensity electric current to the cranium through electrodes applied to both sides of the head. Various CES-based devices have been approved by the United States Food and Drug Administration as an adjuvant treatment for depression, anxiety, and insomnia.[29]

The exact mechanism of CES effect is still unclear. Some physiological changes by CES treatment are considered to explain the mechanism of CES effect. First, CES treatment seems to induce changes in electroencephalography. Electroencephalography signals are classified according to frequencies, and among them, alpha waves (8–13 Hz) are known to be related to relaxation.[30] CES treatment appears to increase the alpha wave,[31] which can be interpreted as CES treatment induces a comfortable state. Next, it is generally believed that CES treatment directly affects the activities of hypothalamus, reticular activating system, and limbic system.[32] Several neuroimaging studies suggested that CES decreases brain activity[33] and change brain hemodynamics.[34] Finally, it is considered that CES may affect levels of neurotransmitters or hormones, such as serotonin, endorphin, gamma-aminobutyric acid-A, or cortisol.[35,36] Since anxiety and stress are known to be closely related to neurotransmitters and hormones,[37,38] their changes due to CES treatment may play an important role.

Surgery is a very stressful situation for patients and such acute stress makes the patients anxious. Several studies of patients undergoing dental procedures showed that CES treatment has an anxiolytic effect.[39,40] More importantly, previous studies by Kim et al[15] and Lee et al[14] reported that CES treatment can effectively reduce preoperative anxiety in patients aged under 65 years. As mentioned earlier, preoperative anxiolysis is very important in the elderly, but geriatric patients were excluded in these studies. Therefore, this study was designed to apply CES pretreatment to elderly patients to determine whether CES provide comparable anxiolytic effect without the risk of over-sedation and respiratory depression, which are possible side effects of midazolam premedication.

Preoperative anxiety does not begin immediately before surgery but usually begins 2 days before surgery and lasts up to 2 days after surgery.[41] In particular, the anxiety on the night before the operation is comparable to the anxiety 1 hour before the surgery.[42] Besides, the anxiolytic effect of CES can be obtained even with only one 20-minute session, but the effect may be prolonged via repeated sessions.[18] Therefore, CES pretreatment was performed twice, on the day before and the day of the surgery. For preoperative anxiolytic purposes, 0.07 to 0.10 mg/kg IM is the dose range of midazolam, which has been widely recommended and studied.[8,27] This dosage is reported to produce adequate sedation without significantly altering blood pressure or HR.[43] In the study of Rochette et al,[44] where midazolam 0.10 mg/kg IM was premedicated in patients with mean age of 73.8 ± 8.2 years, 95% of patients experienced clinically satisfactory anxiolytic effect without adverse reactions. In the present study, however, the setting dose of midazolam was 0.07 mg/kg, the lowest dose in the recommended range, considering the physiologically reduced organ function and altered redistribution kinetics.

Although the exact mechanism is unclear, this study demonstrated that CES pretreatment reduces preoperative anxiety in the elderly patients, as it did in previous studies on patients under 65 years of age.[14,15] The result that anxiety scores in PHA were lower in the CES group than in the M group can be contributed by the protocol that CES pretreatment was done twice for the prolonged effect, while midazolam was administered in the lowest recommended dose due to concerns about physiologically reduced organ functions of elderly patients. Moreover, since the sedation scores in the PHA were significant higher in the M group, the accuracy of the anxiety assessment in the M group could have been less reliable due to altered consciousness level. Although there was no statistical significance (P = .05), the anxiety scores in the OR were lower in the CES group. We expect statistical significance could be obtained by increasing the number of experimental groups.

The levels of oxygen saturation in the PHA and the OR were significantly lower in the M group than in the CES group. The respiratory depressant effects of midazolam may be more critical in geriatric patients than in young patients since the normal aging process is accompanied by physiologically reduced organ function and modified redistribution kinetics.[10] CES may be a pretreatment option for elderly patients at risk of respiratory depression induced by midazolam administration.

The limitation of this study is that anxiety may vary depending on the types of surgery and diagnosis. The more accurate data could be obtained if the study was conducted on patients undergoing the same surgery with the same diagnosis.

As described earlier, preoperative anxiety is influenced by various factors. In this study, the extent of the surgery was indirectly assessed using the total operation and anesthesia time, and 2 groups showed no statistical difference. However, there may still be heterogeneity within the study population in the type of surgery or diagnosis, which may affect the results of this study. In addition, no correction was made for various sociodemographic factors that could have an impact on the results. Therefore, more accurate data could be obtained if a large-scale study that adjusts for these factors is conducted. It is another limitation that patient blinding cannot be performed. Only observer blinding could be performed because it is a comparative study of the device and the drug.

The focus of this study is the results up to the induction of anesthesia. As there are reports that the degree of preoperative anxiety affects postoperative outcomes, follow-up studies examining the long-term effects of CES pretreatment might be important. Also, mechanisms of CES treatment were not investigated in this study. Since there is no definitive evidence for the mechanism of CES pretreatment, further studies are necessary, especially in the preoperative setting.

Nevertheless, this is the first study to investigate the preoperative anxiolytic effect of CES pretreatment in geriatric patients. In this study, CES pretreatment reduced preoperative anxiety without respiratory depression and over-sedation in elderly patients, compared with midazolam. Therefore, we expect CES pretreatment can be a useful pretreatment option for preoperative anxiolysis, especially in elderly patients at high risk of hypoxia following midazolam premedication. Furthermore, with adequately managed anxiety, patients might be stable physiologically as well as psychologically, and better postoperative outcome could be expected.

5. Conclusion

In 65- to 79-year-old patients with American Society of Anesthesiologists Physical Status Classification II or III, CES pretreatment, in comparison with the midazolam premedication, resulted in lower anxiety levels in PHA with less risk of over-sedation and respiratory depression before surgery.

Acknowledgments

The authors thank Jaehyeong Cha of the Medical Statistics Counseling Office at Korea University Ansan Hospital for advice on statistical analysis.

Author contributions

Conceptualization: Byeong Seon Park, Sejong Jin, Woon Young Kim.
Data curation: Da Som Kang, Yoon Ji Choi, Yoon Sook Lee.
Formal analysis: Byeong Seon Park, Sejong Jin, Woon Young Kim, Da Som Kang, Yoon Ji Choi, Yoon Sook Lee.
Writing – original draft: Byeong Seon Park, Sejong Jin, Woon Young Kim.
Writing – review & editing: Byeong Seon Park, Sejong Jin, Woon Young Kim.

References

[1] Perks A, Chakravarti S, Manninen P. Preoperative anxiety in neurosurgical patients. J Neurosurg Anesthesiol. 2009;21:127–30.
[2] Badner NH, Nielson WR, Munk S, et al. Preoperative anxiety: detection and contributing factors. Can J Anaesth. 1990;37(4 Pt 1):444–7.
[3] McDonald S, Page MJ, Beringer K, et al. Preoperative education for hip or knee replacement. Cochrane Database Syst Rev. 2014;5:CD003526.
[4] Ali A, Lindstrand A, Sundberg M, et al. Preoperative anxiety and depression correlate with dissatisfaction after total knee arthroplasty: a prospective longitudinal cohort study of 186 patients, with 4-year follow-up. J Arthroplasty. 2017;32:767–70.
[5] Kumar A, Dubey PK, Ranjan A. Assessment of anxiety in surgical patients: an observational study. Anesth Essays Res. 2019;13:503–8.
[6] Watanabe Y, Higuchi H, Ishii-Maruhama M, et al. Effect of a low dose of midazolam on high blood pressure in dental patients: a randomised, double-blind, placebo-controlled, two-centre study. Br J Oral Maxillofac Surg. 2016;54:443–8.
[7] Griffin CE, 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13:214–23.
[8] Reves JG, Fragen RJ, Vinik HR, et al. Midazolam: pharmacology and uses. Anesthesiology. 1985;62:310–24.
[9] Sun GC, Hsu MC, Chia YY, et al. Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study. Br J Anaesth. 2008;101:632–9.
[10] Fredman B, Lahav M, Zohar E, et al. The effect of midazolam premedication on mental and psychomotor recovery in geriatric patients undergoing brief surgical procedures. Anesth Analg. 1999;89:1161–6.
[11] Drummond GB. Comparison of sedation with midazolam and ketamine: effects on airway muscle activity. Br J Anaesth. 1996;76:663–7.
[12] Gonzalez Castro LN, Mehta JH, Brayanov JB, et al. Quantification of respiratory depression during pre-operative administration of midazolam using a non-invasive respiratory volume monitor. PLoS One. 2017;12:e0172750.
[13] Montravers P, Dureuil B, Desmonts JM. Effects of i.v. midazolam on upper airway resistance. Br J Anaesth. 1992;68:27–31.
[14] Lee SH, Kim WY, Lee CH, et al. Effects of cranial electrotherapy stimulation on preoperative anxiety, pain and endocrine response. J Int Med Res. 2013;41:1788–95.
[15] Kim HJ, Kim WY, Lee YS, et al. The effect of cranial electrotherapy stimulation on preoperative anxiety and hemodynamic responses. Korean J Anesthesiol. 2008;55:657–61.
[16] Taylor DN, Lee CT, Katims JJ. Effects of cranial transcutaneous electrical nerve stimulation in normal subjects at rest and during psychological stress. Acupunct Electrother Res. 1991;16:65–74.
[17] Chapman CR. Psychological aspects of postoperative pain control. Acta Anaesthesiol Belg. 1992;43:41–52.
[18] Kirsch DL, Nichols F. Cranial electrotherapy stimulation for treatment of anxiety, depression, and insomnia. Psychiatr Clin North Am. 2013;36:169–76.
[19] Rintala DH, Tan G, Willson P, et al. Feasibility of using cranial electrotherapy stimulation for pain in persons with Parkinson's disease. Parkinsons Dis. 2010;2010:569154.
[20] Lim S, Oh Y, Cho K, et al. The question of preoperative anxiety and depression in older patients and family protectors. Anesth Pain Med (Seoul). 2020;15:217–25.
[21] Wang Y, Dong Y, Li Y. Perioperative psychological and music interventions in elderly patients undergoing spinal anesthesia: effect on anxiety, heart rate variability, and postoperative pain. Yonsei Med J. 2014;55:1101–5.
[22] Mari G, Costanzi A, Crippa J, et al. Surgical stress reduction in elderly patients undergoing elective colorectal laparoscopic surgery within an ERAS Protocol. Chirurgia (Bucur). 2016;111:476–80.
[23] Stamenkovic DM, Rancic NK, Latas MB, et al. Preoperative anxiety and implications on postoperative recovery: what can we do to change our history. Minerva Anestesiol. 2018;84:1307–17.
[24] Eberhart L, Aust H, Schuster M, et al. Preoperative anxiety in adults - a cross-sectional study on specific fears and risk factors. BMC Psychiatry. 2020;20:140.
[25] Celik F, Edipoglu IS. Evaluation of preoperative anxiety and fear of anesthesia using APAIS score. Eur J Med Res. 2018;23:41.
[26] Munoz HR, Dagnino JA, Rufs JA, et al. Benzodiazepine premedication causes hypoxemia during spinal anesthesia in geriatric patients. Reg Anesth. 1992;17:139–42.
[27] Wong HY, Fragen RJ, Dunn K. Dose-finding study of intramuscular midazolam preanesthetic medication in the elderly. Anesthesiology. 1991;74:675–9.
[28] Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. Eur Respir J. 1999;13:197–205.
[29] Brunyé TT, Patterson JE, Wooten T, et al. A critical review of cranial electrotherapy stimulation for neuromodulation in clinical and non-clinical samples. Front Hum Neurosci. 2021;15:625321.
[30] Müller-Putz GR. Electroencephalography. Handb Clin Neurol. 2020;168:249–62.
[31] Kang W, Lee J, Kim YR, et al. Analyzing the advantages of subcutaneous over transcutaneous electrical stimulation for activating brainwaves. Sci Rep. 2020;10:7360.
[32] Gilula MF. Cranial electrotherapy stimulation and fibromyalgia. Expert Rev Med Devices. 2007;4:489–95.
[33] Feusner JD, Madsen S, Moody TD, et al. Effects of cranial electrotherapy stimulation on resting state brain activity. Brain Behav. 2012;2:211–20.
[34] Gense de BD, Sesay M, Stinus L, et al. Cerebral blood flow modulation by transcutaneous cranial electrical stimulation with Limoge's current. J Neuroradiol. 2012;39:167–75.
[35] Krupitsky EM, Burakov AM, Karandashova GF, et al. The administration of transcranial electric treatment for affective disturbances therapy in alcoholic patients. Drug Alcohol Depend. 1991;27:1–6.
[36] Liss S, Liss B. Physiological and therapeutic effects of high frequency electrical pulses. Integr Physiol Behav Sci. 1996;31:88–95.
[37] Jacobson L. Hypothalamic-pituitary-adrenocortical axis: neuropsychiatric aspects. Compr Physiol. 2014;4:715–38.
[38] Borrow AP, Stranahan AM, Suchecki D, et al. Neuroendocrine regulation of anxiety: beyond the hypothalamic-pituitary-adrenal axis. J Neuroendocrinol. 2016;28:10.1111/jne.12403.
[39] Winick RL. Cranial electrotherapy stimulation (CES): a safe and effective low cost means of anxiety control in a dental practice. Gen Dent. 1999;47:50–5.
[40] Koleoso O, Osinowo H, Akhigbe K. The role of relaxation therapy and cranial electrotherapy stimulation in the management of Dental Anxiety in Nigeria. IOSR J Dent Med Sci. 2013;10:51–7.
[41] Johnston M. Anxiety in surgical patients. Psychol Med. 1980;10:145–52.
[42] Lichtor JL, Johanson CE, Mhoon D, et al. Preoperative anxiety: does anxiety level the afternoon before surgery predict anxiety level just before surgery? Anesthesiology. 1987;67:595–9.
[43] Artru AA, Dhamee MS, Seifen AB, et al. A re-evaluation of the anxiolytic properties of intramuscular midazolam. Anaesth Intensive Care. 1986;14:152–7.
[44] Rochette A, Jullien Y, Lubrano JF, et al. Midazolam as an intramuscular premedication agent: definition of posology as a function of age. Ann Fr Anesth Reanim. 1982;1:663–6.