

Effects of Dezocine-Remifentanil Intravenous Anaesthesia on Perioperative Signs, Serum TNF- α and IL-6 in Liver Cancer Patients undergoing Radiofrequency Ablation

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ABSTRACT

Objective: To analyse the impact of dezocine-remifentanil intravenous anaesthesia on perioperative signs, serum tumour necrosis factor- α (TNF- α), and interleukin-6 (IL-6) in liver cancer patients undergoing radiofrequency ablation (RFA).

Study Design: An experimental study.

Place and Duration of Study: Renmin Hospital of Wuhan University, Wuhan, China, from January 2017 to February 2018.

Methodology: Eighty patients with small hepatocellular carcinoma (SHCC) were selected as the research object. They were divided into Group A and Group B with the random number table method, with 40 cases in each group. Group A were given dezocine-remifentanil intravenous anaesthesia and Group B were given midazolam-remifentanil intravenous anaesthesia. Patients' situations in the surgery were compared between the two groups. Changes in heart rate (HR), mean arterial pressure (MAP) and blood oxygen saturation (SpO₂) were recorded before the surgery (T₀), at 5 minutes after the RFA (T₁) and at the end of the RFA (T₂). Levels of tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) on the 1st day after the RFA were compared between the two groups.

Results: The wake-up time in Group A was shorter than Group B ($p < 0.001$), and the VAS pain score in Group A was lower than Group B ($p < 0.001$). At T₁, the MAP in Group A was higher than Group B ($p < 0.001$). There was no significant difference in MAP between the two groups at T₀ and T₂ ($p = 0.881, 0.696$, respectively). At T₁ and T₂, the HR in Group A was lower than Group B (all $p < 0.001$). There was no significant difference in HR between the two groups at T₀ ($p = 0.684$). There was no significant difference in SpO₂ between the two groups at T₀, T₁ and T₂ ($p = 0.654, 0.884$ and 0.798 , respectively). On the 1st day after the RFA, the level of TNF- α , IL-6 in Group A were lower than those of Group B (all $p < 0.001$). There was no significant difference in the incidence of intraoperative complications between the two groups ($p = 0.644$).

Conclusion: Compared with midazolam-remifentanil intravenous anaesthesia, the dezocine-remifentanil method has a better analgesic effect, shorter wake-up time, and can effectively regulate the expression of inflammatory cytokines TNF- α and IL-6. However, the effect of remifentanil on the respiratory function is dose-dependent. Therefore, respiratory cycle monitoring and management should be strengthened during the surgery.

Key Words: *Dezocine, Midazolam, Remifentanil, Liver tumours, Radiofrequency ablation, Tumour necrosis factor- α , Interleukin-6.*

INTRODUCTION

Radiofrequency ablation (RFA) is currently considered to be an effective minimally invasive treatment for small hepatocellular carcinoma. It has the characteristics of less trauma and faster postoperative recovery. It is the latest method for the treatment of primary and metastatic liver cancers.^{1,2} However, RFA often has a short operative time with strong intraoperative stimulation but less than resection, so general local anaesthesia or a single use of analgesic drugs cannot achieve satisfactory results.³ To improve the comfort of patients

during the RFA treatment and raise the thoroughness of the RFA treatment, intravenous anaesthesia can be used. Since remifentanil works faster and has small impacts on hemodynamics and hormone levels, it is often used for intravenous anaesthesia. However, the large dosage of remifentanil can easily cause respiratory depression.^{4,5} Dezocine is a synthetic drug of the benzomorphan group, an agonist of κ -opioid receptors and an antagonist of μ -opioid receptors. It has moderate analgesic and sedative effects and is very safe without respiratory depression.⁶ Under high temperature, RFA is prone to cause endotoxemia and releases cytokines such as interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α), which will aggravate the inflammatory reaction and cause tissue damage.⁷ Currently, the effects of dezocine-remifentanil intravenous anaesthesia on perioperative signs, serum TNF- α and IL-6 in liver cancer patients undergoing radiofrequency ablation (RFA) remain unclear.

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Received: April 19, 2018; Accepted: September 09, 2018

This study was conducted to determine the anaesthetic effect and safety of dezocine combined with remifentanyl and the impact on inflammatory factors in the RFA surgery, with a view to provide a reference for the anaesthetic management in the radiofrequency ablation of liver cancer.

METHODOLOGY

This study was conducted at the Renmin Hospital of Wuhan University, Wuhan, China, from January 2017 to February 2018. Eighty patients with small hepatocellular carcinoma, who underwent RFA, were selected as the research object. Inclusion criteria were patients who had RFA indications, no cardiovascular diseases, severe liver and kidney dysfunction, and had consented for the procedure. Exclusion criteria were patients with central nervous and mental diseases, history of long-term use of opioids, acute and chronic infections and patients taking non-steroidal anti-inflammatory drugs (NSAIDs) or hormones.

The study was approved by the Hospital Ethical and Research Committee, and all patients signed the informed consents. Eighty patients were divided into Group A and Group B by random number table method, with 40 cases in each group. Group A were given dezocine-remifentanyl intravenous anaesthesia and Group B were given midazolam-remifentanyl intravenous anaesthesia.

The two groups of patients were given regular fasting and no drinking before the surgery. Intraoperative detection of heart rate (HR), mean arterial pressure (MAP) and blood oxygen saturation (SpO₂) were performed during the surgery. The nasal oxygen inhalation were given at an oxygen flow of 2 L/minute. Group A: intravenous dezocine, loading dose 0.8 mg/kg. Group B: intravenous midazolam, loading dose 0.05~0.1 mg/kg. The loading doses in both groups were diluted to 20 ml with 0.9% sodium chloride solution and the injection time was 10 min. At 5 minutes after injection, intravenous remifentanyl at a loading dose of 0.2 μ g/Kg was given. After the start of the surgery, remifentanyl was pumped at 0.05 μ g/(Kg/minute). The speed of remifentanyl administration was adjusted according to hemodynamics. If patients showed hypotension [BP 90/60 mmHg (1 mmHg = 0.133 KPa)], ephedrine would be used to boost the blood pressure. If patients showed hypertension (BP \geq 140/90 mmHg), urapidil would be given to reduce the blood pressure. If patients showed bradycardia (HR \leq 60 times/min), atropine would be immediately used. For tachycardia (HR \geq 100 times/min), esmolol would be immediately used. For respiratory depression (SpO₂ <95%), mask-assisted ventilation would be given and mask-pressurised ventilation would also be selected when necessary. Anaesthesia was discontinued in both groups at the end of the surgery.

The postoperative wake-up time was recorded in both groups and the visual analogue scale (VAS) was used to evaluate the degree of pain in patients. The score ranged from 0 to 10 points. The higher the score was, the severer the pain would be. Changes of HR, MAP and SpO₂ before the surgery (T₀), at 5 min after the RFA (T₁) and at the end of the RFA (T₂) were recorded. The levels of TNF- α and IL-6 on the 1st day after the RFA were measured with the double antibody sandwich enzyme-linked immunosorbent assay (ELISA). The incidences of complications such as respiratory depression, hypotension, nausea and vomiting in the two groups during the surgery were recorded.

SPSS 21.0 statistical software was used for data analysis. Count data were expressed in n (%) and the χ^2 test was performed. Measurement data were expressed as mean \pm SD. The independent samples t-test was used for comparison between the groups. A difference with a p-value less than 0.05 was considered statistically significant.

RESULTS

Among the 80 patients, 41 (51.25%) were males and 39 (48.75%) were females; the age ranged from 29 to 67 (52.73 \pm 3.18) years; tumour diameter 1~5 (3.24 \pm 0.58) cm; body mass 44~72 (60.36 \pm 2.43) kg; ASA Grade I 37 cases (46.25%), ASA Grade II 43 cases (53.75%).

The wake-up time in Group A was shorter than Group B (p<0.001), and the VAS pain score in Group A was lower than Group B (p<0.001, Table I).

At T₁, the MAP in Group A was higher than Group B (p<0.001). There was no significant difference in MAP between the two groups at T₀ and T₂ (p=0.881, 0.696, respectively). At T₁ and T₂, the HR in Group A was lower than Group B (all p<0.001). There was no significant difference in HR between the two groups at T₀ (p=0.684). There was no significant difference in SpO₂ between the two groups at T₀, T₁ and T₂ (p=0.654, 0.884 and 0.798, respectively, Table II). On the first day after the RFA, the level of TNF- α IL-6 in Group A were lower than those of Group B (all p<0.001, Table III).

The incidence of intraoperative complications in Group A was 5.00% (2 cases), *i.e.* mild respiratory depression, and nausea and vomiting in one case each. The incidence of intraoperative complications in Group B was 7.50% (n=3), *i.e.* mild respiratory depression, hypotension, and nausea and vomiting in one case each. There was no significant difference in the

Table I: Comparison of wake-up time and VAS pain scores in the two groups.

Group	n	Wake-up time (min)		VAS pain scores (score)	
		Mean \pm SD	p-value	Mean \pm SD	p-value
Group A	40	5.34 \pm 0.68	<0.001	1.41 \pm 0.46	<0.001
Group B	40	9.02 \pm 1.01		3.95 \pm 0.56	

Table II: Comparison of MAP, HR and SpO₂ in the two groups at different time points.

Index	Group	n	T ₀		T ₁		T ₂	
			Mean ±SD	p-value	Mean ±SD	p-value	Mean ±SD	p-value
MAP (mmHg)	Group A	40	95.02 ±5.99	0.881	81.45 ±3.54	<0.001	83.17 ±4.05	0.696
	Group B	40	94.86 ±3.04		72.62 ±4.56		82.75 ±5.43	
HR (frequency/min)	Group A	40	88.59 ±3.84	0.684	63.08 ±5.57	<0.001	76.26 ±7.09	<0.001
	Group B	40	89.01 ±5.26		72.16 ±6.08		83.04 ±7.60	
SpO ₂ (%)	Group A	40	98.04 ±1.01	0.654	93.28 ±1.62	0.884	93.91 ±1.27	0.798
	Group B	40	98.17 ±1.52		93.34 ±2.03		94.02 ±2.40	

Table III: Comparison of TNF- α and IL-6 levels in the two groups on the 1st day after the RFA.

Group	n	TNF- α (pg/mL)		IL-6 (pg/mL)	
		Mean ±SD	p-value	Mean ±SD	p-value
Group A	40	31.74 ±5.72	<0.001	103.41 ±15.19	<0.001
Group B	40	43.66 ±5.40		152.38 ±25.32	

incidence of intraoperative complications between the two groups (p=0.644).

DISCUSSION

Radiofrequency ablation for liver cancer is a minimally invasive operation that can effectively treat small hepatocellular carcinoma. The radiofrequency electrode needle can raise the local centre temperature to 90°C or above, resulting in the solidification and necrosis of liver cancer tissues and thus killing cancer cells.^{8,9} Radiofrequency ablation for liver cancer does not require muscle relaxation and the operative time is short. However, the patient usually has a high fever, abdominal pain and other discomforts, so it is necessary to maintain a moderate degree of sedation and analgesia, and intravenous general anaesthesia without tracheal intubation is always selected.

Remifentanyl, as a new-type ultrashort opioid analgesic agent, works fast and can be quickly metabolised, without drug accumulation. In clinical practice, the dosage is highly controllable as the infusion speed can be adjusted according to the patient's intraoperative blood pressure, SpO₂, etc.^{10,11} In addition, remifentanyl is mainly metabolised by non-specific hydrolysis in blood and tissues, and a small amount of unmetabolised drugs can be antagonised by opioid receptor antagonists without affecting liver and kidney function.^{12,13}

Dezocine has a stronger analgesic effect than other opioids.¹⁴ In addition, dezocine can relax the gastrointestinal smooth muscle, reduce the occurrence of adverse reactions such as nausea and vomiting, and has few adverse reactions to respiratory depression, and there is generally no significant respiratory depression at therapeutic doses. Dezocine also has a sedative effect and the patient can be awakened, which can help with the patient's short breath holding action required by the RFA for liver cancer, and also can achieve moderate sedation and analgesia. It is an ideal

intraoperative and postoperative intravenous analgesic agent.¹⁵⁻¹⁷

The results of this study showed that there were significant differences between the two groups in postoperative wake-up time and VAS pain scores. The decrease of HR at T₁ and T₂ in Group A was significant and obviously lower than that in Group B. The reason may be that the effect of remifentanyl on the respiratory function was dose-dependent, and the increased dose may cause respiratory depression. In addition, because some elderly patients had decreased respiratory and drug metabolism functions, the risk of respiratory depression during anaesthesia increased.¹⁸ There was no significant difference in the incidence of intraoperative complications between the two groups, but mild respiratory depression occurred in two cases in this study. Therefore, clinical attention should be paid to the dynamic monitoring of the respiratory circulation. The speed of remifentanyl infusion should be adjusted according to the changes of HR to improve the safety of the surgery.

TNF- α and IL-6 are important pro-inflammatory factors, in which TNF- α can activate endothelial cells, cause neutrophil aggregation, promote the release of IL-6 and other inflammatory factors. IL-6 can be transformed into hepatocyte activating factors under stress conditions and induce the production of acute-phase reactive proteins.^{19,20} Remifentanyl can reduce the concentration of serum TNF- α and decrease the inflammatory level of the body. Dezocine can regulate the level of cytokines during the perioperative period of liver cancer RFA and reduce tumour angiogenesis.²¹ The results of this study showed that the levels of TNF- α and IL-6 in Group A after the RFA were lower than those in Group B, suggesting that dezocine-remifentanyl intravenous anaesthesia had more advantages in regulating the release of cytokines.

CONCLUSION

Compared with midazolam-remifentanyl intravenous anaesthesia, the dezocine-remifentanyl method has a better analgesic effect, shorter wake-up time, and can effectively regulate the expression of inflammatory cytokines TNF- α and IL-6. However, the effect of remifentanyl on the respiratory function is dose-

dependent. Therefore, respiratory cycle monitoring and management should be strengthened during the surgery.

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