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Review Article

Sufentanil and remifentanil combined with dezocine anesthesia for radical resection of liver cancer and its effect on liver and kidney function

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Abstract: Objective: To study the effect of sufentanil and remifentanil combined with dezocine on radical resection of liver cancer and its effect on liver and kidney function. Methods: Altogether 137 patients who underwent radical resection of liver cancer in Hanchuan Traditional Chinese Medicine Hospital of Hubei from February 2016 to June 2018 were collected; 72 of whom were treated with sufentanil combined with dezocine as the observation group (OG) and 65 of whom were treated with remifentanil combined with dezocine as the control group (CG). The stress state, VAS score, liver and kidney function index and postoperative adverse reactions of the two groups were observed 15 minutes before anesthesia (T0), at skin incision (T1), at surgery completion (T2) and 24 hours (T3) after operation. Results: The stress state of the OG at T1, T2 and T3 was greatly lower than that of the CG, and the VAS score of the OG was lower than that of the CG. There was no remarkable difference in adverse reactions between the two groups, and no difference in liver function indicators ALT, AST and renal function indicators Cr and BUN. Conclusion: Sufentanil combined with dezocine can provide more stable hemodynamics, reduce stress responses and reduce postoperative pain, but there is no difference in the liver and kidney function compared with remifentanil.

Keywords: Sufentanil, remifentanil, dezocine, radical resection of liver cancer

Introduction

Hepatocellular carcinoma (HCC) is one of the most familiar digestive tract tumors worldwide, with extremely high morbidity and mortality. It is currently the sixth most common cancer and ranks third in cancer mortality in the world [1]. We have not fully understood the etiology and mechanism of HCC, but have found that hepatitis B virus, hepatitis C virus and other toxic infection and excessive drinking can lead to the development of HCC [2]. Primary HCC is the main type of HCC and is one of the most common malignant tumors in China. Currently, the patients with primary HCC in China accounts for nearly 55% of the world's total, ranking second in tumor-related mortality rate in China [3]. At present, the most effective and possibly completely curable treatment for primary HCC is radical resection of liver cancer [4]. Hepatectomy surgery may have different degrees of damage to patients' liver function, and oxidative stress occurring during the surgery may also affect liver function and renal function [5-7].

Opioids are common analgesic and sedative drugs used in clinic, and they are used in many operations. Different opioids have different sedative effects, hemorheological effects and adverse reactions on patients [8]. Remifentanil is a μ opioid receptor agonist of fentanyl, characterized by rapid onset of action and rapid metabolism through non-specific esterases in plasma and interstitial tissue, so its half-life is short and its blood concentration is relatively stable during long-term anesthesia [9]. Sufentanil is also a μ opioid receptor agonist of fentanyl, its onset speed is also fast, and it is found that in the use process, it has fewer adverse reactions to premature delivery of patients. Its analgesic effect is very strong, which

is 8 times of fentanyl. It is the most effective opioid agonist used clinically and has a short awakening time and certain liver protection effects [10]. Dezocine is an opioid analgesic drug with antagonistic effect on μ receptors, and it is also a κ receptor agonist. Dezocine is commonly used in the world due to its high tolerance, less adverse reactions and low drug dependence, accounting for 44% of the opioid analgesic market in China [11, 12]. However, it is not clear about the differences of the effects of sufentanil combined with dezocine and remifentanil combined with dezocine in radical resection of liver cancer, and the effects of the two groups of drug schemes on patients' sensory function needs further discussion.

Therefore, this study provides the direction and basis for clinical application by comparing the clinical effects of sufentanil and remifentanil combined with dezocine anesthesia, respectively, for radical resection of liver cancer and observing the effects on liver and kidney function.

Methods

Data of the patients

Altogether 137 patients who underwent radical resection of liver cancer in Hanchuan Traditional Chinese Medicine Hospital of Hubei from February 2016 to June 2018 were collected; 72 of whom were treated with sufentanil combined with dezocine as the observation group (OG), including 39 males and 33 females, with an average age of 48.3±6.3 years. The other 65 patients were treated with remifentanil combined with dezocine as the control group (CG), including 38 males and 27 females. This study has been approved by the Medical Ethics Committee, and all patients were informed and signed the informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: All patients were diagnosed with primary HCC by imaging and pathology [13]; patients could be treated by radical surgery; the clinical data of the patients were complete, and the patients were followed up; the patients signed an informed consent form after understanding the purpose of this study.

Exclusion criteria: Patients were allergic to the drugs used in our study; patients complicated with other tumors; patients with severe inflammation; patients with severe immune deficiency; patients with congenital liver, kidney and heart functional defects.

Reagents and kits

Plasma cortisol (Cor) ELISA test kit (Elabscience Company, Wuhan, China, E-EL-0157c); angiotensin-II (A-II) ELISA test kit (Jianglai Biology Co. Ltd., Shanghai, China, JL10881); automatic biochemical analyzer (Beckman Instruments, Inc., U.S., AU5800); Propofol (Jiabo Pharmaceutical Co., Ltd., Guangdong, China); remifentanil hydrochloride (Jiangsu Nhwa Pharmaceutical Co., Ltd.); sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd.); hydromorphone (Yichang Humanwell Pharmaceutical Co., Ltd.); fentanyl (Jiangsu Nhwa Pharmaceutical Co., Ltd.); tramadol (Hubei Xinghua Pharmaceutical Co., Ltd.); midazolam (Yichang Humanwell Pharmaceutical Co., Ltd.); etomidate (Jiangsu Nhwa Pharmaceutical Co., Ltd.); atracurium (Jiangsu Hengrui Medicine Co., Ltd.).

Anesthesia program

All patients were established with peripheral venous access. Arterial blood pressure was monitored and anesthesia induction was conducted. Intravenous injection of 0.05 mg/kg of midazolam, 0.3 mg/kg of etomidate, 0.20 mg/kg of atracurium, and 1.5 mg/kg of propofol was carried out for anesthesia induction. The OG was also given 0.3 μg/kg of sufentanil for anesthesia induction, while the CG was given 1 μg/kg of remifentanil for anesthesia induction. During the anesthesia maintenance phase, the anesthesia pump was used for continuous administration. The OG used 4-8 mg/kg/h of propofol and 0.20-0.30 μg/kg/h of sufentanil, while the CG used 4-8 mg/kg/h of propofol 4-8 and 2-4 ng/m/h remifentanil. The bispectral index (BIS) of the two groups of patients was kept between 40-60, and the hemodynamic changes were less than 20% of the baseline. Two groups of patients were given 0.15 mg/kg of dezocine 30 min before the end of the operation, propofol was stopped 10 min before the end of operation, sufentanil or remifentanil was stopped at the end of the operation. Patient controlled analgesia (PCA) was applied after the patient opened their eyes. PCA consisted of 12 mg of hydromorphone and 100 mL of normal saline with an injection speed of 1 mL/h, a single dose of 1 mL, and with a locking time of

10 minutes. In PACU and general wards, 1 μg/kg of fentanyl and 50 mg of tramadol were injected intravenously as rescue analgesics.

Detection methods

A total of 8 ml of venous blood from the elbow on the non-venous transfusion side was collected 15 minutes before anesthesia (T0), at skin incision (T1), at surgery completion (T2), and 24 hours (T3) after anesthesia. The blood was placed in a procoagulant tube. The blood serum was collected after centrifugation (3000×g at 4°C for 10 min). Cor and A-II levels were detected by ELISA, and 100 μL of STD or sample was put into each well. The sample was cultured at 37°C for 90 minutes. The liquid was taken out. Then 100 μL of biotin detection kit was added and cultured at 37°C for 1 hour. Suction and rinsing were carried out 3 times. Next 100 μl of HRP conjugate was added and incubated at 37°C for 30 minutes. Suction and rinsing were carried out 5 times. Then 90 μL of matrix reagent was added and incubated at 37°C for 15 minutes. After that 50 μL of stop solution was added immediately, the absorbance of the sample was read at 450 nm. The results were calculated. Liver function indicators alanine aminotransferase (ALT), aspartate aminotransferase (AST), and renal function indicators creatinine (Cr) and blood urea nitrogen (BUN) were detected by automatic deepening instrument.

Observation indicators

Main observation indicators: The variation of mean arterial pressure (MAP) and heart rate (HR), the expressions of Cor and A-II, liver function indicators ALT, AST, and renal function indicators Cr and BUN were compared between the two groups at T0, T1, T2 and T3.

Secondary observation indicators: The incidence of adverse reactions in the 2 groups 1 day after operation was compared. The postoperative pain of the two groups was analyzed and compared using the visual analogue scale (VAS), 1 day after operation between the two groups.

Statistical analysis

This study used SPSS 20.0 (SPSS Co., Ltd., Chicago, USA) to carry out statistical analysis on the collected data; GraphPad Prism 7 (Graphpad software Co., Ltd., San Diego, USA) was used to visualize pictures of the collected data, and chi-square test to test the usage (%) of counting data, which was expressed as X^2. Measurement data were expressed by Means ± SD; all measurement data conformed to normal distribution. The comparison of multiple time points of groups was tested by repeated analysis of variance, and back testing used bonferroni test, which was expressed by F. Rank sum test that was used for grade data, which was expressed as Z. $P<0.05$ was considered as statistically significant.

Results

Clinical data

There was no statistical difference in gender, age, BMI, ASA classification, type, surgical site, lesion number, tumor size and clinical symptoms between the two groups, as shown in **Table 1**.

Comparison of surgical conditions

By comparing the operation conditions of the two groups, it was found that there was no remarkable difference between them in the total operation time, anesthesia time, BIS, bleeding volume and clamping porta hepatis time. The consumption of propofol in the OG was significantly lower than that in the CG ($P<0.05$), as shown in **Table 2**.

MAP and HR changes

By comparing the changes of MAP and HR at T0, T1, T2 and T3 of the two groups, it was found that there was no remarkable difference in MAP and HR at T0 between the two groups. MAP and HR of the two groups at T1 were higher than those at T0; MAP and HR at T2 were higher than those at T0 and lower than those at T1; MAP and HR at T3 were lower than those at T1. MAP and HR at T3 of the OG were not significantly different from those at T0 and T2. MAP and HR at T3 of the CG were not significantly different but they were significantly higher than T0. Those of OG at T1, T2, and T3 were lower than those of the CG, see **Table 3**.

Expression of Cor and A-II

By comparing the changes of Cor and A-II at T0, T1, T2 and T3, it was found that Cor and A-II at

Table 1. Clinical data

	Observation group (n=72)	Control group (n=65)	X^2/t/Z	P
Gender				
Male	39 (54.17)	38 (58.46)		
Female	33 (45.83)	27 (41.54)	0.256	0.613
Age (years)	48.3±6.3	46.9±5.6	1.369	0.173
ASA classification				
I	21 (29.17)	15 (23.08)		
II	35 (48.61)	32 (49.23)		
III	16 (22.22)	18 (27.69)	0.942	0.346
Type				
HCC	31 (43.06)	27 (41.54)		
Cholangiocarcinoma	27 (37.50)	28 (43.08)		
Others	14 (19.44)	10 (15.38)	0.605	0.739
Surgical site				
Right hemihepatectomy	30 (41.67)	29 (44.62)		
Left hemihepatectomy	42 (58.33)	36 (55.38)	0.121	0.728
Number of lesions (number)				
≤2	39 (54.17)	35 (53.85)		
>2	33 (45.83)	30 (46.15)	0.001	0.970
Tumor size (cm)				
≤2	42 (58.33)	39 (60.00)		
>2	30 (41.67)	26 (40.00)	0.039	0.843

Table 2. Comparison of surgical conditions

Factor	Observation group (n=72)	Control group (n=65)	t value	*P* value
Total operation time (min)	188.65±44.65	192.27±46.47	0.465	0.643
Anesthesia time (min)	206.46±53.67	218.59±52.49	1.335	0.1842
BIS	48.67±3.25	47.92±3.07	1.385	0.1685
Bleeding volume (mL)	292.26±34.25	297.38±32.76	0.892	0.374
Clamping porta hepatis time (min)	25.47±5.68	24.66±4.73	0.902	0.369
Propofol consumption (mg)	1223.28±135.25	1545.34±193.19	11.390	<0.001

T0 were not significantly different between the two groups. Cor and A-II at T1 were higher than those at T0; Cor and A-II at T2 were higher than those at T0 and significantly lower than those at T1. Cor and A-II in T3 were significantly lower than those at T1; Cor and A-II at T3 were not significantly different from those at T0 and T2 in OG. Cor, A-II at T3 of the CG were not significantly different from those at T2, and higher than those at T0; and those of OG at T1, T2 and T3 was lower than those of CG, see **Table 4**.

Postoperative VAS score comparison

By comparing the postoperative VAS scores of the two groups, it was found that the VAS score of the OG (1.25±0.53) was significantly lower than that of the CG (1.53±0.72) (P<0.05), as shown in **Figure 1**.

Changes of liver and kidney function before and after operation

By comparing the changes of liver function indicators ALT, AST and renal function indicators Cr and BUN before and after the operation, it was found that there was no remarkable difference in ALT, AST, Cr and BUN before the operation between the two groups. ALT, AST, Cr and BUN after the operation were higher than those before the operation, and there was no remarkable difference in ALT, AST, Cr and BUN between the two groups after the operation (P>0.05), as shown in **Table 5**.

Table 3. MAP and HR changes

Group	MAP (mmHg)				HR (times/min)			
	T0	T1	T2	T3	T0	T1	T2	T3
Observation group (n=72)	86.87±9.51	95.38±12.32A	90.64±8.24A,B	88.22±8.54B	77.17±8.36	82.56±9.46A	79.73±8.56A,B	77.42±8.34B
Control group (n=65)	87.44±9.76	100.38±14.74A	95.35±8.63A,B	93.52±8.98A,B	76.88±8.20	86.48±10.43A	83.62±9.74A,B	81.54±9.37A,B
T	0.346	2.161	3.267	3.540	0.205	2.307	2.488	2.723
P	0.730	0.032	0.001	<0.001	0.838	0.023	0.014	0.007

Note: A means that compared with T0, P<0.05. B means that compared with T1, P<0.05.

Table 4. Expression of Cor and A-II

Group	Cor (nmol/L)				A-II (ng/dL)			
	T0	T1	T2	T3	T0	T1	T2	T3
Observation group (n=72)	231.74±64.98	267.54±77.14A*	252.63±73.57A*,#	238.63±68.53#	40.06±10.32	57.24±12.76*	48.58±11.77*,#	44.06±9.14#
Control group (n=65)	225.76±59.43	301.62±84.65*	283.16±82.15*,#	268.36±78.46*,#	41.63±11.24	63.28±15.94*	55.72±13.43*,#	49.27±11.36*,#
t value	0.560	2.466	2.295	2.367	0.852	2.459	3.316	2.970
P value	0.576	0.015	0.023	0.019	0.396	0.015	0.001	0.004

Note: * means that compared with T0, P<0.05; # means that compared with T1, P<0.05.

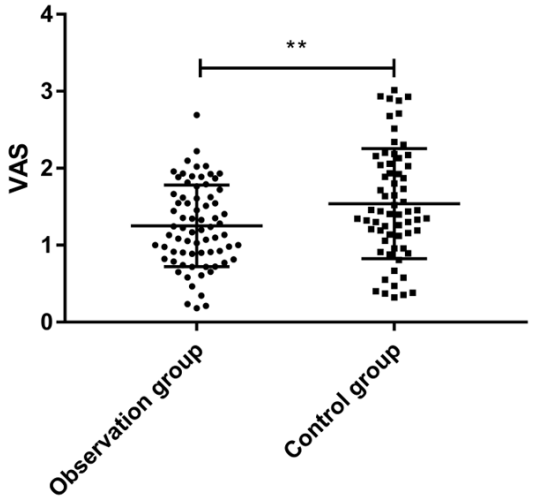

Figure 1. Postoperative VAS score comparison. The postoperative VAS score of the OG was significanlty lower than that of the CG (t=2.609, P=0.001). ** indicates that P<0.01.

Adverse reaction

By comparing the occurrence of adverse reactions between the two groups, it was found that there was no significant difference in respiratory depression, nausea, vomiting, hypotension, bradycardia and vertigo between them (P>0.05), as shown in **Table 6**.

Discussion

In our study, the basic operating conditions of the two groups were first compared. It was found that the consumption of propofol in the OG was lower than that in the CG, but there was no remarkable difference in the total operating time, anesthesia time, BIS, bleeding volume and lamping porta hepatis time. Propofol is mainly used for anesthesia maintenance [14, 15]. We suspected that the reason for the different consumption of propofol is that sufentanil combined with dezocine can provide more stable anesthetic effect. BIS is relatively stable, while remifentanil combined with dezocine is weaker than sufentanil for BIS stability, so more propofol is needed to maintain anesthesia effect.

At the same time, we also compared the influence of the two groups on the hemodynamic indicators MAP and HR, and found that there was no remarkable difference in MAP and HR at T0 between them. MAP and HR at T1 of the two groups were higher than those at T0; MAP and HR at T2 were higher than those at T0 and lower than those at T1; MAP and HR at T3 were lower than those at T1, MAP and HR at T3 of the OG were not largely different from those at T0 and T2. MAP and HR at T3 of the CG were not significantly different but were significantly higher than those at T0. Those of the OG at T1, T2, and T3 were significantly lower than those of the CG, which also suggested that the stability of sufentanil combined with dezocine for hemorheology was stronger than that of remifentanil combined with dezocine. Moreover, some studies have shown that higher stress responses of patients during surgery will also lead to larger hemodynamic changes [16, 17]. Therefore, it is also possible that the stress response caused by sufentanil is smaller than that of remifentanil, thus resulting in this phenomenon. There were also some studies which suggested that anesthesia with propofol and remifentanil may often cause unnecessary bradycardia and hypotension [18], which may be caused by unstable hemodynamics during anesthesia.

In some literature, it was reported that the stress reaction of patients during surgery will cause changes in the expression of Cor and A-II [19]. Therefore, we also compared the levels of Cor and A-II before and after surgery in the two groups. It was found that Cor and A-II at T1 were significantly higher than those at T0, Cor and A-II at T2 were significantly higher than those at T0 and significantly lower than those at T1, Cor and A-II at T3 were significantly lower than those at T1. There was no significant difference in Cor and A-II of T3 with T0 and T2 in the OG, and there was no significant difference in Cor and A-II of T3 with T2 in the CG, but those at T3 were significantly higher than those at T0. The OG was significantly lower than the CG at T1, T2 and T3. This showed that compared with remifentanil, sufentanil can clearly reduce the stress response of patients. In the study of Qi et al. [20], the anesthesia of sufentanil and remifentanil in colorectal cancer was compared. It was found that the blood sugar, cortisol, interleukin-6 and C-reactive protein in sufentanil group after surgery were not different from those before surgery. However, these indicators in remifentanil group were increased during surgery and anesthesia, which also showed that sufentanil can better reduce the stress response during surgery compared with remifentanil. At the same time, our point of view

Table 5. Liver and kidney function before and after operation

		Observation group (n=72)	Control group (n=65)	t	P
ALT (U/L)	Preoperative	47.68±15.37	49.12±14.38	0.565	0.573
	Postoperative	198.37±58.27	203.65±62.94	0.510	0.611
AST (U/L)	Preoperative	58.92±21.54	56.46±19.62	0.696	0.488
	Postoperative	228.56±64.37	234.57±67.36	0.534	0.594
Cr (μmol/L)	Preoperative	83.45±36.39	87.35±34.85	0.639	0.524
	Postoperative	104.37±53.27	111.65±34.85	0.767	0.445
BUN (mmol/L)	Preoperative	9.53±1.24	9.67±1.33	0.638	0.525
	Postoperative	10.86±2.32	11.21±2.57	0.838	0.404

Table 6. Adverse reactions

	Observation group (n=72)	Control group (n=65)	X^2	P
Respiratory depression	4 (5.56)	5 (7.69)	0.254	0.614
Nausea and vomiting	3 (4.17)	6 (9.23)	1.427	0.232
Hypotension	2 (2.78)	1 (1.54)	0.245	0.621
Bradycardia	2 (2.78)	3 (4.62)	0.328	0.567
Vertigo	3 (4.17)	5 (7.69)	0.772	0.380

was supported. They also found that sufentanil had shorter immune recovery period and recovery time and less adverse reactions compared with remifentanil. However, in our study, we also compared the adverse reactions of the two groups after operation, but we found that there was no difference in respiratory depression, nausea, vomiting, hypotension, bradycardia and vertigo adverse reactions between the two groups. We suspected that it was because our research applied dezocine during anesthesia. Some literature also showed that dezocine had fewer adverse reactions during anesthesia and could enhance the effect of other sedative anesthetic drugs [21]. In addition, we compared the VAS scores of the two groups, and compared the postoperative pain by using VAS scores. It was found that those in the OG were significantly lower than those in the CG.

In the end, we compared the liver and kidney function indicators ALT, AST, Cr and BUN of the two groups of patients. There was no significant difference in ALT, AST, Cr and BUN between the two groups before operation. ALT, AST, Cr and BUN of the two groups after operation were higher than those before operation, and there was no remarkable difference in ALT, AST, Cr and BUN between the two groups after operation. This showed that the effects of sufentanil and remifentanil on liver and kidney function were not different, and both have been reported to have liver function protective effects in previous studies [22, 23].

However, this study also has some shortcomings. First, this study does not subdivide the study subjects according to their characteristics. Because of different age groups or other factors, there are some differences in the body functions of these patients. Secondly, we did not further explore the patient's non-kinetics, hoping to add corresponding experiments to discuss it in the future. Finally, the sedative effect of opioid drugs is sometimes affected by the dosage [24, 25], so it is also hoped that further research will be conducted on the effects of different dosages of sufentanil and remifentanil and the optimal dosage in subsequent studies.

In summary, sufentanil combined with dezocine can provide more stable hemodynamics, reduce stress responses and reduce postoperative pain, but there is no difference between sufentanil and remifentanil in liver and kidney function.

Disclosure of conflict of interest

None.

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