Biomedical Research 2017; Special Issue: S552-S556 *ISSN 0970-938X*
www.biomedres.info

Effect of intraoperative single administration of sub-anesthesia ketamine on breast cancer patients with depression.

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Abstract

Objective: To observe the effect of single administration of sub - anesthesia ketamine on breast cancer patients with depression.

Methods: Fifty breast cancer patients with depression (Hamilton depression scale, HAMD score ≥ 17) selecting modified radical mastectomy for breast cancer were randomly divided into ketamine group and control group. Each group has 25 cases. One hour after the induction of general anesthesia, ketamine (0.5 mg/kg) and isofibrillar saline were infused intravenously within 10 min respectively. HAMD was used to assess the depression status at 1 day before operation and 1, 3 and 7 days after operation. The Social Support Scale (SSRS) was performed 1 day before operation and 7 days after operation. Visual Analogue Scale/Score (VAS) scores were used to evaluate the pain status at 1, 3 and 7 days after operation. The time of surgery, the time of extubation, the use of vasoactive drugs, the situation and the recovery period and postoperative adverse reaction were recorded.

Results: There were no significant differences among the scores of SSRS, VAS and HAMD between the two groups or intra-group before operation (P>0.05). There was no significant difference between the two groups after operation (P>0.05), indicating that ketamine significantly improved depression symptoms of breast cancer patients with depression in the first three days postoperatively; The HAMD score of the ketamine group was still lower than that of the control group at 7 days after operation, but the difference was not statistically significant (P>0.05). Compared with preoperative group, there was no significant difference in the HAMD score of the control group on the first day after operation (P>0.05).

Conclusions: Intraoperative single administration of sub-anesthesia ketamine significantly may have an effect on postoperative breast cancer patients with depression. But the effect may decrease along with the time.

Keywords: Depression, Breast cancer, Ketamine.

Accepted on March 29, 2017

Introduction

Depression has become the world's fourth predominant disease, accounting for the second in the Chinese disease burden spectrum. Breast cancer is one of the most common malignancies in women [1]. Based on specific social and physiological stress reactions, many women breast cancer patients will experience depression breast cancer in the diagnosis and treatment. Some patients may have symptoms of the clinical diagnostic criteria for depression. Hegel et al. [2] found that more than 40% of breast cancer patients had depression-related symptoms and signs before operation including stress, self-abandonment, fatigue, pessimism and despair. 11% patients achieved the diagnosis of depression, and the incidence of postoperative depression is about 10% -25% [3].

The higher incidence of depression in perioperative breast cancer may be related to the great psychological burden [4] and follow-up figure change [5] and sexual dysfunction [6] caused by surgery, as well as discomfort with stress and side effects, disruption of daily life and other factors. How to reduce the symptoms of depression, intervene the occurrence of postoperative depression of breast cancer, make it go through the perioperative period, promote the patients' recovery and physical and mental health, and even the long-term survival rate of perioperative breast cancer patients with depression, has become an increasingly important issue.

The current clinical treatment of breast cancer associated with depression is mainly drug therapy and psychological intervention [7,8]. There are five major classes of antidepressants used in clinic: monoamine oxidase inhibitors, tricyclic antidepressants, serotonin reuptake inhibitors, dopamine reuptake inhibitors, and selective norepinephrine reuptake inhibitors [9]. Other treatment measures includes psychological intervention and social support,

electroconvulsive therapy, sleep deprivation therapy, acupuncture and moxibustion treatment, but most of these therapeutic slowly onset and have little effect. Ketamine is an antagonist of N-Methyl-D-Aspartate (NMDA) receptors, both in human studies and in animal models of depression, it have shown that ketamine with a rapid and powerful antidepressant effect. In 2008-2015, print news media articles were significantly more likely to encourage clinical use of ketamine to treat depression [10]. Some case reports found that ketamine was associated with electroconvulsive therapy for treatment-resistant depression in the elderly [11]. Moreover, the basic research suggested that the broad overlap of biologic responses produced by LY3020371 and ketamine supports the hypothesis that mGlu2/3 receptor blockade might be a novel therapeutic approach for the treatment of TRD patients [12]. However, the study of its effect on perioperative depression is still rare. It was not yet used for perioperative breast cancer patients with depression reported. This study was designed to investigate whether intraoperative ketamine can improve postoperative depression in patients with breast cancer associated with depression.

Materials and Methods

Cases selection

All the first breast cancer patients treated breast cancer radical mastectomy from 2014/05 to 2015/03 in the First Affiliated Hospital of Nanchang University were recruited: All patients were asked for medical history and conduced routine examination including electrocardiogram, chest X-ray, breast ultrasound, breast puncture Biopsy, blood, etc., A clear preoperative diagnosis and general condition assessment has been done. There was no significant difference in age, height, BMI, operation time, social support and postoperative pain between the two groups ($P>0.05$). The trial was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. All subjects were included in the trial after the patients' informed consent.

Inclusion criteria

1. Women patients with who underwent modified radical mastectomy of unilateral breast cancer, aging between 30-55 years old; 2. The years of education were ≥ 5 years, ASA (American Society of Anesthesiologists) I-II grade; 3. All the patients underwent operation within 1 week of diagnosis, no preoperative radiotherapy and chemotherapy treatment; 4. HAMD score ≥ 17 points; 5. All patients were married and generational, mainly by the immediate family care after surgery. Exclusion criteria 1. Antidepressant treatment within 2 months; 2. The previous personality disorder, mental retardation, brain damage or brain disease, combined with schizophrenia, mania and other mental illness; 3. Before operation, patients combined with hyperthyroidism or hypothyroidism, severe cardiovascular disease, diabetes, severe anemia, and heart, lung, liver, kidney function abnormalities; 4. Immune system diseases, or the use of drugs affecting the immune system obviously; 5. Pregnancy or lactation; 6. There is a history of illicit drug use (such as K powder, marijuana, ecstasy, etc.); 7. Also participate in other clinical trials. 8. Refused to participate.

Main test equipment, narcotic drugs and assessment scale

The Drager Fabius GS Premium Anesthesia Workstation, the Detex-Ohmeda S/5 multi-parameter monitor, the Aspect Medical Systems A-2000 BIS monitor was supplied by Drager, Germany, Datex-Ohmeda, Finland and Aspect Medical Systems, USA respectively; Liquid injection of atracurium benzoic acid, midazolam and ketamine hydrochloride were from Hubei Yichang Renfu Pharmaceutical Co., Ltd;Rating scale: The general scoring criteria are: 0-7 points, no depressive symptoms; 7-17 points, maybe depression; 17-24 points, mild to severe depression; more than 24 points, severe depression. The social support rating scale included three dimensions: objective support (3), subjective support (4), and use of social support (3). The higher the scale, the greater the social support. Visual analgesia scale: This method converts subjects' subjective feelings of pain into a point position between 10 cm segments. 1-3 cm: mild pain, 4-7 cm: moderate pain, 8-10 cm: severe pain. The patients were randomly divided into two groups by random double-blind design: the ketamine group and the control group, each group of 25 cases; the perioperative psychological scale results of each patient were recorded; Anesthesia was performed by a fixed anesthesiologist and the incidence of adverse events during the administration was recorded. During the course of the study, all the other treatments were performed during the perioperative period, such as anti-inflammatory, hemostasis and nutritional support.

Preparation and plans before anesthesia

All patients required routine fasting for 12 h and prohibition of drinking for 4 h. Electrocardiogram (ECG), Blood Pressure (BP), Pulse (P), Heart Rate (HR), blood oxygen saturation (SpO_2) were monitored by routine anesthesia. Lactated Ringer's solution was injected into the peripheral venous access. Anesthesia induction: All patients were induced in the monitoring of Bispectral Index (BIS). According to the physical condition, intravenous injection of midazolam 0.05 mg/kg, propofol 1.5-2.5 mg/kg, 0.5-0.6 mg/kg and fentanyl 2-4 μg/kg. Endotracheal intubation was performed after induction of anesthesia, and mechanical ventilation was performed to monitor the end-tidal carbon dioxide partial pressure ($PetCO_2$). Anesthesia maintenance: Targeted infusion of propofol 1.5-4.0 μg/ml, atracurium 4-12 μg/kg/min, remifentanil 4-8 μg/kg/h, to maintain $PetCO_2$ was maintained within 35-40 mmHg and the BIS values are between 40-60. Two groups can appropriately receive dopamine, atropine, esmolol, ephedrine and other cardiovascular active drugs for recording to maintain hemodynamic stability. Vital signs were maintained during the operation, and the operation time was recorded to reach no significant difference in between the two groups. Intraoperative

intervention: patients in ketamine group at 1h after the start of anesthesia were injected with 0.5 mg/kg ketamine diluted to 50 ml intravenously, the control group for isotonic saline 50 ml within 10 min. During administration, changes in blood pressure, heart rate, and BIS parameters were observed.

Postoperative analgesia: 1 μg/kg of fentanyl and 4 mg of ondansetron were used to make analgesic connection and antiemetic, and patient-controlled Intravenous Analgesia (PCIA) was applied: Sufentanil 0.75-1 μg/kg+butorphanol 2 mg+ondansetron 16 mg, analgesic time is 24 h.

Observation indexes and acquisition process

General information: Age, height, weight, home address and contact information, education, major caregivers, family income, occupation, complications and so on were recorded.

Inventory acquisition: (HAMD score) and social support (SSRS score) at 1 day before surgery; (HAMD score) and pain (VAS score) at 1 and 3 days after surgery; (HAMD score), pain (VAS score) and social support (SSRS score) on the 7th day after surgery.

Statistical processing

SPSS 13.0 software was used for statistical analysis, and the measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). The t test for independent samples was used for comparison among the groups. The variance analysis or paired sample t test was used for intra-group comparison. Counting data was presented with the number of cases and use chi-square test or Fisher exact probability method. $P<0.05$ means the difference was statistically significant.

Results

The comparison of preoperative and postoperative social support, postoperative pain between the two groups

There was no significant difference in the age, height, weight, Body Mass Index (BMI), the years of schooling between the ketamine group and the control group ($P>0.05$)) (Table 1). There was no significant difference in the SSRS and scores VAS scores between the two groups before and after operation ($P>0.05$) (Table 2).

Table 1. *Comparison of general information ($\bar{x} \pm s$).*

Groups	N	Age	Height (Cm)	Weight (Kg)	BMI (Kg/M^2)	Schooling years (Years)
Control	25	43.27 ± 6.60	155.27 ± 5.23	52.09 ± 7.52	21.63 ± 3.15	8.11 ± 3.59
Ketamine	25	42.36 ± 7.28	157.55 ± 4.70	54.27 ± 8.84	21.89 ± 3.71	8.55 ± 3.88

Table 2. *The comparison of SSRS, VAS scores between the two groups before and after surgery ($\bar{x} \pm s$, n=25).*

	SSRS		VAS		
	1 d before surgery	7 d after surgery	1 d after surgery	3 d after surgery	7 d after surgery
Control	47.27 ± 6.17	48.64 ± 5.41	1.64 ± 1.36	1.45 ± 1.28	1.09 ± 0.83
Ketamine	45.72 ± 4.98	46.00 ± 5.23	1.36 ± 1.12	1.50 ± 0.93	0.82 ± 0.60

Operation time and usage of vascular active drug during the operation

As shown in Tables 3 and 4, there was no significant difference in the operation time and the usage of vasoactive drugs between the two groups ($P>0.05$).

Table 3. *Comparison of operation time between the two groups ($\bar{x} \pm s$, n=25).*

Groups	Operation time
Control group	157.73 ± 52.79
Ketamine group	159.09 ± 42.30

Table 4. *The comparison of the usage of vasoactive drugs between the two groups (cases, n=25).*

Groups	Atropine		Dopamine		Esmolol	
	Yes	No	Yes	No	Yes	No
Control	1	24	1	24	3	22
Ketamine	2	23	0	25	2	23

Comparison of perioperative HAMD score

In Table 5, the preoperative HAMD scores of the patients between the two groups has no significant difference ($P>0.05$). The HAMD scores of ketamine group were significantly lower than those of the control group at 1 and 3 days after operation ($P<0.05$), indicating that ketamine could significantly improve the depression symptoms of breast cancer patients with depression in the first three days after operation. At the 7th day after operation, ketamine group still had lower HAMD score than the control group, but there was no significant difference between two groups ($P>0.05$).

There was no significant difference in the HAMD score between in the control group at 1 day after operation compared with pre-operation. At 3 and 7 days after operation, HAMD score and preoperative ratio varied degrees of decline compared with those before operation, but there was no significant difference (P>0.05). While the HAMD scores in the ketamine group were significantly lower than those before operation (P<0.05) at the 1st, 3rd and 7th day after operation, the depression scores of both groups decreased to the lowest at the 3rd day after operation.

Table 5. The comparison of HAMD scores of perioperative patients between the two groups ($\bar{x}$ ± s, n=25).

Groups	1 d before surgery	1 d after surgery	3 d after surgery	7 d after surgery
Control group	18.55 ± 3.21	18.64 ± 3.83	16.27 ± 4.45	17.36 ± 6.25
Ketamine group	18.82 ± 2.82	12.55 ± 4.50*#	10.64 ± 4.33*#	13.45 ± 5.21#

Note: compared with the control group after surgery, *P<0.05; compared with preoperative after surgery, # P<0.05.

The comparison of extubation time, recovery period and adverse reactions during postoperative recovery period

1 case of nausea, 2 cases of irritability and 1 case of mild respiratory depression were found in ketamine group. In the control group, 2 cases of nausea and 1 case of irritability were found. No symptoms such as excitement occurred in the two groups and other serious adverse reactions. There was no significant difference in the incidence of adverse reactions between the two groups.

The duration of extubation was slightly longer in the ketamine group than that in the control group, but the difference was not statistically significant (P>0.05). There was no significant difference in the postoperative recovery of adverse reactions between the two groups (P>0.05). The results showed that sub-anesthetic dose of ketamine alone did not prolong the extubation time and did not increase the recovery period or postoperative adverse reaction in patients undergoing breast cancer radical mastectomy (Tables 6 and 7).

Table 6. The comparison of extubation time between the two groups ($\bar{x}$ ± s, n=25).

Groups	Extubation time
Control	10.02 ± 3.35
Ketamine	8.49 ± 2.88

Table 7. The comparison of the adverse reactions between the two groups after surgery (cases, n=25).

	Nausea	Dizziness	Headache	Euphoric	Cognitive impairment
Control	6	8	1	2	0
Ketamine	5	5	2	2	0

Discussion

The antidepressant effect of ketamine has been demonstrated in psychiatric and animal studies. Although some physicians have attempted to apply their antidepressant effect to the perioperative period and have achieved initial results, these studies are still rare. In this study, based on previous studies of ketamine for breast cancer patients in the anesthesia, for the first time we explored its impact on postoperative depression in breast cancer patients with depression, once again proved the antidepressant effect of ketamine.

After the administration of ketamine, the HAMD scores of the ketamine group at 1 and 3 days after operation was significantly lower than that before operation (P<0.05), and decreased obviously compared with the control group. However, there was no distinct change in HAMD scores of control group at 1, 3 and 7 days after operation compared with that before surgery. The results are basically the same as those of most psychiatrists in the study of depressive patients: the antidepressant effect of a single dose of subanesthetic ketamine is usually initiated within a few tens of minutes to several hours and The antidepressant effect at 4-72 h is significant, some cases of antidepressant efficacy can be sustained to 1-2 weeks after administration [5]. The results demonstrated that sub-anesthesia dose of ketamine could significantly improve the depressive symptoms of patients with intraoperative breast cancer complicated with depression, and maintained for a long time. It has been confirmed that glutamate system plays an important role in the pathophysiology of depression. An abnormal increase in glutamate concentration in the brain leads to depression [6,7], whereas ketamine inhibits Gamma-Aminobutyric Acid (GABA) neurons and blocks glutamate receptor-NMDA receptors, to promote free glutamate concentration increased at nerve endings [8] to achieve antidepressant effect. The release of BDNF and the activation of mammalian target of Rapamycin (mTOR) within 30 min were induced by the increase of free glutamate concentration, then regulated the expression of synaptic Protein translation, rapidly increased the density and function of spinous processes in the brain-medial prefrontal cortex (mPFC), which are closely related to depression behavior [9]. The HAMD score of the ketamine group was still lower than that of the control

group on the 7th day after operation, without significant difference (P>0.05), but it had significant difference compared with the preoperative score, suggesting that the antidepressant effect of ketamine was time and group interaction. The HAMD score of the experimental group at 7th day after operation was still lower than that of the preoperative, indicating that ketamine still had certain antidepressant effect, but no significant difference with the control group, and influence of time factor on depression, possibly associated with the psychological stress caused by chemotherapy.

In this study, the HAMD scores were 18.55 ± 3.21, 18.64 ± 3.83, 16.27 ± 4.45, 17.36 ± 6.25 in the control group for 1 day before operation and 1, 3, 7 days after operation, respectively. Depression score decreased on the third day, slightly increased on the seventh day; However, Jinyun et al. [13] reported that the depression symptoms of patients with fracture of perioperative acute stress-related symptoms is reduced at the 1st day after operation, then undulating (Self-Rating Depression Scale, SDSof 58.2 ± 6.0, 53.8 ± 5.7, 53.8 ± 6.1 and 54.0 ± 6.0, respectively). The possible cause of the differences was the differences in the case choice. The trauma of breast cancer patients is caused by the surgery, 24 h after surgery was the high-incidence time for various discomfort (such as chest straps, dizziness, nausea, affect sleep, etc.) brought by surgery and anesthesia. In addition, Chen et al. [14] also pointed out that depression of patients with tympanoplasty postoperative aggravated than preoperative condition. All these indicated that the trend of perioperative depression varies based on the type of surgery, anesthesia, age, sex, etc. [15].

In conclusion, Intraoperative single administration of sub-anesthesia ketamine significantly may have an effect on postoperative breast cancer patients with depression. But the effect may decrease along with the time.

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