

Original Article

Anesthesia effect of sufentanil in rats undergoing radical gastrectomy

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Abstract: Objective: Gastric carcinoma (GC) is one of the malignant tumors located in the epidermis of gastric mucosa, and it occurs with relatively high incidence. This study aims to explore the anesthetic effect and corresponding recovery quality of different doses of sufentanil in rats undergoing radical gastrectomy. Methods: SD rats were randomly divided into a low concentration group (LC), medium concentration (MC) group, high concentration (HC) group and the control group. The differences of anesthesia effect, anesthesia recovery quality, anesthesia depth, expression of tumor necrosis factor- α (TNF- α) interleukin-6 (IL-6), oxidative stress levels, respiratory function parameters and secondary effects were compared and analyzed. Results: Expression levels of TNF- α and IL-6 in HC group was higher than other groups ($P < 0.05$). At 3 h, 12 h and 24 h post administration, the HC group had a significantly higher malondialdehyde (MDA) levels but lower superoxide dismutase (SOD) levels than LC and MC groups ($P < 0.05$). However, both LC and MC groups showed better parameters of respiratory recovery and less secondary effects than the HC group ($P < 0.05$), and the LC group had the least symptoms. Conclusion: High concentration sufentanil has the greatest depth of anesthesia, but poor recovery quality and obvious secondary effects. Low concentration sufentanil caused little damage, but fell short of the anesthesia depth. Therefore, medium concentration of sufentanil has the best anesthesia effect.

Keywords: Sufentanil, gastrectomy, anesthesia

Introduction

Gastric carcinoma (GC) is a kind of malignant tumor located in the epidermis of gastric mucosa, with a high incidence as a leading cause of malignant tumors. Due to continuous development of the economy and society and increasing pressure, the incidence of gastric cancer gradually tends to be found in younger patients [1]. There are various causes related to gastric cancer, including environment, genetics, diet and other factors. The incidence of GC is high in eastern Asia and other countries, but is very low in northwestern countries, such as Europe, northern Asia and other regions [2]. GC has evolved from chronic gastritis, through which processes in which normal cells transform into cancer cells [3]. The present clinical treatment of gastric cancer is based on surgery, assisted

by chemotherapy and other comprehensive treatment methods, but the effect is not ideal and often is easy to relapse [4]. Early gastric cancer has no obvious characteristic, only a small number of patients have slight symptoms such as stomach pain and anorexia, which are usually treated as general gastric diseases instead of gastric cancer. Thus, more than 80% of gastric cancer is not found until the middle and late stage [5]. In clinic, radical gastrectomy, also called curative gastrectomy, is a common surgical method for gastric cancer, which means that the primary tumor, together with the metastatic lymph nodes and the involved infiltrated tissues, are all excised with good therapeutic effect. Sufentanil primarily acts upon μ opioid receptors and it has longer actuation duration. Scholars believe that the lipophilicity of sufentanil is about twice that of

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fentanyl and it can easily pass through the blood-brain barrier with a higher binding rate with plasma proteins. Now, sufentanil is widely used in clinical operations as an anesthesia related drug with the characteristics of strong analgesic effects and long duration, thus it is an ideal patient-controlled intravenous analgesic given after operation [6]. However, different concentrations of sufentanil have different effects and different complications. This study aims to analyze the anesthesia effect of different concentrations of sufentanil on rats through various aspects and perspectives, and explores the specific indicators of sufentanil anesthesia.

Materials and methods

Experimental animals

Twenty healthy male SD rats in similar age, weighing 231-289 g, were purchased from Guangdong Medical SD rat center. The rats were raised separately in clean animal houses with good ventilation conditions according to standard feeding methods with free access to standard pellet feed and drinking water. Room temperature was controlled at $22\pm 2^{\circ}\text{C}$ and the relative humidity was 40%-60% with 12 hours of light and dark cycle (8:00-20:00/20:00-8:00). All the experimental animals were allowed one week to adapt to the environment before the experiment. Animal experiments were approved by the animal Ethics Committee of Heji Hospital Affiliated to Changzhi Medical College. Besides, ARRIVE guidelines and the EU Directive 2010/63/EU for animal experiments have also been followed in the experiments.

Establishment and grouping of animal models

First, cytarabine solution (ml22916-1, Shanghai sobao Biotechnology Co., Ltd.) was injected into the abdomen of rats (150 mg/kg). After 36 h, a whole body irradiation was carried out at 10 Gy for 18 h and then human gastric cancer cell MGC803 suspension (0.6 mL, 5×10^6 cells) was inoculated into the inner part of the rat near the groin to establish the gastric cancer rat model. During this period, all rats lived in the same environment. Barium meal examination was used to confirm if the model was successful by checking whether the gastric wall was thickened and whether there was a mass in the cavity [7].

The selected rats were randomly divided into 4 groups as following (5 rats in each group). The low concentration group (LC group): Rats in this group were injected with 50 $\mu\text{g}/\text{kg}$ sufentanil (F0054990-1EA, Wuhan Humanwell Pharmaceutical Group Co., Ltd.) for intraoperative anesthesia. The medium concentration group (MC group): Rats in this group were injected with 150 $\mu\text{g}/\text{kg}$ sufentanil for intraoperative anesthesia. The high concentration group (HC group): Rats in this group were injected with 250 $\mu\text{g}/\text{kg}$ sufentanil for intraoperative anesthesia. The control group (co group): Rats in this group were fed normally without any treatment.

Detection of anesthesia effect in rats through righting reflex experiment

Detection of anesthesia effect in rats through labyrinthine righting reflex (LRR) experiment as the following steps: After anesthesia, three groups of rats were placed in an 800 mL beaker, and the beakers were overturned every 2 minutes. The disappearance of LRR is assessed when the rats could not be right themselves to the ground with at least one foot within 10 seconds, performed three times continuously. The latent period of LRR disappearance was recorded from administration of anesthesia to disappearance of LRR. The latency and duration of LRR were recorded.

Recovery quality of anesthesia in rats

The recovery quality was assessed by detecting the recovery of the arm strength of rats. Two hind limbs were tied and two forelimbs of the rats were hung on the balance bar. The time of holding the balance bar is used as the judgment standard. The longer the hanging time was, the stronger the arm strength was.

Anesthesia depth score of rats

Method: The depth of anesthesia was evaluated according to pedal retraction response (PWR) established by Antunes et al [8]. The intensity of the exercise is determined by stretching the legs and pinching the interphalangeal area of the foot with the fingernails of the forehead and thumb. The response score range is 1-5, in which 1 represents no response, 5 represents obvious response. The lower the score is, the deeper the degree of anesthesia is (**Table 1**).

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Table 1. Scoring standard of anesthesia depth

Depth score	Symptom
1	No response to PWR stimulation, slow and deep breathing
2	Slight increase in muscle tone due to PWR stimulation
3	Mild retraction in the constricted limb and is considered to be a stronger reflex response, also equals to "lighter" anesthesia
4	Obvious response in the measured leg and occasionally movement in other places due to PWR and increased respiratory rate
5	Slight whisker movement or blinking, rapid leg withdrawal and spontaneous PWR leading to other limb movements

Note: PWR: pedal retraction response.

Detection of TNF- α and IL-6 expression in rats

TNF- α and IL-6 kits were purchased from Shanghai Xinfan Biotechnology Co., Ltd (ML-Elisa-1420). According to the instructions of the ELISA kits, the serum of rats in the four groups was stored at -80°C, upon thawing it was centrifuged for 20 min. A 100 μ L sample was washed at 37.5°C, and rested for 60 min. Then 60 mL termination solution was mixed together, and the mixture was allowed to incubate for 20 min. At last, the optical density was measured.

Changes of oxidative stress after anesthesia in rats

After anesthesia, the serum of rats in four groups was collected by routine methods. The content of malondialdehyde (MDA) and superoxide dismutase (SOD) in serum were checked through thiobarbituric acid method, and xanthine oxidase method, respectively. The related detection kits were purchased from Suzhou Greis Biotechnology Co., Ltd. (CLS-A003-1) and all the experiments were conducted strictly following the instructions.

Respiratory function parameters of rats

The parameters of respiratory function were measured by the lung function detector in the following testing conditions: the flow rate of the air pump is 1.5 L/min, the gain is magnified by one time, the sensor is magnified by 200 times, and the sampling rate is 500 Hz. Respiratory function parameters included respiratory rate per minute (RR) and expiratory time (ET). During the experiment, the baseline values of respiratory parameters were recorded. After that, the respiratory parameters of anesthetized rats

were measured, and the mean value was the baseline value.

Secondary effects

The secondary effects of anesthesia in rats, including convulsion, muscle relaxation and saliva secretion were observed and recorded.

Statistical analysis

The results were analyzed by SPSS 22.0 software. The enumeration data was expressed by n (%), and was then tested by continuous correction chi square test. Measurement data was expressed as mean \pm standard deviation ($\bar{x} \pm sd$). Comparison between two groups was conducted through variance analysis and followed by Bonferroni test. $P < 0.05$ was considered as a significant difference.

Results

Comparison of anesthesia effects

Rats in the LC group have the longest latency of LRR but the shortest duration of LRR. Rats in the HC group have the shortest latency of LRR but the longest duration of LRR. The anesthesia effect of MC group was much better than that of LC group ($P < 0.05$) but was much weaker than that of HC group ($P < 0.05$). Thus, rats in the HC group have the best anesthesia effects among these three groups ($P < 0.05$; **Table 2**).

Comparison of anesthesia recovery quality

There was little difference in the holding time before administration among the LC group, MC group and HC group ($P > 0.05$). However, with the prolongation of time, the holding time of rats in the LC group and MC group gradually

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Table 2. Comparison of anesthesia effects of rats in three groups ($\bar{x} \pm sd$)

Group	LRR Latency (min)	LRR Duration (min)
LC group (n=5)	6.48±2.68	36.14±6.84
MC group (n=5)	3.14±0.85 ^a	83.49±14.25 ^a
HC group (n=5)	1.21±0.32 ^{a,b}	178.34±31.69 ^{a,b}
F	13.324	62.713
P	<0.001	<0.001

Note: ^aP<0.05 vs. LC group; ^bP<0.05 vs. MC group. LRR: labyrinthine righting reflex; LC: low concentration group; MC: medium concentration; HC: high concentration.

recovered, but there was still no significant change in holding time of rats in HC group. The holding time of rats in the HC group was obviously shorter than that of the LC group and MC group (P<0.05; **Table 3**).

Comparison of anesthesia depth scores

After administration, the rats in the HC group have the lowest score of anesthesia depth and better anesthesia effect. The score of anesthesia depth in LC group was the highest. The anesthesia depth of rats in HC group was evidently deeper compared with LC group and MC group (P<0.05; **Table 4**).

Comparison of the expression level of TNF- α and IL-6

After administration, the expression levels of TNF- α and IL-6 in CO group were the lowest. The expression levels of both TNF- α and IL-6 in HC group were much higher than those in LC group and MC group (P<0.05; **Table 5**).

Comparison of oxidative stress levels

Rats in LC group have the lowest level of MDA and the highest level of SOD but rats in the HC group have the highest level of MDA and the lowest level of SOD. At 3 h, 12 h and 24 h post administration, rats in the HC group had significantly higher expression level of MDA and sharply lower expression level of SOD compared with that in LC group and MC group (P<0.05; **Table 6**).

Comparison of respiratory function parameters

As the baseline value, significant changes were not shown at any time in the CO group. In the HC group, the most significant inhibition of respiratory function was found with rapidly

decreased RR and quickly increased ET value (P<0.05). The respiratory parameters began to recover gradually 15 minutes later. The recovery of respiratory parameters in HC group was much lower than that of LC group and MC group (P<0.05; **Figure 1**).

Comparison of secondary effects

The secondary effects of the HC group were the most serious with the symptoms such as muscle rigidity and convulsion. The LC group had the least symptoms with no secretions. The secondary effect of the HC group was clearly more serious than that of LC group and MC group (P<0.05; **Table 7**).

Discussion

At present, the detection rate and cure rate of gastric cancer in China are still relatively low. Radical surgery is one of the main treatment methods for gastric cancer patients. Thus, surgical treatment should be given priority as far as possible for patients who meet the requirements of surgical indications to remove the tumor focus, reduce the spread and metastasis of tumor cells, and prolong the survival of patients. Laparoscopic radical gastrectomy is a widely used minimally invasive surgery in recent years, which greatly reduces the trauma caused by surgery and relieves the physiological and psychological stress response of patients [9-11]. However, it is difficult to select an appropriate anesthetic in radical gastrectomy because the existing anesthetic has good anesthetic effect but with large side effects. Therefore, sufentanil was selected as the main anesthetic in our present study due to its strong lipophilicity and persistence. Sufentanil can easily pass through the blood-brain barrier, possessing a high binding rate with plasma protein and it has stronger analgesic effect and longer action time.

Our study showed that the HC group had best anesthesia effect and the deepest anesthesia degree. Besides, the holding time of HC group was much shorter than that of LC group and MC group. It has also been reported that sufentanil is a new type of narcotic analgesic with high efficacy and fat solubility. It can quickly get into the brain through the blood-brain barrier, thus playing an anesthetic role. Simultaneously, there is a significant correlation between the time it takes for the drug to get to the brain and

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Table 3. Comparison of holding time of rats in three groups ($\bar{x} \pm sd$)

Group	LC group (n=5)	MC group (n=5)	HC group (n=5)	F	P
Before administration	20.56±5.48	19.68±4.29	21.39±6.49	0.121	0.886
After the restoration of righting reflex					
20 minutes	10.26±3.45	6.14±1.02 ^a	3.16±0.78 ^{a,b}	14.073	<0.001
40 minutes	16.54±4.28	8.36±2.14 ^a	2.48±0.98 ^{a,b}	31.352	<0.001
60 minutes	18.59±6.49	9.47±5.31 ^a	4.75±1.32 ^{a,b}	6.680	0.011

Note: ^aP<0.05 vs. LC group; ^bP<0.05 vs. MC group. LC: low concentration group; MC: medium concentration; HC: high concentration.

Table 4. Comparison of anesthesia depth scores of rats in three groups ($\bar{x} \pm sd$)

Group	LC group (n=5)	MC group (n=5)	HC group (n=5)	F	P
After administration					
10 minutes	3.14±1.56	1.49±0.68 ^a	1.34±0.47 ^{a,b}	4.800	0.029
30 minutes	3.68±1.75	2.34±1.17 ^a	1.95±0.89 ^{a,b}	2.365	0.136
50 minutes	4.16±2.04	3.08±1.36 ^a	2.37±1.21 ^{a,b}	1.630	0.236
70 minutes		4.43±1.49	3.74±1.36 ^b	20.943	<0.001

Note: ^aP<0.05 vs. LC group; ^bP<0.05 vs. MC group. LC: low concentration group; MC: medium concentration; HC: high concentration.

Table 5. Comparison of the expression of TNF- α and IL-6 of rats in four groups ($\bar{x} \pm sd$)

Group	TNF- α (ng/mL)	IL-6 (pg/mL)
LC group (n=5)	16.26±2.38	6.59±1.03
MC group (n=5)	21.91±4.25 ^a	8.19±3.49 ^a
HC group (n=5)	39.16±3.94 ^{a,b}	13.07±1.80 ^{a,b}
CO group (n=5)	14.56±1.59 ^{a,b,c}	5.14±0.65 ^{a,b,c}
F	7.544	5.376
P	<0.001	<0.001

Note: ^aP<0.05 vs. LC group; ^bP<0.05 vs. MC group; ^cP<0.05 vs. HC group. LC: low concentration group; MC: medium concentration; HC: high concentration; CO: control; TNF: tumor necrosis factor; IL: interleukin.

drug concentration [12, 13]. The results showed that, through intraperitoneal administration, the onset time of sufentanil was significantly shortened, and the duration of sufentanil was significantly increased with increasing dose, showing a dose-dependent manner [14, 15]. The results of animal experiments also showed that the onset time of anesthesia at a single dose 400 $\mu\text{g}/\text{kg}$ group was shortened to 2 minutes compared with that in the single dose 150 $\mu\text{g}/\text{kg}$ group, indicating that the concentration of sufentanil was inversely proportional to the onset time of anesthesia. However, some deaths occurred among the rats in the 400 $\mu\text{g}/\text{kg}$ group with the dose

increasing. Of course, excessive anesthesia will cause physiological environment disorder, which may lead to death [16, 17].

The levels of TNF- α , IL-6 and MDA in the HC group were evidently higher and the level of SOD was much lower than those in the LC group and MC group. However, the respiratory function was most significantly inhibited, RR decreased rapidly and ET increased rapidly in the HC group. Besides, the recovery of respiratory parameters in the HC group was lower than that in the LC group and MC group and the secondary effects of the HC group were the most serious among these three groups. Previous study showed that the levels of TNF- α and IL-6 in rats with tumors decreased significantly after sufentanil injection, which indicated that sufentanil could effectively reduce the expression of inflammatory factors, but the expression of IL-6 was increased on the contrary when the concentration of sufentanil was too high [18, 19]. Some studies have shown that sufentanil can effectively stabilize the hemodynamics of gastric cancer patients and reduce the postoperative oxidative stress response in dose dependent manner [20-22]. The above results show that sufentanil has significant correlation with TNF- α , IL-6, MDA and SOD *in vivo*, and its anesthesia effect may be achieved by improving the expression levels of TNF- α and IL-6.

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Table 6. Comparison of oxidative stress levels of rats in three groups ($\bar{x} \pm sd$)

Group	LC group (n=5)	MC group (n=5)	HC group (n=5)	F	P
MDA (nmol/mL)					
3 h	6.49±1.48	8.42±1.13 ^a	9.46±1.43 ^{a,b}	6.181	0.014
12 h	5.48±0.89	7.01±1.45 ^a	14.26±2.64 ^{a,b}	33.451	<0.001
24 h	5.13±0.64	6.49±1.84 ^a	3.42±1.32 ^{a,b}	53.546	<0.001
SOD (U/mL)					
3 h	178.49±16.48	154.38±15.95 ^a	135.06±13.48 ^a	10.036	0.002
12 h	149.27±15.34	128.45±14.29 ^a	98.45±16.84 ^{a,b}	13.529	<0.001
24 h	138.58±17.95	136.73±11.79 ^a	112.39±9.49 ^{a,b}	5.813	0.017

Note: ^aP<0.05 vs. LC group; ^bP<0.05 vs. MC group. LC: low concentration group; MC: medium concentration; HC: high concentration; MDA: malondialdehyde; SOD: superoxide dismutase.

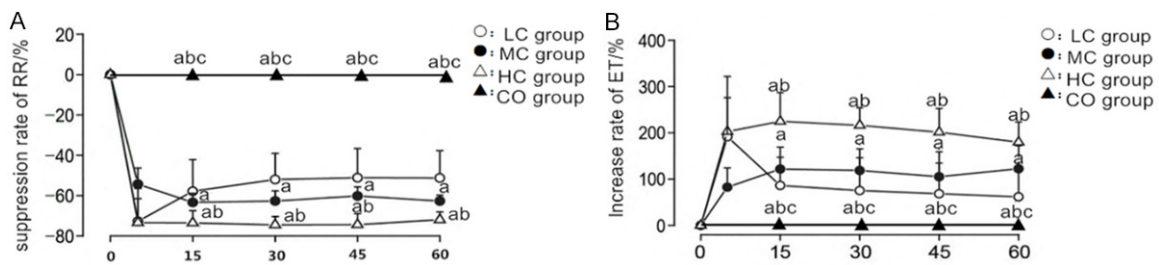


Figure 1. Comparison of respiratory function parameters among the rats in three groups. A: Suppression rate of RR of rats in three groups (%); B: ET proliferation rate of rats in three groups (%). ^aP<0.05 vs. LC group; ^bP<0.05 vs. MC group; ^cP<0.05 vs. HC group. RR: respiratory rate per minute; ET: expiratory time; LC: low concentration group; MC: medium concentration; HC: high concentration; CO: control.

Table 7. Comparison of secondary effects ($\bar{x} \pm sd$)

Group	Muscle relaxation	Horror	Secretion rate (%)
LC group (n=5)	Mild	No	0
MC group (n=5)	Tension	Slight	35.26
HC group (n=5)	Stiffness	Serious	71.34
χ^2			71.618
P			<0.001

Note: LC: low concentration group; MC: medium concentration; HC: high concentration.

rats. High concentration sufentanil has the greatest depth of anesthesia, but poor quality of anesthesia recovery and obvious secondary effects. Low concentration sufentanil caused little damage to rats, but the depth of anesthesia was insufficient. Therefore, medium concentration of sufentanil has the best anesthesia effect.

Disclosure of conflict of interest

None.

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There also exist some deficiencies in the research processes of this experiment. Due to the limitation of cost and time, a large number of samples have not been tested, and the influence of other factors cannot be excluded, which may also bring some deviation in the results. In addition, our study was largely limited because only one kind of drug was used. In our future research, more experimental methods will be conducted to provide more favorable experimental basis for the correlation between sufentanil and anesthesia effects.

Different concentrations of sufentanil have a certain correlation with the anesthetic effect of

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