

# Influence of Preemptive Analgesia with Oxycodone Hydrochloride on Stress Hormone Level of Geriatric Patients undergoing Gastrointestinal Surgery

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## ABSTRACT

**Objective:** To determine the influence of preemptive analgesia with oxycodone hydrochloride on stress hormone level of geriatric patients undergoing gastrointestinal surgery, and evaluate the analgesic effect.

**Study Design:** Randomised controlled trial.

**Place and Duration of Study:** Department of Anaesthesiology, Baoding First Central Hospital, from January to December 2017.

**Methodology:** Geriatric patients who were to undergo gastrointestinal surgery were classified into observation group and control group of 30 patients each. For the observation group, intravenous injection of 0.1mg/kg oxycodone hydrochloride injection was conducted 10 mins before anesthesia induction. For the control group, intravenous injection of 10 ml normal saline was conducted. Eight ml of venous blood was drawn 10 mins before injection (T0), after operation (T1), 2 hours after operation (T2), 6 hours after operation (T3), and 24 hours after operation (T4). Serum concentration of cortisol, epinephrine, noradrenaline was determined after the completion of surgery (T1), 2-hour after surgery (T2), 6-hour after surgery (T3) and 24-hour after surgery (T4). for both groups. Visual analogue scale (VAS) score was used for assessment of pain when the surgery was completed; and after the surgery, was compared for both groups.

**Results:** Serum concentrations of epinephrine and noradrenaline in observation group were significantly reduced at T1 and T2 ( $p < 0.05$ ), and serum concentrations of cortisol and glucose were significantly reduced at T1, T2 and T3 ( $p < 0.05$ ). At 2 and 6-hours after operation, the VAS score was significantly lower than that of the control group ( $p < 0.05$ ).

**Conclusion:** Giving oxycodone hydrochloride to geriatric patients receiving gastrointestinal surgery can reduce stress hormone release in the postoperative period, and can facilitate postoperative recovery.

**Key Words:** *Sold, Gastrointestinal surgery, Oxycodone hydrochloride, Preemptive analgesia, Stress response.*

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## INTRODUCTION

According to international regulations, people over the age of 65 are defined as the elderly or geriatric; in China, citizens over the age of 60 are defined as the elderly or geriatric. Physiological functions of geriatric patients generally present degenerative changes, and their endurance capacity also declines. Besides, diabetes and other system diseases are often accompanied, which severely affects patients' cardiopulmonary compensation function.<sup>1-3</sup>

When gastrointestinal disease is treated with open surgery, the incision size is large, and postoperative pain may be severe, thus seriously affecting patients' circulation, breathing, internal

secretion, metabolism, gastrointestinal function recovery and wound healing, etc. Besides, a series of inflammatory and stress responses are initiated.<sup>4</sup> Oxycodone is a common double agonist of opium k receptor and  $\mu$ -receptor, and can hinder neurosensory pathway and reduce body sensitivity to harmful feeling so as to reach the purpose of postoperative analgesia, called preemptive analgesia.<sup>5</sup>

The aim of this study was to determine the effect of oxycodone hydrochloride for geriatric patients undergoing gastrointestinal surgery, on serum concentration changes of cortisol, epinephrine, norepinephrine and glucose after the surgery and postoperative analgesia.

## METHODOLOGY

The study was approved by the Institutional Ethics Committee of Baoding First Central Hospital, and written informed consent was obtained from all participants.

General data of 60 patients, who received stomach, duodenum, colon and other intestinal tract surgeries under general anesthesia at Baoding First Central Hospital from January 2017 to

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December 2017, were collected. They were classified into an observation group and a control group of 30 cases each. Exclusion criteria were abnormal liver and kidney function before operation; history of coronary heart disease; severe hypertension, gastrointestinal ulcer; history of abuse of sleeping pills and narcotic drug. Those undergoing any surgery of stomach, duodenum, colon and other intestines were selected in this surgery group patients. They all signed the informed consent form. The sample size was calculated using the sample size formula of the repeated measurement data as follows:

$$N = \frac{(Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2 \times \sigma^2 \times 2[1 + (T-1)\rho]}{v^2 T}$$

Where  $(1-\beta)$  is the test efficiency, which is the value of the standard normal distribution  $(1-\alpha/2)$  percentile. When  $\alpha$  is 0.05, then  $Z_{0.05/2}=1.96$ ; is the standard normal distribution  $(1-\beta)$  Percentile value, taking  $\beta$  as 0.1,  $Z_{0.1}=1.28$ ;  $\sigma$  is the mean standard deviation of outcome variables,  $\rho$  is the cortisol relation coefficient between repeated measures,  $T$  is the number of follow-up measurements, and  $v$  is the difference between the mean values of the outcome variables between the groups. According to the formula, the sample size of the five parts of cortisol, epinephrine, norepinephrine and glucose, and VAS was calculated, and the largest sample was 29. Therefore, the sample size of this study I was 30.

For the observation group, intravenous injection of 0.1 mg/kg oxycodone hydrochloride injection was conducted 10 mins before anesthesia induction. For the control group, intravenous injection of 10 ml normal saline was conducted. Anesthesia induction: intravenous injection of 0.05 mg/kg midazolam, 4 ug/kg fentanyl, 2.0 ng/ml propofol or 0.2 mg/kg etomidate, and 0.9 mg/kg rocuronium bromide was carried out for anesthesia induction. After consciousness and autonomous respiration disappeared, and the underjaw was flabby, trachea cannula was conducted. Intermittent mechanical positive pressure ventilation was carried out at tidal volume (VT) of 6-8 ml / Kg, respiratory rate (RR) of 14-16 times / minute, oxygen flow of 1.5ml / Kg, respiratory ratio of 1: 2, maintaining PET (Co2) 35-45mmHg. During the surgery, 3-4mg/kg propofol and Remifentanyl 0.08-0.1ug/ (Kg/minute) were infused at the constant speed.

Eight ml of venous blood was drawn 10 mins before injection (T0), after the operation (T1), after 2 hours (T2), after 6 hours (T3), after 24 hours (T4); 8ml venous blood was drawn at T0 (10 mins before injection), T1, T2, T3 and T4, and cortisol, epinephrine, norepinephrine and glucose values were measured. Visual analog scale (VAS) was used for pain assessment Score of the 2 groups when the surgery was completed, 2h, 6h, 12h and 24h after the surgery was evaluated. SPSS17.0 statistical package was used for data statistics and processing. Measurement data were expressed with  $\bar{x} \pm s$ , and independent sample t test was used for inter-group comparison, frequency or percentage was used for counting data.  $\chi^2$  test was used to compare enumeration data.  $\alpha=0.05$  was applied as the test level.

## RESULTS

The patient's age was 60-75 ( $66.5 \pm 7.1$ ) years; gender was not

limited, 49 males and 11 females; body weight was 50-77 ( $66.1 \pm 1.8$ ) kg; 35 patients were ASA grade I and 25 patients were grade II. General information of both groups is shown in Table I.

General information comparison difference had no significance ( $p>0.05$ ), are shown in Table II. The concentrations of epinephrine and norepinephrine in the observation group were significantly lower than those in the control group (EP1 = 0.001, EP2 = 0.001; NP1 = 0.001; NP2 = 0.001); the concentrations of cortisol and glucose in the observation group were significantly lower than those in the control group (CP1 = 0.001, CP2 = 0.001, CP3 = 0.001; GP1 = 0.001, GP2 = 0.001, GP3 = 0.001). The VAS score of the observation group at the end of surgery, 2h and 6h after surgery was significantly lower than the control group ( $p=0.001$ ;  $p_1=0.001$ ;  $p_2=0.001$  respectively), as shown in Table III.

**Table I: General information statistics of patients (n=60).**

	Observation group (n=30)	Control group (n=30)	t / $\chi^2$	P
Gender				
Male	20 (66.7%)	19 (63.3%)		
Female	10 (33.3%)	11 (36.7%)	0.073	0.787
Body mass (kg)	66.1 $\pm$ 1.8	66.0 $\pm$ 1.4	0.240	0.811
ASA grade				
I	17 (56.7%)	18 (60%)		
II	13 (43.3%)	12 (40%)	0.069	0.793
Type of surgery (stomach / intestines)				
Stomach	8 (26.7%)	9 (30%)		
Intestines	22 (73.3%)	21 (70%)	0.082	0.775
Duration of surgery (min)	100.1 $\pm$ 11.2	98.9 $\pm$ 12.9	0.385	0.702
Intraoperative blood loss (ml)	202.4 $\pm$ 50.5	196.9 $\pm$ 58.9	0.388	0.699

General statistics of patients before and during surgery,  $p>0.05$

## DISCUSSION

All patients received a midline laparotomy incision, with potential for severe postoperative pain. Besides, the surgery involved visceral organs, and patients had visceralgia. The heart, liver, lung and kidney functions of senile patients degenerate, and their medicine metabolism function declines. The half-life period of medicine lengthens obviously. When the surgery and anesthesia further weaken various functions of body, patients' postoperative breathing, circulation and cognition function will be affected.<sup>6</sup> Oxycodone hydrochloride mainly acts on the central nervous system and smooth muscle, and has definite analgesic effect on internal organs. Besides, it will not cause euphoria, gastrointestinal motility and respiratory depression.<sup>7-9</sup> In recent years, it has been applied clinically through multiple ways, such as preemptive analgesia. Preemptive analgesia means that the anaesthetic is applied before the surgery to hinder neurosensory pathway and reduce body sensitivity to harmful feeling so as to reach the purpose of postoperative analgesia.<sup>10</sup>

When the body is suddenly subjected to strong harmful stimulation (such as trauma, operation, blood loss, infection, poisoning, hypoxia, etc.), the concentration of adrenocorticotrophic hormone in the blood increases rapidly through the hypothalamus, and the massive secretion of glucocorticoid is called stress response. Moderate stress can make the body enhance the ability to resist all kinds of stimuli. However, overstimulation will damage internal environment of body, thus leading to the decrease in the bearing capacity of body.<sup>11</sup>

**Table II: Comparison of serum cortisol, epinephrine, norepinephrine and glucose concentration of 2 groups (x±s) (n=60).**

Laboratory indicator	Group	T0	T1	T2	T3	T4
Cortisol (ng/ml)	Observation group	145.1 ±31.6	154.7 ±28.8*	158.1 ±26.9*	156.9 ±29.1*	156.1 ±21.9
	Control group	151.2 ±28.1	242.6 ±21.5 <sup>#</sup>	217.5 ±27.2 <sup>#</sup>	192.9 ±23.8 <sup>#</sup>	156.9 ±26.8
t		<b>0.790</b>	<b>13.396</b>	<b>8.255</b>	<b>5.245</b>	<b>0.127</b>
p		<b>0.433</b>	0.001	0.001	0.001	<b>0.900</b>
Epinephrine (pg/ml)	Observation group	15.2 ±3.5	16.0 ±3.4*	16.2 ±3.2*	15.2 ±3.5	15.9 ±3.2
	Control group	14.8 ±4.1	27.6 ±4.8 <sup>#</sup>	24.2 ±4.4 <sup>#</sup>	14.8 ±4.1	15.8 ±3.5
t		<b>0.406</b>	<b>10.801</b>	<b>8.255</b>	<b>0.406</b>	<b>0.115</b>
p		<b>0.686</b>	0.001	0.001	<b>0.686</b>	<b>0.908</b>
Norepinephrine (pg/ml)	Observation group	344.2 ±98.6	386.8 ±103.1*	381.9 ±92.7*	383.3 ±95.5	359.1 ±102.1
	Control group	352.3 ±0.38	479.1 ±108.1 <sup>#</sup>	461.3 ±101.2 <sup>#</sup>	428.5 ±99.1 <sup>#</sup>	358.7 ±101.2
t		<b>0.450</b>	<b>3.384</b>	<b>3.169</b>	<b>1.799</b>	<b>0.015</b>
p		<b>0.654</b>	<b>0.001</b>	<b>0.002</b>	<b>0.077</b>	<b>0.988</b>
Glucose (mmol/L)	Observation group	5.5 ±0.5	5.8 ±0.7*	5.6 ±0.4*	5.5 ±0.4*	5.4 ±0.5
	Control group	5.6 ±0.4	7.9 ±0.8 <sup>#</sup>	7.8 ±0.7 <sup>#</sup>	7.1 ±0.7 <sup>#</sup>	5.5 ±0.6
t		<b>0.855</b>	<b>10.820</b>	<b>14.946</b>	<b>10.870</b>	<b>0.701</b>
p		<b>0.396</b>	0.001	0.001	0.001	<b>0.486</b>

Comparison between each time point and T0 in the group, <sup>#</sup>p<0.05; inter-group comparison, \*p<0.05.

**Table III: Postoperative pain scores of both groups (n=60).**

Group	No.	Completion of surgery	2h after surgery	6h after surgery	12h after surgery	24h after surgery
Observation group	30	4.3 ±0.8*	4.4 ±0.9*	4.6 ±1.5*	5.0 ±0.9	4.5 ±0.9
Control group	30	6.3 ±0.6	6.0 ±0.4	5.6 ±0.4	5.3 ±0.8	4.5 ±0.5
t		10.955	8.898	3.528	1.365	0.000
p		0.001	0.001	0.001	0.178	1.000

Inter-group comparison, \*p<0.05

Under the stimulation of anesthesia, tube pulling, pain and surgery, renin angiotensin (RAS), aldosterone (ADS), epinephrine, cortisol and catecholamine (CA) secreted by the body will increase. The too high hormone level will stimulate stress response of the body, which is adverse to recover.<sup>12</sup> The concentration of cortisol, epinephrine, norepinephrine and glucose is an important indicator to reflect stress intensity.<sup>13</sup> Cortisol owns high sensitivity, and its level is closely related to stress response intensity and duration. The higher the cortisol level, the more arcuate the stress response.<sup>14</sup> Internal and external stimulation of the body can cause sympathetic nerve excitation of the patients receiving gastrointestinal surgery, and result in serum CA level rise, the increase of serum cortisol, epinephrine and norepinephrine level, gluconeogenesis rise and glucose level rise.<sup>15</sup> Senile patients are often combined with hypertension and other underlying diseases.

The resilience of their aorta and surrounding artery declines, and nervous system and blood vessel regulation capacity reduce. Under stress stimulation, their circulatory system compensation capacity weakens, and thus the occurrence rate of severe complications of heart, brain and kidney increases.<sup>16</sup> This study showed that, serum epinephrine, norepinephrine, cortisol and glucose concentration of observation group declined to different degree after the surgery, indicating that preemptive analgesia effect of oxycodone hydrochloride can reduce patients' stress hormone level. This may be related to action, peak and hold time of oxycodone hydrochloride in the body of old people. Ligang *et al.*<sup>17</sup> considered that, oxycodone relieved stress response caused in the tube pulling period and reduced serum epinephrine, and cortisol level. Moreover, oxycodone can make cortisol and testosterone drop, thus inhibiting overstress response caused by surgery and other

stimulation.<sup>8</sup> Some research shows that opioids restrain stress response of body through inhibiting secretion of adrenocorticotrophic hormone and  $\beta$ -endorphin or acting on stress hormone precursor.<sup>18</sup> The literature indicates that oxycodone can well inhibit stress response level after the surgery.<sup>19</sup> The above research results are close to this study.

Oxycodone hydrochloride owns double agonist effect of  $\kappa$ -receptor and  $\mu$ -receptor, and is widely applied in postoperative analgesia.<sup>20</sup> Its effect feature is similar to morphine. It can effectively restrain central nervous excitation through inhibiting peripheral nerve sensitivity, with very ideal analgesic effect. In this study, preemptive analgesia method was applied for the senile patients receiving gastrointestinal surgery. VAS score of the patients in the observation group significantly declined when the surgery was completed, 2h and 6h after the surgery. This proves that analgesic effect of oxycodone hydrochloride is obvious, and its timeliness may be related to half-life period of medicine.

## CONCLUSION

Oxycodone hydrochloride preemptive analgesia can reduce the secretion of stress hormones and inhibit the occurrence of over-stress reaction in elderly patients undergoing gastrointestinal surgery in a certain period of time, and has specific analgesic effect, with safety.

## ETHICAL APPROVAL:

The study was approved by the Institutional Ethics Committee of Baoding First Central Hospital.

## PATIENTS' CONSENT:

Written informed consents were obtained from all participants.

## CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION:

JZ, HY: Designed this study and prepared this manuscript.

YZ: Collected and analysed clinical data.

KZ: Significantly revised this manuscript.

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