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Case Control Study

Combined sevoflurane-dexmedetomidine and nerve blockade on post-surgical serum oxidative stress biomarker levels in thyroid cancer patients

Du D *et al.* Sevoflurane-dexmedetomidine and nerve blockade influence oxidative stress

Dan Du, Qiao Qiao, Zheng Guan, Yan-Feng Gao, Qiang Wang

Abstract

BACKGROUND

The incidence of thyroid cancer is increasing annually. Clinical routine thyroid surgery can be performed under acervical plexus block, but cannot mediate the stress response during the surgery. If thyroid surgery is performed under nerve block, an inappropriate level of blockade may occur. Similarly, the stress response caused by surgery is more serious than that caused by conventional anesthesia. Therefore, it is important to combine blockade with more effective anesthesia methods.

AIM

To investigate the effects of combining sevoflurane-dexmedetomidine inhalation general anesthesia with the cervical plexus nerve block on the post-surgical levels of the serum oxidative stress biomarkers levels in thyroid cancer patients.

METHODS

We enrolled 96 thyroid cancer patients admitted to the hospital between January 2019 and December 2020. Participants were divided into a control group ($n = 47$) and an experimental group ($n = 49$). The experimental group received a combination of inhaled sevoflurane-dexmedetomidine and cervical plexus block, while the control group received conventional general anesthesia. The groups were compared for serum levels of monocyte chemotactic protein-1 (MCP-1) and glutathione peroxidase (GSH-Px) before and after surgery, and the adrenocorticotrophic hormone (ACTH) and norepinephrine (NE) levels at 1 and 12 h post-surgery. The Bispectral index (BIS) and the incidence of anesthesia side effects were also compared.

RESULTS

Following surgery, MCP-1 was significantly lower in the experimental group compared to the control group, whereas GSH-Px was significantly higher than that in the control group ($P < 0.001$). The serum ACTH and NE levels were significantly lower in the experimental group than those the control group at 1 and 12 h post-surgery ($P < 0.001$). BIS was significantly lower in the experimental group than that in the control group at 20 minutes into the operation, but the direction of the difference was reversed at eye opening ($P < 0.001$). The incidence of side effects was 10.20% (5/49) and 12.76% (6/47) in the experimental and control groups, respectively, the difference being non-significant.

CONCLUSION

Sevoflurane-dexmedetomidine inhalation general anesthesia combined with cervical plexus nerve block can reduce the postoperative stress and inflammatory responses in thyroid cancer patients, while maintaining high anesthesia effectiveness and safety.

Key Words: Sevoflurane; Dexmedetomidine; Cervical plexus block; Thyroid cancer; Anesthesia; Side-effects

INTRODUCTION

Thyroid cancer commonly presents as a malignant tumor occurring in the thyroid follicular epithelium. The incidence of thyroid cancer is increasing annually^[1]. Monocyte chemoattractant protein (MCP-1) is a chemoattractant protein involved in the body's inflammatory response^[2]. Glutathione peroxidase (GSH-Px), a decomposition enzyme, is considered a sensitive indicator of the human stress response^[3]. Adrenocorticotrophic hormone (ACTH) and norepinephrine (NE) are both important indicators of oxidative stress^[4]. Clinical radical thyroidectomy is typically performed under general anesthesia using tracheal intubation, but can cause reversible unconsciousness and an absence of pain sensation. Cervical plexus nerve block, a novel form of anesthesia, has the advantages of simple implementation and an effective analgesic effect. However, it is reportedly associated with fear and anxiety in patients due to factors such as the need for an unnatural body position. Zhang *et al*^[5] found that inhaled sevoflurane combined with dexmedetomidine is rarely used in China. Therefore, this study investigated the use of sevoflurane-dexmedetomidine inhalation general anesthesia combined with the cervical plexus nerve block in comparison with conventional general anesthesia in 96 thyroid cancer patients admitted to our hospital. We subsequently compared the serum levels of MCP-1, GSH-Px, ACTH, and NE between the two groups.

MATERIALS AND METHODS

Participant recruitment

We recruited patients with a diagnosis of thyroid cancer who were admitted to hospital between January 2019 and December 2020. The inclusion criteria were: (1) the patient met all the diagnostic criteria for thyroid cancer^[6]; (2) diagnosis of thyroid cancer *via* pathological examination; and (3) the patient was scheduled to receive radical thyroidectomy in our hospital. The exclusion criteria were: (1) a history of allergic reaction to anesthesia; (2) use of an anticoagulant or antifibrinolytic medication within

the preceding week; (3) severe coagulation dysfunction; (4) neurological diseases which would prevent the patient from cooperating with the treatment; and (5) an incomplete patient history. Ninety-six patients were recruited and were divided into two groups. The control group comprised 47 patients (22 men) with a mean age of 61.17 ± 5.98 (range 51-75) years. The pathological types were papillary carcinoma ($n = 28$), follicular carcinoma ($n = 15$), undifferentiated carcinoma ($n = 2$) and myeloid carcinoma ($n = 2$). The tumor-nodes-metastasis (TNM) classification of the patients was as follows: 15 cases were stage III, 22 were stage II, and 10 were stage I. The experimental group comprised 49 patients (23 men), with a mean age of 61.02 ± 5.39 (range 51-75) years. The pathological types were papillary carcinoma ($n = 30$), follicular carcinoma ($n = 15$), undifferentiated carcinoma ($n = 3$) and myeloid carcinoma ($n = 1$). The TNM classification was: 16 stage III, 21 stage II, and 12 stage I cases. The age, sex, pathological type, and TNM classification did not significantly differ between the two groups ($P > 0.05$).

Procedure

Patients in both groups received radical thyroidectomy and were fasted of food and water for 8 h before surgery. The patient received an intravenous line and their vital signs were monitored in the form of Bispectral index, blood pressure, oxygen saturation, heart rate, and electrocardiogram.

The experimental group received general anesthesia by sevoflurane-dexmedetomidine inhalation combined with cervical plexus nerve block anesthesia. For cervical plexus nerve block anesthesia, a mixture of 1% lidocaine (H11022295, Shanxi Jinxin Shuanghe Pharmaceutical Co., LTD.) and 0.375% ropivacaine (H20060137, AstraZeneca Pharmaceutical Co., LTD.) was injected using an ultrasound-guided single needle method, 8 mL into the deep cervical plexus on the affected side and 4 mL into the superficial cervical plexus. Further, 1 $\mu\text{g}/\text{kg}$ dexmedetomidine (Jiangsu Nhwa Pharmaceutical Co., LTD. National Drug Approval H20110085) was injected intravenously, and sevoflurane was inhaled continuously to induce a concentration of

5%-6%, and 0.6 mg/kg rocuronium was injected intravenously after the patient lost consciousness. Sevoflurane 1.5%-3% and dexmedetomidine 0.5 µg/kg were used to maintain an anesthesia depth and BIS of 40-60.

The control group received conventional general anesthesia in the form of midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd. H20143222) at 0.05-0.1 mg/kg and sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., H20054171) at 0.3-0.5 µg/kg, etomidate at 0.3-0.5 mg/kg, and Rocuronium at 0.6 mg/kg. Mechanical ventilation was provided with a tidal volume of 6-8 mL/kg, the breaths rate is 10-14 times per minute, and an inhalation-exhalation ratio of 1:2. The partial pressure of end-expiratory carbon dioxide was maintained at 35-45 mmHg. After intubation, propofol (4-6 mg/kg per hour), remifentanyl (0.15-0.5 µg/kg per minute), and cis-atracurium (0.1 mg/kg per hour) were continuously administered until the end of operation, to maintain a BIS of 40-60.

If the patient's heart rate fell below 50 beats per minute, 0.5 mg atropine was injected intravenously. If the systolic blood pressure fell below 80 mmHg, 10 mg ephedrine was injected intravenously. Post-surgically, the endotracheal tube was removed when the patient had the following vital signs: the respiratory rate reached 16 breaths per minute with a tidal volume of 6 mL/kg, and the patient could open their eyes on command and clench their first strongly.

Outcome measures

The serum levels of MCP-1 and GSH-Px levels were measured before and after surgery. The serum ACTH and NE levels were measured 1 and 12 h after surgery. BIS was recorded, as were any side effects of the anesthesia. All outcome measures were compared between the experimental and control groups.

Serum analysis

A 2.5-mL sample of fasting venous blood was taken from each patient before the surgery, immediately after the surgery, and again at 1 and 12 h after the surgery. High-speed centrifugal delamination was used to separate the serum and the separated

serum was sent to the laboratory. MCP-1 was detected *via* solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) with the MCP - 1 ELISA kit (Shanghai Tongwei Industrial Co., LTD). GSH-px was detected using the GSH-PX ELISA kit (Wuhan Mercer Biotechnology Co., LTD). ACTH was detected using the ACTH ELISA kit (Shanghai Zhenke Biotechnology Co., Ltd). NE was detected using the double antibody sandwich method with the NE ELISA kit (Shanghai Enzyme-linked Biotechnology Co., LTD). The serum levels of MCP-1 and GSH-Px were the mean values detected after the operation. Serum ACTH and NE were measured in the samples retrieved at 1 and 12 h post-surgically.

BIS measurement

BIS was recorded before the operation, for 20 min during the operation, and at the point that the patient opened their eyes. A BIS score of 100 indicates a fully awake state, and 0 indicates the complete absence of electrical brain activity. This range is divided into the following states: 85–100 represents awake, 65–85 represents a sedative state, 40–65 represents anesthesia inhibition, and < 40 indicates the possibility of burst suppression.

Postoperative anesthesia side effects

The occurrence of side effects such as headache, ataxia, and lethargy was recorded in detail by experienced nurses and compared between the two groups. The rate of toxicity and side effects = (incidence of headache + incidence of ataxia + incidence of somnolence)/total number of cases × 100%.

Statistical analysis

SPSS version 20.0 was used for the statistical analyses. Age, MCP-1, GSH-Px, ACTH, and NE were presented as means ± SD. An independent-samples *t*-test was performed for between-group comparisons and a paired sample *t*-test was performed for within-group comparisons. The rates of anesthesia and incidence of adverse reactions of

anesthesia were expressed as the percentages, and a χ^2 test was used to compare groups. Statistical significance was set at $P < 0.05$.

RESULTS

Serum MCP-1 and GSH-Px before and after surgery

Before surgery, there was no significant difference in the serum GSH-Px or MCP-1 Levels between the groups ($P > 0.05$). After surgery, compared with the control group, the serum MCP-1 was significantly lower and GSH-Px was significantly higher in the experimental group (Table 1).

Serum ACTH and NE at 1 and 12 h after surgery

The serum ACTH and NE levels in the experimental group were significantly lower than those in the control group at 1 and 12 h post-surgically (Table 2).

BIS

The BIS in the experimental group was significantly lower than that in the control group during surgery, but exhibited the opposite trend at the point when the patient opened their eyes (Table 3).

Toxicity and side effects

The incidence of adverse reactions in the experimental group was 10.20% (5/49), and in the control group was 12.76% (6/47); this difference was not significant ($P > 0.05$), as shown in Table 4.

DISCUSSION

Routine thyroid surgery can be completed under cervical plexus block in clinical practice^[7]; however, sometimes a more radical thyroidectomy is required. Radical surgical procedures can affect thyroid gland lobules and cervical lymph nodes^[8,9]. Although general anesthesia commonly used in clinical practice can block the limbic

system and the hypothalamic projection system, it cannot mediate the stress response during surgery^[10,11]. If thyroid surgery is performed under nerve block, an inadequate level of blockade may occur. Similarly, the stress reaction caused by surgery is more severe, with patients often experiencing anxiety, panic, and other negative emotions. It is therefore extremely important to combine blockade with more effective anesthesia methods^[12,13].

Severe stress reactions can increase the risk of complications and mortality during surgery. Sevoflurane is a highly effective anesthetic inhalant, is more stable to heat and strong acids, and exerts analgesic and muscle relaxation effects during anesthesia. Dexmedetomidine hydrochloride can stimulate the α receptors and vascular motor centers in the locus coeruleus region of the brainstem to suppress the sympathetic^[14] response. MCP-1 is a chemokine that affects the recombination of human monocytes and the production of inflammatory cytokines. The expression of GSH-Px, a peroxide-decomposing enzyme, is indicative of oxidative stress^[15]. The results of this study showed that, compared with that in the control group, serum MCP-1 in the experimental group was significantly decreased, and GSH-Px was significantly increased post-surgically. This suggests that sevoflurane-dexmedetomidine general anesthesia combined with cervical plexus blockade can reduce the inflammatory response and oxidative stress response associated with surgery.

Surgical trauma can cause changes in hormone secretion that persist after surgery. Thus, the stress response caused by surgery can be detected in the form of changes in ACTH and NE^[16]. In this study, the serum ACTH and NE levels ¹ in the experimental group were significantly lower than those in the control group at 1 and 12 h post-surgically. Sevoflurane-dexmedetomidine may activate the α receptors in the solitonal nucleus postsynaptic membrane, thus inhibiting sympathetic excitation and reducing NE release elicited by activity at central and peripheral nerve endings, consequently inhibiting plasma catecholamines^[17]. As such, sevoflurane-dexmedetomidine general anesthesia combined with cervical plexus block may reduce the inflammatory response and oxidative stress in patients. Studies in the USS indicate that the combined use of

sevoflurane-dexmedetomidine acts quickly, with a markedly improved analgesic effect and high anesthesia effectiveness^[18,19]. The results of this study are consistent with those findings, in that the BIS during surgery was significantly lower in the experimental group ($P < 0.05$). Dexmedetomidine exerts little effect on the hemodynamics, as it binds to central α_2 receptors while controlling sympathetic activity through the inhibition of α and β adrenoceptor control of vascular tension, and reducing adverse reactions. Meanwhile, sevoflurane also has the advantage of entailing fewer adverse reactions during anesthesia. This study showed ³ that there was no significant difference in the incidence of adverse reactions between the two groups, although these results are inconsistent with previous studies^[20]. This inconsistency may be related to the dosage used.

In this study, sevoflurane-dexmedetomidine general anesthesia combined with cervical plexus nerve block exhibited high effectiveness, together with a reduced inflammatory response and stress indicators. However, the number of patients in this study was small, so larger-scale studies are needed in the future.

CONCLUSION

Sevoflurane-dexmedetomidine complex inhalation general anesthesia combined with the cervical plexus nerve block can reduce the postoperative inflammatory response in patients undergoing radical thyroidectomy for thyroid cancer, while inhibiting the stress response associated with surgery and maintaining high anesthetic quality and safety.

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Table 1 Serum monocyte chemotactic protein-1 and glutathione peroxidase of patients in the two groups before and after surgery (mean \pm SD)

Group	MCP-1 (pg/mL)			<i>t</i>	<i>P</i> value	GSH-Px (pg/mL)			<i>t</i>	<i>P</i> value
	Pre- operation	Post- operation				Pre- operation	Post- operation			
Experimental group (<i>n</i> = 49)	146.23 \pm 10.05	215.25 \pm 10.11		34.229	< 0.001	1939.65 \pm 10.14	1823.21 \pm 10.15		55.053	< 0.001
Control group (<i>n</i> = 47)	145.61 \pm 10.21	554.41 \pm 10.23		205.944	< 0.001	1941.54 \pm 10.09	1642.17 \pm 10.57 ^{ab}		144.328	< 0.001
<i>t</i>	0.129	163.359	-	-	-	0.915	85.602	-	-	-
<i>P</i> value	0.898	< 0.001	-	-	-	0.362	< 0.001	-	-	-

MCP-1: Monocyte chemotactic protein-1; GSH-Px: Glutathione peroxidase.

Table 2 Serum adrenocorticotrophic hormone and norepinephrine levels in the two groups at 1 and 12 h after surgery (mean \pm SD)

Group	ACTH (pg/mL)			<i>t</i>	<i>P</i> value	NE (pg/mL)			<i>t</i>	<i>P</i> value
	1 h after operation	12 h after operation				1 h after operation	12 h after operation			
Experimental group (<i>n</i> = 49)	26.22 \pm 1.21	28.25 \pm 1.65		6.442	< 0.001	600.11 \pm 5.23	622.19 \pm 5.43		21.276	< 0.001

Control group (n = 47)	27.98 ± 1.05	29.99 ± 1.14	8.114	< 0.001	623.32 ± 5.14	642.17 ± 5.01	17.590	< 0.001
t	7.598	5.987	-	-	21.928	18.716	-	-
P value	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-

ACTH: Adrenocorticotrophic hormone; NE: Norepinephrine.

Table 3 Bispectral index in the two groups at different time points (mean ± SD)

Group	Pre-operation	20 min after the surgery started	Open eyes
Experimental group (n = 49)	95.31 ± 4.15	46.76 ± 3.55	75.31 ± 3.05
Control group (n = 47)	95.08 ± 3.89	53.04 ± 3.61	68.85 ± 3.41
t	0.269	8.601	9.790
P value	0.789	< 0.001	< 0.001

Table 4 Toxicity and side effect rate in the two groups, *n* (%)

Group	Headache	Ataxia	Drowsiness	Toxicity and side effect rate
Experimental group (<i>n</i> = 49)	2 (4.08)	2 (4.08)	1 (2.04)	5 (10.20)
Control group (<i>n</i> = 47)	1 (2.13)	3 (6.38)	2 (4.26)	6 (12.76)
χ^2	-	-	-	0.155
<i>P</i> value	-	-	-	0.694

3%

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