

Effect of dezocine combined with propofol on pain mediators, inflammatory reaction and immune response indexes in patients undergoing colonoscopy.

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Abstract

Objective: To investigate the effect of dezocine combined with propofol on pain mediators, inflammatory reaction and immune response indexes in patients undergoing colonoscopy.

Methods: 96 cases undergoing colonoscopy in our hospital from March 2016 to March 2017 were randomly divided into observation group (48 cases, anesthetized by dezocine combined with propofol) and control group (48 cases, anesthetized by sole propofol). The expression of 5-Hydroxytryptamine (5-HT), Dopamine (DA), Norepinephrine (NE), prostaglandin (PGE₂), Substance P (SP), tumor necrosis factor - α (TNF- α), Interleukin (IL)-1 β , IL-6, IL-8, C-Reactive Protein (CRP) in serum, and the counts of Th1 cells and Th2 cells of all cases were detected respectively before and 30 min after colonoscopy.

Results: The time of insertion and retreat of colonoscopy of the observation group was obviously shorter, and the incidence of adverse reactions in the observation group was significantly lower than that in the control group ($P < 0.05$). There were no significant differences in laboratory indexes between 2 groups before colonoscopy ($P > 0.05$). 30 min after colonoscopy, 5-HT, DA, NE, PGE₂, SP, TNF- α , IL-1 β , IL-6, IL-8, CRP in all patients increased markedly and the intragroup differences had statistical significance ($P < 0.05$). The above indexes in the observation group were significantly lower than those in the control group ($P < 0.05$). There were no significant changes in Th1 and Th2 in 2 groups ($P > 0.05$).

Conclusion: Dezocine combined with propofol in anaesthesia for colonoscopy can inhibit the increase of pain mediators and inflammatory reaction indexes and will not affect patients' immune function. It may help to shorten the examination time and reduce adverse reactions.

Keywords: Dezocine, Propofol, Colonoscopy, Pain mediators, Inflammatory factor, Immune function.

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Introduction

Colonoscopy is a kind of minor outpatient surgery, which is often used as an important diagnostic measure for many intestinal diseases [1]. Patients may suffer acute pain when they are undergoing colonoscopy due to the invasive procedure. Therefore, reliable sedative and analgesic measures are required for the patients. Propofol, as an anesthetic, was often applied in previous colonoscopy and it can ensure the patients a faster recovery time and sooner discharge from the hospital [2]. However, this anesthetic has the disadvantage of weak analgesic effect, intraoperative agitation, postoperative abdominal pain and other adverse reactions, and may induce toxicity in respiratory and circulatory system because of the large dosages, and using sole propofol will have a strong inhibition in respiratory system [3]. Combination of fentanyl and other anesthetics for improvement of analgesia contributes to enhancement of analgesic effect, but it may cause more respiratory inhibition, Post-Operative Nausea and Vomiting (PONV) and other adverse reactions [4]. Dezocine, one kind of opioid anesthetic, has reliable analgesic effect as well as less influence on respiratory system than fentanyl, and it is suitable for combination with propofol in colonoscopy, especially for

those patients with respiratory dysfunction. 5-Hydroxytryptamine (5-HT), Dopamine (DA), Norepinephrine (NE), Prostaglandin (PGE₂) and Substance P (SP) in serum are important mediators of pain and are directly involved in the occurrence and worsening of pain [5,6].

The pain induced by colonoscopy can lead to stress response and in turn resulting in inflammation. Thus influence the expression of inflammatory factors and the immune function [7]. The results of the previous studies have revealed that dezocine combined with propofol in colonoscopy could bring more stable hemodynamics, lower incidence rate of adverse reactions by reducing the dosage of propofol [8,9]. However, studies based on targeted analysis of the effect of dezocine combined with propofol on pain mediators, inflammatory reaction and immune response indexes in patients undergoing colonoscopy were lacking. This study focused on the above issues by adopting prospective randomized controlled trials, which might help reveal the effect of this combined anesthetic method on patients undergoing colonoscopy.

Materials and Methods

General materials

96 patients undergoing colonoscopy in our hospital were recruited from March 2016 to March 2017, carrying on prospective randomized controlled trials and the study was approved by the Ethical Committee, which meets the requirements of National Health and Family Planning Commission of the People's Republic of China. The patients were randomly divided into 2 groups according to their hospitalized sequence. 48 cases of observation group: 28 males

and 20 females; aged from 28~62 years, with a mean of 47.71 ± 12.43 y; weighed from 48~73 kg, with a mean of 57.13 ± 4.82 kg; according to American Society of Anaesthesiologists (ASA) classification, 31 cases of stage I and 17 cases of stage II. Control group of 48 cases: 26 males and 22 females; aged from 30~64 y, with a mean of 49.33 ± 11.83 y; weighed from 47~71 kg, with a mean of 56.83 ± 5.12 kg; according to ASA classification, 33 cases of stage I and 15 cases of stage II. General information between the two groups, including age and gender etc. showed no significant difference ($P > 0.05$) (Table 1).

Table 1. Comparison of general information between two groups (n , ($\bar{x} \pm SD$)).

Group	Gender		Age	Weight	ASA	
	Female	Male			I	II
Observation group (48 cases)	20	28	47.71 ± 12.43	57.13 ± 4.82	31	17
Control group (48 cases)	22	26	49.33 ± 11.83	56.83 ± 5.12	33	15
t/χ^2	0.169		0.654	0.296	0.188	
P	0.681		0.515	0.768	0.665	

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients aged from 18~69 y; (2) ASA Stage I~II; (3) patients with normal organ function; (4) Patients and authorized agents voluntarily signed informed consent, willing to accept intravenous anesthesia.

Exclusion criteria: (1) Patients have received previous abdominal or pelvic surgery [10]; (2) Patients allergic to related drugs; (3) Patients with poor bowel preparation; (4) Patients with recent acute gastrointestinal bleeding, uncontrolled hypertension, Inflammatory Bowel Disease (IBD) or complicated with serious heart and lung disease.

Anesthesia methods

All patients were restricted from food and water for 8 h before colonoscopy and received conventional intestinal cleansing for bowel preparation. Venous pathway of upper limb was established before colonoscopy. Then all detection instruments were connected to closely monitor the Heart Rate (HR), Mean Arterial Pressure (MAP), Respiratory Rate (RR), Saturation of Pulse Oximetry (SpO_2) and Electrocardiogram (ECG) etc. of patients. Oxygen inhaled by masks with oxygen at the flow of 2 L/min. The control group received propofol intravenous injection (Guangdong Jiabo Pharmaceutical Co., Ltd, NMPN: H20051843, 10 ml: 100 mg) of 2.0 mg/kg and to keep the level of anesthesia by adjusting the infusion speed of the pump according to HR, MAP, RR etc. of patients; while the observation group first received slow intravenous injection of dezocine (Yangtze River Pharmaceutical Group, Ltd, NMPN: H20080329, 1 ml: 5 mg) of 5 mg, then received propofol 10 min later (the method was the same as the control group). Colonoscopy was undergone in the two groups until the loss of eyelash reflex. Added immediate intravenous propofol of

0.5~1 mg/kg if the body appeared restlessness, frown or other reactions; applied vasoactive drugs if the patients' blood pressure dropped to less than 70% of the base level; oxygen saturation was restored by using mask inhalation if blood oxygen saturation decreased to less than 90% of the base level. The patients were escorted into anaesthetic recovery room after surgery.

Observation indexes

The time of insertion and retreat of colonoscopy, recovery time and adverse reactions of the two groups were observed to evaluate the examination effect of the patients. All patients should be hospitalized for at least 30 min after colonoscopy. The peripheral blood was taken before and 30 min after colonoscopy, and was centrifuged at 2500 r/min 10 min later. Then the supernatant was taken and frozen in -80°C refrigerator for testing the following indexes: (1) Pain mediators including the levels of 5-HT, DA, NE, PGE2 and SP in serum by adopting fluorescence spectrophotometry; (2) Inflammatory reaction indexes including the levels of C-Reactive Protein (CRP), Tumor Necrosis Factor- α (TNF- α), Interleukin (IL)-1 β , IL-6, IL-8 by adopting enzyme-linked immunosorbent assay (ELISA) (Shanghai Enzyme lian Biotechnology Co., Ltd); (3) Immune response indexes including the levels and ratios of Th1/Th2 cells, and flow cytometry was used to detect and calculate the results.

Statistical analysis

The SPSS software version 19.0 was used for data analysis. The results of the measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm SD$). Independent sample t-test was used for between-group comparison and paired t-test was used

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for within-group comparison. The ratios for count data were analyzed by using the chi-square (χ^2) test and $P < 0.05$ was considered statistically significant.

Results

Comparison of general information of the two groups undergoing colonoscopy

All patients completed the colonoscopy successfully. The time of insertion and retreat of colonoscopy in the observation group was significantly shorter than that in the control group. Adverse reactions which occurred during the detection period

were significantly less in the observation group than those in the control group ($P < 0.05$) (Table 2). There were 7 cases of adverse reactions in the observation group, among which, 3 cases of body movement during colonoscopy and 4 cases of nausea and vomiting after colonoscopy. While there were 18 cases of adverse reactions in the control group, among which, 5 cases of body movement and 4 cases of respiratory inhibition during colonoscopy; 7 cases of nausea and vomiting and 2 cases of self-described severe abdominal pain after colonoscopy. During the colonoscopy period, adverse reactions subsided after treatment. Adverse reactions which occurred after colonoscopy were not treated by special intervention, and they all disappeared within 60 min.

Table 2. Comparison of general information of the two groups undergoing colonoscopy ($(\bar{x} \pm SD)$, n (%)).

Group	Time of insertion of colonoscopy (min)	Time of retreat of colonoscopy (min)	Recovery time (min)	Adverse reactions
Observation group (48 cases)	8.54 ± 0.72	5.17 ± 0.85	3.08 ± 0.84	7 (14.58)
Control group (48 cases)	11.74 ± 1.82	7.14 ± 1.15	3.15 ± 1.08	18 (37.50)
t/ χ^2	11.33	9.54	0.35	6.54
P	0	0	0.72	0.01

Comparison of the changes of pain mediators before and after colonoscopy

There was no significant difference between the levels of 5-HT, DA, NE, PGE2 and SP in serum of the two groups before colonoscopy ($P > 0.05$). In contrast, the above indicators were

increased after colonoscopy, and the differences within group were statistically significant ($P < 0.05$). The levels of 5-HT, DA, NE, PGE2 and SP in serum were significantly lower in the observation group than in the control group after colonoscopy ($P < 0.05$) (Table 3).

Table 3. Comparison of the changes of pain mediators before and after colonoscopy ($\bar{x} \pm SD$).

Group	5-HT (mg/ml)		DA (ng/ml)		NE (ng/ml)		PGE2 (pg/ml)		SP (pg/ml)	
	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy
Observation group (48 cases)	251.83 ± 51.71	385.17 ± 68.24*	5.14 ± 1.45	6.82 ± 1.53*	44.71 ± 6.17	89.68 ± 20.24*	58.34 ± 11.72	88.17 ± 25.83*	67.71 ± 12.14	92.81 ± 11.71*
Control group (48 cases)	248.17 ± 53.08	435.31 ± 51.82*	5.08 ± 1.37	8.25 ± 0.85*	45.38 ± 6.24	145.73 ± 27.15*	55.82 ± 10.82	138.53 ± 26.27*	68.63 ± 10.68	127.68 ± 15.58*
t	0.34	4.05	0.21	5.66	0.53	11.47	1.09	9.47	0.39	12.4
P	0.73	0	0.84	0	0.6	0	0.28	0	0.69	0

Note: compared with control group before colonoscopy, * $P < 0.05$.

Comparison of the changes of inflammatory response indexes before and after colonoscopy

The differences between the levels of TNF- α , IL-1 β , IL-6, IL-8 and CRP in serum of the two groups showed no statistical significant before colonoscopy ($P > 0.05$). In contrast, the above indexes were significantly increased after colonoscopy, and the differences within group were statistically significant ($P < 0.05$). And the levels of TNF- α , IL-1 β , IL-6, IL-8 and CRP in serum

were significantly lower in the observation group than in the control group after colonoscopy ($P < 0.05$) (Table 4).

Comparison of the changes of immune response indexes before and after colonoscopy

There was no significant difference within the group in terms of the levels of Th1, Th2 and Th1/Th2 before and after colonoscopy ($P > 0.05$). And the above indexes also showed no

significant difference between the two groups before and after colonoscopy ($P > 0.05$) (Table 5).

Table 4. Comparison of the changes of inflammatory response indexes before and after colonoscopy ($\bar{x} \pm SD$).

Group	TNF- α (pg/ml)		IL-1 β (pg/ml)		IL-6 (pg/ml)		IL-8 (pg/ml)		CRP (μ g/ml)	
	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy
Observation group (48 cases)	13.38 ± 4.82	19.82 ± 7.14*	4.85 ± 0.82	9.83 ± 1.42 [†]	8.31 ± 1.15	12.54 ± 1.53*	24.17 ± 5.18	104.48 ± 10.17*	10.48 ± 2.08	16.82 ± 2.42 [†]
Control group (48 cases)	13.52 ± 3.85	27.14 ± 7.53*	4.95 ± 0.64	15.71 ± 2.04*	8.54 ± 0.86	24.14 ± 2.08*	23.58 ± 5.42	181.68 ± 20.42*	10.83 ± 1.82	23.82 ± 2.52 [†]
t	0.16	4.89	0.67	16.39	1.11	31.12	0.55	23.45	0.88	13.88
P	0.88	0	0.51	0	0.27	0	0.59	0	0.38	0

Note: compared with control group before colonoscopy, * $P < 0.05$.

Table 5. Comparison of the changes of immune response indexes before and after colonoscopy ($\bar{x} \pm SD$).

Group	Th1 (%)		Th2 (%)		Th1/Th2	
	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy	Pre-colonoscopy	Post-colonoscopy
Observation group (48 cases)	12.41 ± 1.58	12.87 ± 1.82	3.35 ± 0.68	3.41 ± 0.53	3.82 ± 0.91	3.74 ± 0.61
Control group (48 cases)	12.93 ± 1.68	12.57 ± 1.75	3.27 ± 0.61	3.36 ± 0.63	3.87 ± 0.68	3.71 ± 0.58
t	1.56	0.82	0.61	0.42	0.3	0.25
P	0.12	0.41	0.55	0.67	0.76	0.81

Discussion

When patients underwent colonoscopy, the intestine was inserted by endoscopy and stirring, friction or other stimulation of intestinal canal was virtually unavoidable, which in turn the pain was caused [11]. When the scope deeply was inserted into the colon, splenic flexure and hepatic flexure, Intestinal pressure increased correspondingly and led to stretch of mesentery, and eventually resulted in spasmodic pain in the organs, therefore, reliable sedatives and analgesics were required for the patients [12]. Propofol is defined as a non-barbiturate and short-acting intravenous anesthetic with the advantages of rapid effect, quick awakening and strong sedative efficacy, which is widely applied in colonoscopy [13]. In our study, propofol was used alone in the control group, and the patients successfully completed colonoscopy, which revealed its applicable value. However, the incidence of adverse reactions in this group was up to 37.50%, indicating its limitations for application, and it matched the results reported by Chen et al. [14]. That used propofol alone. The main cause was probably due to its relatively weak analgesic effect and strong inhibition of respiratory and circulatory system, which highlighted the requirement of drug combination [15].

Several studies about endoscopic detection and treatments have suggested that dezocine combined with propofol was used for anesthesia, which could effectively reduce the dosage of propofol as well as the incidence of adverse reactions, and thus

improved the efficacy of colonoscopy for treatments [16,17]. On this basis, the application of combined dezocine and propofol in our study contributed to the low rate of adverse reactions (14.58%), which is significantly less than that of the control group ($P < 0.05$). Besides, the time of insertion and retreat of colonoscopy was significantly shortened on account of the better anesthetic effect ($P < 0.05$). The results showed no significant changes in recovery time between the two groups (observation group: 3.08 ± 0.84 min; control group: 3.15 ± 1.08 min), indicating that the application of combined dezocine and propofol would not seriously impact the recovery of neural function in patients.

The expression levels of pain mediators are directly correlated to pain perception in patients, including NE, DA, 5-HT etc., which can induce pain through sensory nerve endings stimulated by the second messenger [18-20]. The studies reported by Ferrari et al. have concluded that PGE2 was involved in induction of hyperpathia in mice with chronic pain and that SP was a common neuropeptide with harmful stimulation which played a role in nociceptive transmission and inducing pain [21,22]. The results of our study found that the expression levels of pain mediators of the two groups were significantly increased after colonoscopy ($P < 0.05$), indicating that colonoscopy can lead to high levels of pain mediators and the relative low index levels in the observation group confirmed the promotion of analgesic effect with combined

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dezocine and propofol. The findings might be because dezocine can activate and inhibit the functions of μ -receptor [23]. Its antagonism helps to relax intestinal smooth muscles, reduce physical stimulation caused by insertion and retreat of colonoscopy and prevent respiratory depression and drug dependence. And its activation helps to inhibit reverse peristalsis of intestines and accordingly reduce the incidence of nausea and vomiting [24]. As the κ -receptor was fully activated, reliable analgesic effect was ensured [25].

The stress response caused by pain and trauma has certain effects on the immune function, which may induce the expression of a variety of inflammatory mediators and result in the stress reactions of the whole body [26]. In this study, the significant increase in TNF- α , IL-1 β , IL-6, IL-8 and CRP 30 min after colonoscopy implied the occurrence of systemic inflammatory response. Concerning that the patients usually complicated with other comorbidities, the systemic inflammatory response may cause further damage to the body and aggravate illness, so active prevention was required. The above inflammatory response indexes were significantly lower in the observation group than in the control group 30 min after colonoscopy ($P < 0.05$), indicating that dezocine combined with propofol contributed to inhibiting systemic inflammatory response, and it might have some relation with its better inhibiting function of pain. Previous studies based on colonoscopy treatment have concluded that the trauma caused by colonoscopy may seriously affect the immune function and prognosis in patients [27]. However, the results of our study showed that carrying colonoscopy alone would not severely affect the immune function, as no significant changes occurred in terms of Th1/Th2 after different anesthetic methods of the two groups ($P > 0.05$). The above indexes were important indicators for reflecting the cellular immune function, so the results of the indexes in our study implied no changes of immune function for colonoscopy [28]. This may be due to the quick detection scheme of colonoscopy, and compared with endoscopic therapy, conducting detection will only have slighter effects on patients.

In summary, dezocine combined with propofol for colonoscopy, could provide operative effectiveness with reliable anaesthesia effect. The application of combined dezocine and propofol inhibited the rising of pain mediators and inflammatory reaction factors under the situation of not affecting the immune response index, and the incidence of adverse reactions was relatively low before and after the colonoscopy. But this study may not comprehensively reveal the effects that dezocine combined with propofol had on patients, which due to the limitations of sample size and the cases recruited in observation. So further researches on this topic were needed for scholars.

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