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Effect of dezocine combined with sufentanil patient−controlled intravenous analgesia on general pain and inflammatory mediators after laparoscopic hepatectomy

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ABSTRACT

Objective: To study the effect of dezocine combined with sufentanil patient-controlled intravenous analgesia on general pain and inflammatory mediators after laparoscopic hepatectomy. **Methods:** A total of 68 patients with primary liver cancer who received laparoscopic surgical treatment in our hospital between July 2014 and December 2016 were collected, the therapies were reviewed, and then patients were divided into the control group (n=35) who received sufentanil PCIA and the observation group (n=33) who received dezocine combined with sufentanil PCIA. Differences in serum levels of pain mediators, acute phase proteins and interleukins were compared between the two groups of patients before and after operation. **Results:** Before operation, the differences in serum levels of pain mediators, acute phase proteins and interleukins were not statistically significant between the two groups of patients. 6h after operation, serum pain mediators SP, NPY, DA and NE levels in observation group were lower than those in control group; acute phase proteins CRP, HP, CER and AAG levels were lower than those in control group; interleukins IL-1 β , IL-6 and IL-8 levels were lower than those in control group. **Conclusion:** Dezocine combined with sufentanil PCIA after laparoscopic hepatectomy is effective in reducing the early postoperative pain mediator levels and relieving systemic inflammatory response.

1. Introduction

Laparoscopic hepatectomy is the most common clinical surgical method for primary liver cancer at present, the laparoscopic trauma is small, but abdominal viscera resection, intraoperative tissue stretch, etc., can all cause postoperative severe pain, and without intervention, it can cause pain-stress and immune function suppression[1,2]. Patient-controlled intravenous analgesia (PCIA) is the most common form of intravenous analgesia after operation. The analgesic effect varies greatly with different specific analgesic drug compatibility[3,4]. Sufentanil is potent opioid with central analgesic effect, it has long analgesic action and has been successfully applied in postoperative analgesia of laparoscopic cholecystectomy, but studies have shown that its monotherapy has limited analgesic effect on liver surgery and other surgeries with larger trauma. Dezocine is an opioid receptor mixed agonist-antagonist, which has the analgesic effect equivalent to that of morphine and can be combined with classic opioids as adjuvant analgesics[5,6]. In the research, dezocine combined with sufentanil was used for postoperative analgesia of patients with laparoscopic hepatectomy, and compared with pure sufentanil analgesia to define the auxiliary analgesic action of dezocine, now reported as follows.

2. Information and methods

2.1 Case information

A total of 68 patients with primary liver cancer who received laparoscopic surgical treatment in our hospital between July 2014 and December 2016 were selected as research subjects, and the family members signed informed consent. The therapies were reviewed, and then patients were divided into the control group (n=35) who received sufentanil PCIA and the observation group

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(n=33) who received dezocine combined with sufentanil PCIA. Control group included 18 men and 17 women that were 43-78 years old; observation group included 17 men and 16 women that were 45-74 years old. The baseline data of the two groups were not significantly different (P>0.05), and the study was approved by the ethics committee.

2.2 Analgesia methods

Analgesia pump configuration drugs for control group of patients were sufentanil + tropisetron, specifically as follows: sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., approved by H20054172) 0.2 μg/kg, and tropisetron (Shandong Luoxin Pharmaceutical Co., Ltd., approved by H20061060) 5 mg. The analgesia pump configuration drugs for observation group of patients were dezocine + sufentanil + tropisetron, specifically as follows: dezocine (Yangtze River Pharmaceutical Group Co., Ltd., approved by H20080329) 0.5 mg/kg, and same usage and dosage of sufentanil and tropisetron as those of control group of patients. The drugs of both groups were diluted into 100 mL by saline, load dosage was 5 mL, and maintenance dose was 2 m/h, and single PCIA dosage was 2 mL.

2.3 Observation indexes

Before operation and 6 h after operation, 2.0 mL cubital venous blood was extracted from two groups of patients, joined by anticoagulant, and then centrifuged at 4 ℃ and 2 500-3 500 r/min for 10-15 min, and upper serum was collected and cryopreserved at -70 ℃ profound hypothermia. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum levels of pain mediators, acute phase proteins, interleukins and so on; pain mediators included substance P (SP), neuropeptide Y (NPY), dopamine (DA) and norepinephrine (NE); acute phase proteins included C-reactive protein (CRP), haptoglobin (HP), ceruloplasmin (CER) and 1-acidic protein (AAG); interleukins included interleukin-1β (IL-1β), interleukin-6 (IL-6) and interleukin-8 (IL-8).

2.4 Statistical processing

Statisticians had professional statistical background, and statistical software was SPSS 22.0. Pain mediators, acute phase proteins and interleukins all belonged to measurement data and were in terms of (Mean ± SD), and comparison between groups was by t test. Statistics P<0.05 was set as the standard of statistical difference in differences.

3. Results

3.1 Pain mediators

Comparison of serum pain mediators SP (μg/mL), NPY (pg/mL), DA (μmol/L) and NE (pg/mL) levels between two groups of patients before and after treatment was as follows: the differences in serum SP, NPY, DA and NE levels were not statistically significant between the two groups of patients before operation (P>0.05); 6 h after operation, serum SP, NPY, DA and NE levels in both groups were higher than those before operation, serum SP, NPY, DA and NE levels in observation group were lower than those in control group, and differences were statistically significant (P<0.05), shown in Table 1.

3.2 Acute phase proteins

Comparison of serum acute phase proteins CRP (mg/L), HP (mg/dL), CER (mg/L) and AAG (mg/dL) levels between two groups of patients before and after treatment was as follows: the differences in serum CRP, HP, CER and AAG levels were not statistically significant between the two groups of patients before operation (P>0.05); 6 h after operation, serum CRP, HP, CER and AAG levels in both groups were higher than those before operation, serum CRP, HP, CER and AAG levels in observation group were lower than those in control group, and differences were statistically significant

Table 1.

Comparison of serum pain mediator levels between two groups of patients before and after operation.

Groups	n	SP		NPY		DA		NE	
		Before operation	6 h after operation	Before operation	6 h after operation	Before operation	6 h after operation	Before operation	6 h after operation
Control group	35	1.52±0.18	4.71±0.59*	103.27±14.85	148.95±17.63*	43.27±5.19	162.59±17.23*	1.21±0.15	1.85±0.27*
Observation group	33	1.54±0.19	2.32±0.35*	102.68±15.27	119.63±13.42*	42.98±5.03	93.77±10.84*	1.23±0.17	1.41±0.18*
t		0.193	8.923	0.215	12.873	0.164	15.482	0.116	7.192
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before operation, *P<0.05.

Table 2.

Comparison of serum acute phase protein levels between two groups of patients before and after operation.

Groups	n	CRP		HP		CER		AAG	
		Before operation	6 h after operation	Before operation	6 h after operation	Before operation	6 h after operation	Before operation	6 h after operation
Control group	35	1.63±0.24	15.48±2.11*	45.28±6.19	93.11±10.75*	220.38±27.19	412.48±56.92*	52.38±6.19	91.62±10.57*
Observation group	33	1.65±0.23	6.34±0.82*	45.76±6.98	72.54±8.93*	221.76±28.53	340.15±40.63*	52.27±6.08	70.25±8.61*
t		0.143	9.283	0.218	12.947	0.168	19.821	0.215	14.382
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before operation, *P<0.05.

Table 3.

Comparison of serum interleukin levels between two groups of patients before and after operation (pg/mL).

Groups	*n*	IL-1 β		IL-6		IL-8	
		Before operation	6 h after operation	Before operation	6 h after operation	Before operation	6 h after operation
Control group	35	0.16±0.03	0.72±0.09*	64.28±8.15	134.26±15.95*	30.27±4.51	78.15±8.94*
Observation group	33	0.17±0.02	0.41±0.06*	63.69±8.06	81.32±9.51*	30.64±4.24	47.66±6.29*
t		0.182	8.972	0.157	14.282	0.216	11.731
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before operation, *$P<0.05$.

($P<0.05$), shown in Table 2.

3.3 Interleukins

Comparison of serum interleukins IL-1 β , IL-6 and IL-8 levels between two groups of patients before and after treatment was as follows: the differences in serum IL-1 β , IL-6 and IL-8 levels were not statistically significant between the two groups of patients before operation ($P>0.05$); 6 h after operation, serum IL-1 β , IL-6 and IL-8 levels in both groups were higher than those before operation, serum IL-1 β , IL-6 and IL-8 levels in observation group were lower than those in control group, and differences were statistically significant ($P<0.05$), shown in Table 3.

4. Discussion

For operation with large trauma, the appropriateness of postoperative analgesia will directly determines the postoperative rehabilitation progress, immunosuppression and risk of postoperative complications. Laparoscopic hepatectomy has been widely used in patients with early-middle primary hepatocellular carcinoma, and the postoperative analgesic effect has become an important part that affects its therapeutic effect. PCIA is one of the main ways for postoperative analgesia of anesthesiology department, which uses postoperative continuous intravenous infusion of analgesic and anti-nausea drugs to achieve sustained analgesic and anti-nausea effect, optimize patients′ subjective feelings after operation and ensure operation security[7,8]. For hepatectomy and other surgeries with large surgical trauma, the choice of postoperative analgesics remains controversial, sufentanil is currently the most common powerful opioid that is with strong analgesic action and long duration, but some patients still feel obvious pain after its monotherapy, so the current clinicians recommend the combined use of analgesics with different mechanisms of action after surgery with large trauma. Dezocine is κ receptor agonist and μ receptor antagonist, studies have confirmed that onset time, analgesic effect and duration after its postoperative application are similar to those of morphine, but it is without obvious respiratory inhibition, and is the ideal auxiliary analgesic drug[9,10]. In the study, sufentanil analgesia alone and dezocine combined with sufentanil analgesic were used in the treatment of patients with laparoscopic hepatectomy respectively, and the analgesia and inflammation inhibition were compared between the two so as to lay the foundation for the choice of analgesic methods for similar patients in the future.

Acute pain is derived from the abnormal expression of various pain mediators in the body, and the contents of pain mediators in circulating blood can objectively reflect the level of patients' subjective pain[11,12]. SP is synthesized from spinal cord ganglion, which is transported to nerve endings and combined with the neuropeptide - 1, 2, and 3 receptors to participate in the pain transfer process. NPY is lowly expressed in normal sensory neurons, its expression is increased after nerve injury or pain signal transfer, and the anti-NPY treatment is an important way to relieve the neuropathic pain[13]. both DA and NE are monoamine neurotransmitters, DA is mainly distributed in the corpus striatum, substantia nigra, globus pallidus and so on of the central nervous system, and the enhancement of DA function will cause the hyperpathia and weakened morphine effect; NE mainly exists in the ventrolateral area of pons locus coeruleus and medulla oblongata reticular structure, it exerts analgesia-inhibiting effect in the brain, and clinical studies have confirmed that accelerating the metabolism of DA and NE can effectively relieve pain symptoms[14]. In the study, serum levels of these pain mediators were compared between two groups of patients before and after surgery, and it was found that compared with those before operation, serum SP, NPY, DA and NE levels were higher in both groups of patients early after operation, indicating that surgical trauma can result in postoperative pain; further compared with control group, the observation group of patients were with lower serum contents of SP, NPY, DA and NE after treatment, confirming that the dezocine combined with sufentanil is with better analgesic effect than sufentanil analgesia alone.

Tissue injury, pain, infection and other stress response can all result in apparent change of acute phase protein levels in a short period of time, and CRP levels increase early after severe pain and can activate complement and promote phagocytosis[15]. The HP synthesis increases with the increased adrenocortical hormone secretion after trauma; CER is the main copper transport protein in the blood, and has the oxidase activity of a variety of substrates, and its expression is increased under stress stimulation. AAG was synthesized by the liver under pain stimulation, and the content increases 6-8h after stress stimulation, and its content is highly consistent with the degree of damage and pain[16,17]. In the study, serum levels of these acute phase proteins were compared between two groups of patients before and after surgery, and it was found that compared with those before operation, serum CRP, HP, CER and AAG contents in both

groups of patients increased early after operation, and were caused by both surgical trauma and postoperative pain; further compared with control group, the observation group of patients were with early postoperative serum levels of CRP, HP, CER and AAG, showing that dezocine combined with sufentanil can effectively suppress the stress reaction, and indirectly confirming the efficiency of the joint analgesic solution.

Inflammation is closely related to pain, both surgical trauma and postoperative pain can directly stimulate the production of a variety of proinflammatory mediators, and systemic inflammatory response can feed back to the central nervous system and increase the monoamine neurotransmitter synthesis to further aggravate the pain perception, thus forming a vicious cycle[18]. IL-1 β , IL-6 and IL-8 are the most deeply studied clinical inflammatory mediators, they are highly expressed in the circulating blood early after stress, and can further induce neutrophil aggregation and secrete a variety of inflammatory factors to increase systemic inflammatory reaction, and detection of serum IL-1 β , IL-6 and IL-8 levels can objectively reflect the extent of systemic inflammation[19]. In the study, serum levels of these inflammatory mediators were compared between two groups of patients before and after surgery, and it was found that compared with those before operation, serum IL-1 β , IL-6 and IL-8 levels in both groups of patients increased early after operation; further compared with control group, the observation group of patients were with early postoperative serum levels of IL-1 β , IL-6 and IL-8 confirming that the potent analgesic action of dezocine combined with sufentanil can avoid the excessive secretion of proinflammatory mediators.

To sum up, it can be concluded that postoperative dezocine combined with sufentanil PCIA for patients with laparoscopic hepatectomy can effectively suppress pain mediator release and relieve systemic inflammatory response, it has effective analgesic effect, and it is worthy of popularization and application in clinical practice in the future.

References

[1] Hong JM, Kim KH, Lee HJ, Kwon JY, Kim HK, Kim HJ, et al. Epidural dexamethasone influences postoperative analgesia after major abdominal surgery. *Pain Physician* 2017; **20**(4): 261-269.

[2] Cao L, Chang Y, Lin W, Zhou J, Tan H, Yuan Y, et al. Long-term survival after resection of hepatocelluar carcinoma: a potential risk associated with the choice of postoperative analgesia. *Anesth Analg* 2014; **118**(6): 1309-1316.

[3] Zhang XK, Chen QH, Wang WX, Hu Q. Evaluation of dexmedetomidine in combination with sufentanil or butorphanol for postoperative analgesia in patients undergoing laparoscopic resection of gastrointestinal tumors: A quasi-experimental trial. *Medicine (Baltimore)* 2016; **95**(50): e5604.

[4] Qin M, Chen K, Liu T, Shen X. Dexmedetomidine in combination with sufentanil for postoperative analgesia after partial laryngectomy. *BMC Anesthesiol* 2017; **17**(1): 66.

[5] Li Z, Wu H, He R, Hu X, Liu S. Oxycodone versus dezocine for postoperative analgesia in patients with cervical cancer treated with radical surgery. *J Cancer Res Ther* 2016; **12**(Supplement): 27-29.

[6] Wu L, Dong YP, Sun L, Sun L. Low concentration of dezocine in combination with morphine enhance the postoperative analgesia for thoracotomy. *J Cardiothorac Vasc Anesth* 2015; **29**(4): 950-954.

[7] Van de Velde M. Remifentanil patient-controlled intravenous analgesia for labor pain relief: is it really an option to consider. *Anesth Analg* 2017; **124**(4): 1029-1031.

[8] Allen S, DeRoche A, Adams L, Slocum KV, Clark CJ, Fino NF, et al. Effect of epidural compared to patient-controlled intravenous analgesia on outcomes for patients undergoing liver resection for neoplastic disease. *J Surg Oncol* 2017; **115**(4): 402-406.

[9] Li NN, Huang YQ, Huang LE, Guo SH, Shen MR, Guo CL, et al. Dezocine antagonizes morphine analgesia upon simultaneous administration in rodent models of acute nociception. *Pain Physician* 2017; **20**(3): E401-E409.

[10]Xu Y, Zhu Y, Wang S, Ren Y, Miao C. Dezocine attenuates fentanyl-induced cough in a dose-dependent manner-a randomized controlled trial. *Int J Clin Exp Med* 2015; **8**(4): 6091-6096.

[11]Lazenka MF, Freitas KC, Henck S, Negus SS. Relief of pain-depressed behavior in rats by activation of d1-like dopamine receptors. *J Pharmacol Exp Ther* 2017; **362**(1): 14-23.

[12]Megat S. (354) Dopamine D1/D5 receptor-mediated mechanisms in the maintenance of pathological painplasticity. *J Pain* 2016; **17**(4S): S63-S64.

[13]Igon'kina SI, Vetrile LA, Kukushkin ML. Effect of anti-norepinephrine antibodies on the development of neuropathic pain. *Bull Exp Biol Med* 2017; **162**(6): 714-717.

[14]Norcliffe-Kaufmann L, Katz SD, Axelrod F, Kaufmann H. Norepinephrine deficiency with normal blood pressure control in congenital insensitivity to pain with anhidrosis. *Ann Neurol* 2015; **77**(5): 743-752.

[15]Liu HF, Ren QM, Wang ZB, Li X, Jiang S, Zhang JT, et al. Comparison of acute phase protein and hemodynamic variables in dogs undergoing video-assisted thoracoscopic vs. open pneumonectomy. *Exp Ther Med* 2017; **13**(5): 2391-2398.

[16]Calapkorur MU, Alkan BA, Tasdemir Z, Akcali Y, Saatçi E. Association of peripheral arterial disease with periodontal disease: analysis of inflammatory cytokines and an acute phase protein in gingival crevicular fluid and serum. *J Periodontal Res* 2017; **52**(3): 532-539.

[17]Sikora M, Krol J, Nowak M, Stefaniak T, Aubertsson G, Kozdrowski R. The usefulness of uterine lavage and acute phase protein levels as a diagnostic tool for subclinical endometritis in Icelandic mares. *Acta Vet Scand* 2016; **58**(1): 50.

[18]Kim KH. Neurourological application of neurogenesis and inflammation and pain mechanisms of rocuronium bromide. *Int Neurourol J* 2016; **20**(4): 274-275.

[19]Mitchell K, Shah JP, Dalgard CL, Tsytsikova LV, Tipton AC, Dmitriev AE, et al. Bone morphogenetic protein-2-mediated pain and inflammation in a rat model of posterolateral arthrodesis. *BMC Neurosci* 2016; **17**(1): 80.