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Clinical efficacy of sufentanil combined with dexmedetomidine in patient-controlled subcutaneous analgesia for advanced cancer pain

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Abstract: To evaluate the efficacy of sufentanil combined with dexmedetomidine in patient-controlled subcutaneous analgesia (PSCA) for advanced cancer pain, 62 patients with advanced cancer pain treated in Department of Oncology of Hebei PetroChina Central Hospital from January 2017 to May 2020 were recruited and assigned via the random number table method to either the control group or the observation group. The control group (group A) received PSCA with sufentanil and the observation group was divided into group B1 receiving PSCA with sufentanil and dexmedetomidine (20:1) and group B2 given PSCA with sufentanil and dexmedetomidine (10:1). The numeric rating scale (NRS) scores of patients in the three groups decreased significantly after medication ($P<0.05$), with significantly lower NRS scores in groups B1 and B2 than in group A ($P<0.05$) and comparable results between groups B1 and B2 ($P>0.05$). Significantly higher Ramsay sedation scores were observed in groups B1 and B2 than in group A after drug administration ($P<0.05$), without significant differences between groups B1 and B2 ($P>0.05$). The incidence of constipation, nausea and vomiting in group B1 and group B2 was significantly lower than that in group A. PSCA with sufentanil and dexmedetomidine is effective in patients with cancer pain.

Keywords: Sufentanil, dexmedetomidine, advanced cancer, cancer pain, patient-controlled subcutaneous analgesia.

INTRODUCTION

In recent years, the incidence of malignant tumors has been showing an upward trend and cancer pain is frequently seen in the advanced stages. It has been reported (Wang *et al*., 2016) that 30%-50% of tumor patients experience varying degrees of pain and the incidence of cancer pain in advanced patients even reaches 60%-80%. Many opioids, predominantly administered orally, are used clinically for cancer pain; however, given the complex etiology of cancer pain in advanced stages, single analgesic drugs fail to yield satisfactory results and a considerable number of patients either remain incapable of oral administration or intolerant to the side effects of oral drugs, which necessitates the exploration of diverse analgesics such as joint medications and different medication methods (Bhatnagar *et al*., 2015). A study (Mohamed *et al*., 2012) showed that sufentanil combined with dexmedetomidine has a safe performance in the intrathecal drug injection system and can successfully lower the dosage of sufentanil with favorable satisfaction. The present study applied dexmedetomidine combined with sufentanil using patient-controlled subcutaneous analgesia (PCSA) for the treatment of cancer pain, analyzed its analgesic effect and investigated the ratio between the two drugs to provide a clinical reference.

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MATERIALS AND METHODS

General information

Sixty-two patients with advanced cancer pain treated in the Department of Oncology of Hebei PetroChina Central Hospital from January 2017 to May 2020 were included and divided into the control group and the observation group according to the random number table method. The control group (group A) received PSCA with sufentanil and the observation group was divided into group B1 receiving PSCA with sufentanil and dexmedetomidine (20:1) and group B2 given PSCA with sufentanil and dexmedetomidine (10:1). In the control group (group A), there were 19 patients, including 9 males and 10 females, with an average age of 53.68±15.48 years and a bodyweight of 54.21±5.00 kg. Group A had 0 cases of gastric cancer, 2 cases of pancreatic cancer, 4 cases of lung cancer, 5 cases of colon cancer, 3 cases of liver cancer, 2 cases of cervical cancer and 3 cases of breast cancer in terms of pathological type. In the observation group (group B1), there were 20 patients, including 12 males and 8 females, with an average age of 56.25±9.31 years and a bodyweight of 54.75±5.37 kg. Group B1 had 4 cases of gastric cancer, 5 cases of pancreatic cancer, 1 case of lung cancer, 2 cases of colon cancer, 4 cases of liver cancer, 2 cases of cervical cancer and 2 cases of breast cancer in terms of pathological type. In the observation group (group B2), there were 23 patients, including 12 males and 11 females, with an average age of 57.22±10.03 years and a weight of 52.78±4.08 kg. Group B2 patients had 1 case of gastric cancer, 3 cases of pancreatic cancer, 6 cases of lung cancer, 5 cases of colon

cancer, 2 cases of liver cancer, 3 cases of cervical cancer and 3 cases of breast cancer in terms of pathological type. All clinical stages of cancers were stage IV. There was no statistically significant difference between the two groups in terms of general information such as gender, age, weight, pathological type and clinical stage (P>0.05).

Inclusion criteria

Patients who were diagnosed with malignant neoplasm by cytopathology, all stage IV; (2) Patients with pain, who had taken high doses of oral opioids, with a pain numeric rating scale (NRS) score of >7 points, intolerant to oral medication for analgesia; (3) Patients with an expected survival of >3 months; (4) Patients who agreed to receive opioid analgesia treatment, participated in this study and signed the consent form, with complete clinical data.

Exclusion criteria

Patients with severe multi-organ failure; (2) Patients with impaired consciousness or difficulty in verbal communication that prevents NRS scoring; (3) Patients who refused to participate in this study; (4) Patients with allergies to sufentanil or dexmedetomidine; (5) Patients with combined II-III degree AV block and bradycardia (heart rate <60 beats/min) (Tisotti *et al*., 2021; Shi *et al*., 2019).

Methods

Patients in all three groups received PCSA for analgesia. The PCSA pump was placed on the medial side of the upper arm unilaterally: After routine disinfection with iodophor, the subcutaneous puncture needle was left under the skin on the inner side of the upper arm and fixed with transparent excipients, with the needle connected to a self-contained pump device through a thin soft tube and analgesic drugs stored in disposable drug storage bags inside the device (Tang *et al*., 2020). The parameters of the pump were adjusted according to patients' conditions (Zhou *et al*., 2015).

Group A was treated with sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., 1 ml: 50ug, Pharmacopoeia H20054171) 2000ug for PCSA analgesia. In group B1, sufentanil 2000ug and dexmedetomidine (Yangtze River Pharmaceutical Group Co., Ltd., State Pharmacopoeia H20183219, 2 mL:0.2 mg) 100ug were diluted in 9ml 0.9% sodium chloride saline to prepare 50ml of liquid for PCSA analgesia (dexmedetomidine concentration was 2ug/ml). In group B2, sufentanil 2000ug and dexmedetomidine (Yangtze River Pharmaceutical Group Co., Ltd., State Pharmacopoeia H20183219, 2 mL:0.2 mg) 200ug were diluted in 9ml 0.9% sodium chloride saline to prepare 50ml of liquid for PCSA analgesia (dexmedetomidine concentration was 4ug/ml). The total amount of 24h sufentanil (oxycodone: morphine = 1:2; sufentanil: morphine = 1:1000; oral: subcutaneous: intravenous = 3:2:1) was derived from the total amount of opioids used orally by the patient in the previous 24 hours, and the electronic analgesia pump parameters were set as per the above data.

Specific parameters: The initial dose was 10% of the patient's total sufentanil dose for the day, and the background infusion dose was the total sufentanil dose for the day/24 hours at a uniform rate. 10% of the total amount of sufentanil for the day was used to relieve the onset of breakthrough cancer pain, with a 1-h maximum extreme dose of 30% of the total sufentanil dose for the day. The analgesic effect was assessed promptly after initiation of the analgesic pump for adjustment of infusion parameters.

Observation indicators

(1) Pain assessment: the pain level was assessed by the numerical rating scale (NRS), with a total score of 10 points. A score of 1 - 3 points indicated mild pain, a score of 4-6 indicated moderate pain and a score of 7-10 indicated severe pain. The analgesic effects of the two groups were analyzed and compared. Markedly effective: the patients' pain scores decreased by >75%. Effective: the patients' pain scores decreased by >50%. Ineffective: the patients' pain scores did not reach the standard of markedly effective or effective, or aggravated. Total effective rate = (markedly effective cases + effective cases) / total number of cases * 100%. The number of breakthrough cancer pain /day, daily sufentanil use and the total amount of 7-day sufentanil use in 1 week were recorded.

(2) Sedation of patients: The sedative effect was evaluated using the Ramsay score, with a total score of 6 points. 1 point indicated unquiet and irritable, 2 points indicated quiet and cooperative, 3 points indicated drowsy and responsive to instructions, 4 points indicated sleepy but can be awakened, 5 points indicated sleepy and responsive to stronger stimuli with a dull response and 6 points indicated deep sleep and cannot be awakened. 2 - 4 points were classified as satisfactory sedation and 5 - 6 points were classified as excessive sedation.

(3) Adverse reactions: the occurrence of hypotension (systolic blood pressure decreased by more than 20 % of the basal value or MAP < 80 mmHg), severe bradycardia (HR < 46 beats / min), severe tachycardia (heart rate > 110 beats / min), respiratory depression (SpO2 < 90 % or respiratory rate < 8 breaths / min), nausea and vomiting, and dry mouth were recorded.

STATISTICAL ANALYSIS

SPSS 22.0 statistical software was used to analyze the data. The measurement data conforming to the normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$) and the variance test was used for the comparison

of measurement data between multiple groups. The count data were expressed as rate (%), and processed using the $\chi 2$ test. $P<0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of general information

There was no significant difference between the three groups in terms of general information such as gender, age, weight, body mass index, and pathological type ($P > 0.05$), as shown in table 1.

Comparison of analgesic effects

The NRS scores of patients in the three groups decreased significantly after medication ($P<0.05$), with significantly lower NRS scores in groups B1 and B2 than in group A ($P<0.05$) and comparable results between groups B1 and B2 ($P>0.05$) (table 2).

Comparison of the number of PCSA presses and daily sufentanil use dose within 1 week after drug administration

PSCA with sufentanil and dexmedetomidine was associated with fewer pump presses in patients within 1 week after drug administration versus without dexmedetomidine and a higher ratio of sufentanil to dexmedetomidine obtained better results ($P<0.05$) (table 3).

Comparison of sedation effects

Significantly higher Ramsay sedation scores were observed in groups B1 and B2 than in group A after drug administration ($P<0.05$), without significant differences between groups B1 and B2 ($P>0.05$) (table 4).

Comparison of adverse reactions

The incidence of constipation, nausea and vomiting in group B1 and group B2 was significantly lower than that in group A ($P<0.05$) (table 5).

DISCUSSION

The occurrence of cancer pain increases along with the increasing incidence of cancer, with frequent symptoms such as anxiety, insomnia and prosopagnosia, which seriously compromise the quality of life of patients. The treatment of advanced cancer pain mainly relies on opioids, but numerous factors associated with the occurrence of advanced cancer pain may prevent pain management with single opioid drugs.

Herein, the NRS scores of the observation group were lower than those of the control group at different time points after drug administration ($P<0.05$) and the total amount of sufentanil used and the number of breakthrough cancer pain within 7days were significantly less in the observation group than in the control group ($P<0.05$), suggesting that the combination of the two could improve the analgesic efficacy. Similar results have been obtained by several previous studies. A previous study (Qin *et al*., 2017) showed that the combination of sufentanil and dexmedetomidine was more effective and had fewer adverse effects than the monotherapy of sufentanil in the treatment of intractable cancer pain. Sufentanil in combination with dexmedetomidine has been applied for the treatment of cancer pain in a prior study and the results revealed better efficacy of combined treatment than the stand-alone treatment of sufentanil for analgesia (Zhao *et al*., 2020). Moreover, previous studies have demonstrated that opioids combined with dexmedetomidine could reduce the use of opioid drugs by about 30%-50% (Gursoy *et al*., 2011; Arain *et al*., 2004). In the present study, the total amount of sufentanil used in group B1 and group B2 was significantly lower than that of the control group, which may be attributed to the synergistic analgesia between the two drugs. Nevertheless, the decrement of sufentanil in group B1 and group B2 was 14.53% and 28.07%, respectively, compared with that of group A, which were lower than the data of previous studies. Such results may be attributable to the small sample size included and the small drug ratios used for the study.

In terms of drug sedation, the Ramsay scores of patients in the observation group were higher than those in the control group at all time points after drug administration ($P<0.05$), suggesting that the combination of the two drugs can achieve favorable sedation and analgesia. Prior research revealed a promising sedative effect of dexmedetomidine in anesthesia (Amorim *et al*., 2017), which is consistent with the findings of the present study. Dexmedetomidine is the dextranomer of medetomidine, a novel adrenergic agonist, which provides analgesic and sedative effects by selectively binding to α2 adrenergic receptors (Barends *et al*., 2017) and features a synergistic analgesic effect with sufentanil with a different analgesic mechanism (Ramsay *et al*., 2014).

Sufentanil is a strong opioid that is prone to adverse effects such as constipation, drowsiness, nausea and vomiting during analgesia. In this study, the incidence of constipation, nausea and vomiting in the observation group was significantly lower than that in the control group ($P<0.05$), which may be ascribed to the reduction of sufentanil with the use of dexmedetomidine. It has also been reported that dexmedetomidine can reduce the incidence of nausea and vomiting (Sridharan *et al*., 2019). The higher incidence of bradycardia in group B2 than in group B1 may be related to the significantly higher dexmedetomidine dose in group B2 than in group B1. Dexmedetomidine is a new highly selective α2 agonist of epinephrine with an affinity ratio of 1620:1 for α2 and α1 receptors and is considered a complete α2 agonist.

Table 1: Comparison of general information of patients in the three groups

Groups	N	Gender		Age/years	Weight/kg	Pathological type
		Male	Female			
Group A	19	9(47.37%)	10(52.63%)	53.68±15.48	54.21±5.00	
Group B1	20	12(60.00%)	8(40.00%)	56.25±9.31	54.75±5.37	
Group B2	23	12(52.17%)	11(47.83%)	57.22±10.03	52.78±4.08	

Table 2: The NRS scores of the three groups of patients before and after drug administration at each time point (score, x± s)

	N	After administration	1h after administration	2h after administration	4h after administration	8h after administration	24h after administration	48h after administration	7d after administration
Group A	19	8.11±0.74	5.53±1.02#	3.95±1.31*#	3.32±1.11*#	3.11±1.049*#	2.95±0.85*#	2.89±0.88*#	2.683±1.1*#
Group B1	20	8.50±0.69	5.10±0.72	3.05±0.76	2.40±1.10	1.75±1.16	1.20±1.15	0.80±1.20	0.90±1.2
Group B2	23	8.17±0.83	5.00±0.74	2.83±0.83	2.00±1.00	1.17±0.78	0.87±0.63	0.35±0.48	0.26±0.45
F		1.54	2.38	7.31	8.17	20.06	31.52	47.33	36.03
P		0.11	0.04	0.01	0.01	0.00	0.00	0.00	0.00

Table 3: Comparison of the number of breakthrough cancer pain after administration, total 7-day sufentanil use and daily dose in the three groups (x± s)

	N	Number of breakthrough cancer pain (times/day)	Total sufentanil use (ug)	Daily dose of sufentanil (ug)
Group A	19	3.16±1.46*#	7288.84±786.80*#	1041.26±112.40*#
Group B1	20	1.70±0.98#	6229.65±560.51#	889.95±80.07#
Group B2	23	1.26±1.01	5242.70±643.85	749.00±92.00
F		14.8	49.05	49.05
P		0.00	0.00	0.00

Table 4: Comparison of Ramsay sedation scores before and after drug administration in the three groups (points, x ± s)

	N	After administration	1h after administration	2h after administration	4h after administration	8h after administration	24h after administration	48h after administration	7d after administration
Group A	19	1.05±0.23	1.11±0.32	1.47±0.51*#	1.63±0.50*#	1.63±0.50*#	1.74±0.45*#	1.84±0.38*#	2.00±0.00*#
GroupB1	20	1.05±0.22	1.25±0.44	2.05±0.22#	2.10±0.31	2.05±0.22	2.05±0.22	2.05±0.22	2.05±0.22#
GroupB2	23	1.04±0.21	1.30±0.47	2.22±0.42	2.13±0.34	2.09±0.29	2.09±0.29	2.09±0.29	2.09±0.29
F		0.01	1.22	18.87	10.34	0.84	6.74	3.89	0.84
P		0.97	0.28	0.00	0.00	0.00	0.004	0.034	0.475

Table 5: Comparison of adverse reactions after drug administration in the three groups [n (%)]

	N	Nausea and vomiting	Constipation	Drowsiness	Urinary retention	Bradycardia	Hypotension
Group A	19	5(26.32%)	4(21.05%)	1(5.26%)	1(5.26%)	0(0%)	0(0%)
Group B1	20	1(5.00%)	0(0%)	0(0%)	1(5.00%)	0(0%)	0(0%)
Group B2	23	1(4.35%)	2(8.70%)	5(21.74%)	1(4.35%)	3(13.04%)	0(0%)
$\chi 2$		6.18	4.98	6.40	0.02	5.35	1.71
P		0.46	0.08	0.04	0.99	0.07	0.43

Note: Compared with the same period in group B1, * indicates P<0.05; compared with the same period in group B2, # indicates P<0.05.

It inhibits the release of norepinephrine upon activation of α2 receptors in sympathetic nerve terminals, leading to a decrease in sedation and sympathetic activation signal output as well as an increase in cardiac vagal activity, which results in a decrease in heart rate and cardiac output (Weerink *et al*., 2017).

CONCLUSION

In summary, PSCA with sufentanil and dexmedetomidine is effective in patients with cancer pain and the hybrid use of the two drugs can cut down the dose of sufentanil, with safety and effectiveness, which is worthy of clinical promotion.

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