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Original Article

Influences of naloxone combined with tramadol onthe analgesic effect and inflammation after laparoscopic surgery

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Abstract: Objective: To investigate the influence of naloxone combined with tramadol on analgesic effect, hemodynamics, and inflammation after laparoscopic surgery. Methods: 100 patients receiving laparoscopic cholecystectomy were included in this study and randomly divided into the tramadol group (n = 50) and the combination group (naloxone + tramadol) (n = 50). Serum concentrations of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were detected. Moreover, the mean arterial pressure (MAP) and heart rate (HR) were monitored at 6, 12, and 24 hours after surgery using a Finometer PRO noninvasive hemodynamic detector. In addition, the visual analogue scale (VAS) was adopted to evaluate the postoperative pain degree. Results: Compared with those in the tramadol group, the score of VAS, MAP, and HR in the combination group were significantly decreased ($p < 0.05$). Furthermore, the serum concentrations of CRP, TNF-α, and IL-6 in the combination group were decreased significantly at 6 and 12 hours after surgery ($p < 0.05$). In addition, the incidence of nausea, vomiting, and chills in the combination group was significantly lower than that in the tramadol group after surgery. Conclusion: Naloxone combined with tramadol can enhance the analgesic effect, inhibit expression of pro-inflammatory cytokines (CRP, TNF-α, and IL-6), alleviate body injury resulting from postoperative stress response, and reduce the incidence of adverse reactions and complications, providing a safe and efficient approach of analgesia for laparoscopic surgery.

Keywords: Naloxone, tramadol, after laparoscopic surgery, analgesia, hemodynamics, inflammation

Introduction

Compared with laparotomy, laparoscopic surgery has fewer traumas, and is currently widely applied in clinical practice. However, there are still a variety of factors that can contribute to pain other than incision pain. Postoperative pain triggers a significant increase of inflammatory cytokines, which can also lead to other complications [1]. The pro-inflammatory cytokine released in the initial stage of inflammation is tumor necrosis factor-α (TNF-α). C-reactive protein (CRP) is a reactive protein during acute phase of inflammation. Moreover, a sustained increase in the level of interleukin-6 (IL-6) suggests an aggravation of inflammation [2]. Control of postoperative acute pain and prevention of the occurrence of central sensitization as well as the release of inflammatory cytokines can help patients recover and improve the quality of life. Conventional opioids are used in minimally invasive surgery in clinical practice to relive postoperative pain, but the respiratory depression and other adverse reactions cannot be ignored. Reducing the dose of opioids and exploring new methods for postoperative analgesia is highly required. In this study, the effect of a small dose of naloxone in combination with tramadol on the analgesic effect, hemodynamics and the level of inflammatory cytokines, in order to provide a reference for clinical practice.

Patients and methods

Patients

A total of 100 patients (ASA grade I or II) receiving laparoscopic cholecystectomy under general anesthesia in our hospital were selected.

Table 1. Comparisons of general conditions

Group	Age	Gender		BMI (kg/m^2)	HR (times)	MAP (mmHg)	ASA	
		Male	Female				I	II
Tramadol group (n = 50)	45 ± 8.8	30	20	23.1 ± 7.9	82 ± 10	88 ± 11	28	22
Combination group (n = 50)	47 ± 5.9	27	23	22.8 ± 7.5	81 ± 8	88 ± 9	25	25

They were aged 18-64 years old. None of the patients suffered from severe cardiopulmonary diseases or other surgical contraindications. They did not take opioids or drugs that affect the central nervous system recently. The patients were randomly divided into the tramadol group (n = 50) and the combination group (naloxone + tramadol) (n = 50). No significant difference of the general conditions including age, gender and body mass index were observed between the two groups. This study was approved by the ethnic committee of Fifth Affiliated Hospital of Guangzhou Medical University and informed consent was obtained from all patients before commencement of the study.

Treatment

Venous access was established in all patients. AVEA ventilator (USA) was used for mechanical ventilation and the vital signs were monitored. All patients received tramadol (100 mg by intravenous injection) after laparoscopic surgery, and patients in the combination group were treated with naloxone (0.4 mg by intravenous injection) apart from tramadol.

Observation indexes

Surgical conditions, including duration of surgery, respiratory rate, bleeding volume and infusion volume were recorded.

Monitoring pain degree and hemodynamic indicators

The visual analogue scale (VAS) was adopted to evaluate the pain degree at 6, 12, and 24 hours after surgery. The lowest score was 0 point (painless), and the highest score was 10 points (sharp pain).

Finometer PRO non-invasive hemodynamic detector (Netherlands, FMS) was used to record the values of the mean arterial pressure (MAP) and the heart rate (HR) at 6, 12,and 24 hours after surgery.

Measurement of serum levels of CRP, TNF-α, and IL-6

Peripheral venous blood (3 mL) was collected before anesthesia induction and at 6, 12, and 24 hours after surgery, respectively followed by centrifuging blood to obtain serum, which was used to measure the concentrations of CRP, TNF-α, and IL-6 by Tecan Sunrise automatic microplate reader (Swiss Dickens).

Statistical analysis

Statistical analysis was conducted using Stat istical Product and Service Solutions (SPSS) 19.0 software. Measurement data are expr essed as mean ± standard deviation (SD) and student *t* test was performed for comparison of difference between two groups. The enumeration data are expressed as n (%) and Chi-square test was used for comparison of the difference. $p < 0.05$ indicated that the difference was statistically significant.

Results

Comparisons of general conditions

There were no statistically significant differences in gender, age, body mass index (BMI), MAP, HR, and ASA grade between the two groups ($p > 0.05$) (**Table 1**).

Comparisons of surgical conditions

In the combination group, the duration of surgery was shorter, breathing was more stable, and bleeding volume and infusion volume were less than those in the tramadol group. Moreover, the difference in respiratory rate was statistically significant, indicating that tramadol-induced respiratory depression was inhibited in the combination group (**Table 2**).

Comparisons of postoperative VAS scores

Compared with those before surgery, VAS scores at 6, 12, and 24 hours after surgery were all significantly decreased. However, VAS

Table 2. Comparisons of surgical conditions

Group	Duration of surgery (min)	Respiratoryrate (times/min)	Bleeding volume (mL)	Infusion voume (mL)
Tramadol group (n = 50)	151.3 ± 3.8	8.0 ± 1.5	30.5 ± 6.8	290.8 ± 3.3
Combination group (n = 50)	116.6 ± 5.2	11.5 ± 1.9*	20.8 ± 7.6	239.5 ± 4.5

Note: Compared with Tramadol group, *$p < 0.05$.

Table 3. Comparisons of postoperative VAS scores

Group	VAS scores			
	Before surgery	At 6 h after surgery	At 12 h after surgery	At 24 h after surgery
Tramadol group (n = 50)	8.9 ± 3.8	6.7 ± 1.9*	6.3 ± 2.8*	6.0 ± 1.9*
Combination group (n = 50)	8.6 ± 4.1	5.3 ± 2.2*,#	4.9 ± 1.9*,#	4.7 ± 2.3*,#

Note: Compared with before surgery in the same group, *$p < 0.05$. Compared with Tramadol group at corresponding time point, *$p < 0.05$.

Table 4. Comparisons of hemodynamic indexes (MAP and HR) at different time points

Group	Time	MAP	HR
Tramadol group (n = 50)	Before surgery	88 ± 11	82 ± 10
	At 6 h after surgery	105 ± 11*	97 ± 11*
	At 12 h after surgery	101 ± 9*	100 ± 10*
	At 24 h after surgery	87 ± 7	86 ± 3
Combination group (n = 50)	Before surgery	88 ± 9	81 ± 8
	At 6 h after surgery	93 ± 8*,#	87 ± 9*,#
	At 12 h after surgery	90 ± 7*,#	90 ± 8*,#
	At 24 h after surgery	88 ±8	83 ± 4

Note: Compared with before surgery in the same group, *$p < 0.05$. Compared with Tramadol group at corresponding time point, #$p < 0.05$.

scores in combination group were reduced significantly at 6, 12, and 24 hours after surgery than those in the tramadol group ($p < 0.05$), suggesting that naloxone enhances the postoperative analgesic efficacy of tramadol (**Table 3**).

Comparisons of hemodynamic indexes (MAP and HR) at different time points

Compared with those before surgery, MR and MAP were increased starting from 6 hours after surgery, but compared with those in tramadol group, MAP and HR had smaller increases at 6 and 12 hours after surgery in combination group ($p < 0.05$), suggesting naloxone affects the hemodynamics (**Table 4**).

Comparisons of inflammatory cytokines (TNF-α, CRP, and IL-6)

Compared with those before surgery, CRP, TNF-α, and IL-6 at 6, 12, and 24 hours after surgery were all significantly decreased ($p < 0.05$) (**Table 5**). Compared with those in the tramadol group, serum concentrations of CRP, TNF-α, and IL-6 in the combination group were decreased more significantly at 6 and 12 hours after surgery ($p < 0.05$), and the levels of inflammatory cytokines in the two groups were similar at 24 hours.

Comparisons of adverse reactions

The total incidence of adverse reactions in the tramadol group was 32.0%, which was significantly higher than that in the combination group (14.0%) ($p < 0.05$) (**Table 6**).

Discussion

Although laparoscopic biliary surgery results in a small incision and a relatively small trauma, the pain caused by various factors such as the postoperative biliary spasm, pneumoperitoneum, traction of the drainage tube, and stimulation of hematoperitoneum and seroperitoneum may stimulate the body to trigger inflammatory responses, release interleukins, tumor necrosis factor, and other cytokines, which can in turn triger an immune response, causing serious consequences. Choosing a sustained and potent analgesic approach is crucial in clinical practice.

The analgesia should achieve the goal that patients' sleep and their off-bed activities are not affected in the resting state. Opioid analgesics can inhibit the excitability of the vagus nerve and affect the recovery of the intestinal

Table 5. Comparisons of hemodynamic indexes (CRP, TNF-α, and IL-6) between the two groups at different time points ($\bar{x} \pm s$)

Group	Time	TNF-α (ng/L)	CRP (mg/L)	IL-6 (ng/L)
Tramadol group (n = 50)	Before surgery	36 ± 13	7.7 ± 1.9	180.1 ± 5.9
	At 6 h after surgery	30 ± 8*	5.1 ± 1.4*	131.2 ± 5.5*
	At 12 h after surgery	27 ± 7*	4.4 ± 1.5*	95.3 ± 3.9*
	At 24 h after surgery	20 ± 6*	3.6 ± 1.3*	78.8 ± 5.8*
Combination group (n = 50)	Before surgery	37 ± 11	7.3 ± 2.2	176.6 ± 2.6
	At 6 h after surgery	21 ± 7*,#	3.2 ± 1.4*,#	110.1 ± 7.8*,#
	At 12 h after surgery	19 ± 7*,#	2.7 ± 1.0*,#	80.7 ± 5.5*,#
	At 24 h after surgery	17 ± 6*	3.0 ± 1.3*	72.8 ± 3.6*

Note: Compared with before surgery in the same group, $^{*}p < 0.05$. Compared with Tramadol group at corresponding time point, $^{\#}p < 0.05$.

Table 6. Comparisons of adverse reactions (n%)

Group	Nausea and vomiting	Skin itch	Chill	Respiratory depression	Urinary retention	Total icidence
Tramadol group (n = 50)	5	3	5	2	1	32%
Combination group (n = 50)	2	1	3	0	1	14%*

Note: Compared with tramadol group, $^{*}p < 0.05$.

function with side effects, such as nausea, vomiting, respiratory depression, thus delaying rehabilitation of patients. In recent years, studies have shown that a small dose of naloxone (an opioid receptor antagonist) can enhance the analgesic efficacy of opioid agonists, and alleviate the nausea, vomiting, itching, and other adverse reactions [3, 4]. Naloxone has central analgesic effect, long duration of analgesia, increased respiratory rate for respiratory depression caused by acute poisoning and prominent analgesic effect. The sustained and effective postoperative analgesia can not only reduce the patient's pain, but also inhibit inflammatory response [5, 6]. Previous studies showed that weak opioid receptor agonist tramadol hydrochloride exerts its analgesic efficacy by inhibiting the re-uptake of norepinephrine and 5-hydroxytryptamine (5-HT) *in vitro* and alleviates the postoperative chill by binding to α2 receptor of the brain [7-9]. Sterner et al. [11] pointed out that TNF-α can produce a medium that can aggravate injury and pain mainly through activated NK cells and T lymphocytes, leading to formation of thrombosis and subsequent blockage of local blood flow of the inflammatory tissues. Furthermore, it can also mediate the release of other inflammatory cytokines, leading to inflammatory cascade reaction and multiple organ injuries [12]. IL-6 is produced by activated T cells and plays a crucial role in the development of inflammatory responses. CRP is an acute-phase protein that is synthesized and metabolized in the liver and is directly involved in the process of stress and inflammatory response caused by postoperative trauma [13]. Several studies have shown that [14-16], a small dose of naloxone with tramadol can not only achieve effective analgesic effect, but also significantly reduce the adverse reactions. The possible mechanism is [17-19] that a small dose of naloxone can increase the density of opioid receptors and promote the release of endogenous opioid peptides to exert its analgesic effect. On the other hand, it reduces consumption of tramadol by specifically blocking the stimulatory G (Gs) proteins-coupled excitatory effects, thereby reducing the adverse reactions of opioids. In the present study, VAS scores in the combination group were significantly lower than those in the tramadol group at 6, 12, and 24 hours after surgery, indicating that naloxone in combination with tramadol enhances postoperative analgesic efficacy. In addition, the duration of surgery was shorter, breathing was more stable, and bleeding volume and infusion volume in the combination group were less than those in the tramadol group. Moreover, the difference in the respiratory rate was statistically significant,

indicating that the tramadol-induced respiratory depression is inhibited in combination group. Furthermore, it was also observed that MAP and HR in the combination group were lower than those in the tramadol group ($p < 0.05$), indicating that there is a small impact of naloxone on the hemodynamic indexes. A previous study demonstrated [20] that a higher than normal value of inflammatory cytokines such as IL-6 has a pain-causing effect on the body. In this study, CRP, TNF-α, and IL-6 showed decreasing trends at 6, 12, and 24 hours after surgery compared with those before surgery. Compared with those in tramadol group, the serum concentrations of CRP, TNF-α, and IL-6 in combination group were decreased more significantly at 6 and 12 hours after surgery ($p < 0.05$), suggesting that naloxone combined with tramadol not only alleviates the postoperative stress and inflammatory response, but also enhances the analgesic effect.

Conclusion

In conclusion, naloxone combined with tramadol can enhance the analgesic effect, inhibit the expression of pro-inflammatory cytokines (CRP, TNF-α, and IL-6), alleviate the body injury resulted from postoperative stress response, and reduce the incidence of adverse reactions and complications, thus providing a safe and efficient method of analgesia for laparoscopic surgery.

Disclosure of conflict of interest

None.

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