European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2014; 18: 3212-3216

Clinical application of remifentanil in local anesthesia for tumor resection in functional brain area

S.-E. CAO, B.-Q. GAO[1], Y.-Q. ZHANG[1], S.-M. YANG, G.-Z. LIU, X.-R. ZHANG

Department of Anesthesia of the First Affiliated Hospital, Xinxiang Medical University, Weihui, Henan, China
[1]Operating Room of the First Affiliated Hospital, Xinxiang Medical University, Weihui, Henan, China

Abstract. – OBJECTIVE: The aim of this study was to investigate clinical application of remifentanil in local anesthesia for resection of tumors in functional brain area.

PATIENTS AND METHODS: Twenty-four patients were randomly divided into two groups: control group and remifentanil group. In remifentanil group remifentanil was infused intravenously with micro pump in 0.05-0.1 μg·kg-1·min-1. The hemodynamic changes and complications during operation were monitored.

RESULTS: The satisfactory degree for surgical procedure was evaluated. The surgery of two groups could be completed in a conscious state. Mean artery pressure (MAP), heart rate (HR) in remifentanil group during opening or closing skull or intra- cranial period were significantly lower than control group ($p < 0.05$). There were no conspicuous complications in two groups such as respiratory depression, nausea, vomitting and dysphoria. Satisfaction rate of remifentanyl group was significantly higher than control group ($p < 0.05$).

CONCLUSIONS: Awake brain tumor surgery could be completed in rational use of remifentanil on the base of good local anesthesia, and hemodynamics were stable and the patients were well tolerated.

Key Words:
Remifentanil, Awake anesthesia, Brain tumor.

Introduction

Remifentanil is a μ-opioid receptor agonist with ultra-short performance, rapid onset, short duration of action and fast clearance. Its metabolism does not depend on the liver and kidney functions, and repeated administrations and continuous infusion do not result in the drug accumulation in the body[1]. The ideal anesthetic agents should meet the needs of quick changes in sedation and analgesia during the surgical operation and easily subject to postoperative evaluation of nerve functions. Remifentanil fits the description of such a drug and has increasingly been used in the clinical settings. However, the majority of publically available data are generated from clinical trials in Europe and North America[2,3]. There are few reports in China that remifentanil has been used to help surgically remove tumors in the functional areas of brain under local anesthesia. From 2009 to 2010, 24 cases of awake craniotomy surgery under remifentanil anesthesia have been successfully performed in our hospital and the results appear promising. We hope to find a safe and effective method of anesthesia for Chinese.

Patients and Methods

Patient General Information

24 patients with intracranial frontal glioma were recruited in this study, including 14 in the left side and 10 in the right side, respectively. Their ages were from 20 to 60 years old and both sexes included. This study was conducted in accordance with the Declaration of Helsinki and approved from the Ethics Committee of First Affiliated Hospital of Xinxiang Medical University. Written informed consent was obtained from all participants. Their ASA classification defined as II or III and the body weight index 30 kg/m. All patients had no alcoholic and drug abuse history. Patients with current diagnosis of opioid-drug allergies, severe heart, lung, liver and kidney dysfunctions were excluded. Eligible patients were randomly divided into remifentanil group and control group, 12 patients for each group.

Prior to the operation, patient's condition, surgical procedure, unforeseen circumstances and guidance with elements of the language and physical movements monitoring were fully discussed and planned accordingly. Additionally,

Corresponding Author: Xiu-Qin Yue, MD; e-mail: yqmhcn@126.com

efforts were made to relieve patient's anxiety and fear and obtain their understanding and trust. Finally, assessments of patient's airway function, language and pattern recognition abilities and lime movement were performed before the operation.

Medication Before Anesthesia

Midazolam 0.02-0.05 mg/kg, hydrochloric acid penehyclidine microphone 1 mg i.v. Patients were monitored for ECG, BP, SpO_2 before the surgery, and 0.2% ropivacaine (dose < 3 mg/kg) was injected locally and allowed to infiltrate to have anesthetic effects. Oxygen was given to the patient wearing a oxygen mask. In the treatment group, remifentanil was given intravenously by a micro pump at a constant flow rate of 0.1 µg/kg · min. The amount of anesthetic used in the operation could be adequately increased when strong stimulus such as nailing, opening and closing the skull occurred or decreased when tumors were being removed. The control group received saline instead of remifentanil. Patients in both groups were kept conscious throughout the procedure. And the brain functions were monitored with a method of continuous counting by the patients. After removal of the tumors, patient's language and movement abilities were assessed again. Patients were well informed for the discomfort due to keeping a certain position for a long time during the operation and the craniotomy drilling. Patients were also advised to tell surgeon and anesthesiologist when any discomfort occurred to them.

Monitoring Parameters

Mean arterial pressure (MAP) and heart rates (HR) were monitored before, during and after craniotomy, intracranial surgery and craniotomy closure. Complications associated with the operation such as respiratory depression (through the monitoring of PCO_2 and PaO_2), nausea, vomiting, body movement, bleeding, cerebral edema and anesthetic toxicity were closed observed and monitored. Patients were required after the operation to give a satisfaction score for the experience of pain and comfort during the operation, the satisfaction scores were defined as: 4, very good; 3, good; 2, fair; 1, poor.

Statistic Analysis

SPSS13.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the date, and single-factor analysis of variance for quantification and χ^2 test was used for data comparison. $p < 0.05$ was considered statistically significant.

Results

General Information

All patients successfully completed the operation. The hemodynamic of these patients was generally stable during the operation and the patients had good compliance of continuously counting numbers. All surgeries went well with clear lesions, good surgical conditions and complete removal of tumors examined under the microscope.

Patients' general information including age, sex, body weight, ASA classification, operation time and statistical significance ($p > 0.05$) (Table I).

Hemodynamic Changes

The MAP and HR of two groups did not show statistically significant differences before the operation, but remifentanil group showed statistically significant lower values compared with control group in MAP and HR during skull drilling, intracranial surgery and craniotomy closure ($p < 0.05$) (Table II).

Comparison of Complications Between Two Groups

Two groups at selected time points showed values of PCO_2 and PaO_2 within normal ranges without statistical significance ($p > 0.05$). Patients did not show nausea, vomiting, cerebral edema and anesthetic toxicity during the operation and the satisfactory scores given by the patients from remifentanil group were significantly higher than those from control group ($p < 0.05$) (Tables III and IV).

Table I. Hemodynamic changes between two groups (n = 12).

Mean age	Sex (F/M)	Body weight (kg)	ASA (II/III)	Operation	Time (min)
Remifentanil	47.3 ± 4.2	6/6	24.8 ± 3.2	7/5	187.2 ± 21.8
Control	46.5 ± 5.6	5/7	25.5 ± 2.5	7/5	183.5 ± 19.6

Table II. General information between remifentanil and control groups (n = 12, $\bar{x} \pm s$).

Gruop	No.	Parameters	Before	Drilling	Intracranial	Closure
Remifentanil	12	MAP (mmHg)	83.1 ± 6.3	78.5 ± 6.2[a]	74.8 ± 5.3[a]	76.2 ± 5.8[a]
		HR (time/min)	80.7 ± 7.2	76.1 ± 5.9[a]	73.7 ± 6.[a]	75.8 ± 6.5[a]
Control	12	MAP (mmHg)	82.8 ± 7.6	92.5 ± 7.3	89.2 ± 5.6	91.5 ± 8.2
		HR (time/min)	79.6 ± 6.4	94.4 ± 9.8	90.5 ± 6.6	93.4 ± 7.

Note: Statistically significant, $^{a}p < 0.05$.

Discussion

Applications of functional neuroimaging, wake-upanesthesia, intraoperative electrophysiological and lesion localization technologies in recent years have significantly improved the quality of neurosurgery[4,5]. Although wake-up anesthetic craniotomy is safe and able to reduce patient's anxiety and fear, it is still a complicated procedure, in which patient's consciousness does not meet the requirements for live monitoring[6,7].

Awake craniotomy technique is capable of avoiding general anesthesia and enabling patents to keep conscious and to communicate with doctors throughout the operation. Thus, the surgical doctors have better chance to precisely locate the functional areas of brain and to remove tumors. As a result, patients have lower rates of disease relapse[8-10]. We have used local infiltrating anesthesia technique with remifentanil administered by a small pump for brain surgery and the results showed that the patients had excellent compliance, cooperated well with surgical doctors and had few complications associated with the anesthesia. Compared with control gruop, patients with remifentanil showed better MAP and HR at selected time points of operation and higher scores of patient satisfaction.

Remifentanil is a μ-opioid receptor agonist and has good analgesic effects with short duration of action and controllability. It is also capable of suppressing cardiovascular stress response of surgery[11,12]. The low-dose regimen of remifentanil could be routinely used to modify hemodynamic responses to tracheal intubation in patients with diverse hemodynamic characteristics[13]. And the complication carsed by removal of LMA can be reduced without any delay in recovery time[14]. Using remifentanil as the sole analgesic allows evaluation of the larynx with direct laryngoscopy and other operation in conscious patient[15-17]. Application of midazolam before surgery has multiple effects of reducing anxiety, inducing hypnosis and anterograde amnesia, and increasing local anesthetic seizure threshold. The combinational use of remifentanil and midazolam in awake

Table III. Changes in respiratory parameters at selected time points (n = 12, $\bar{x} \pm s$).

Gruop	No.	Parameters	Before	Drilling	Intracranial	Closure
Remifentanil	12	PCO_2 (mmHg)	38.1 ± 4.3	38.5 ± 3.2	39.5 ± 5.0	41.2 ± 3.5
		PaO_2 (mmHg)	88.3 ± 6.4	87.5 ± 3.7	86.8 ± 4.4	86.2 ± 5.1
Control	12	PCO_2 (mmHg)	37.3 ± 3.8	39.5 ± 4.5	38.7 ± 4.0	40.6 ± 3.8
		PaO_2 (mmHg)	87.3 ± 4.1	87.8 ± 4.4	88.1 ± 5.4	88.7 ± 3.5

Table IV. Comparison of satisfactory scores between two groups (n=12).

Gruop	No	Anxiety	Nausea vomiting	Cerebral edema	Anesthetic toxicity	Satisfatory scores
Remifentanil	12	0	0	0	0	3.3 ± 0.6[a]
Control	12	0	0	0	0	2.4 ± 0.5

Note: Statistically significant $^{a}p < 0.05$.

craniotomy surgeries enables to facilitate the rapid adjustment of analgesic depth and ensure the patients' cooperation, while reducing patients' bad memories of the surgical operation. Remifentanil has been reported to have many side effects including respiratory depression, nausea, vomiting and anxiety. Some research showed remifentanil can improve respiratory pattern and decreased inspiratory muscles effort in patients, but did not affect oxygenation or sedation[18]. However, the results of this study show that values of PCO_2 and PaO_2 at selected time points are all in the normal ranges when remifentanil is administered at 0.05-0.1 µg/kg · min[19,20] and that no carbon dioxide accumulation and hypoxic respiratory depression were observed, possibly due to the low dose of remifentanil, indicating that this dose can be safely used in such type of surgery.

Despite the fact that patients well tolerated the procedure due to the shallow locations of the tumors and short duration of operations and that the relatively smooth completion of the surgical operation under the conscious sedation in this study, we would like to suggest that the awake anesthetic craniotomy would be better performed for those patients who are relatively young with good functions of heart and lungs, and strong mentality, to make sure the safety and smooth cooperation between patient and doctor throughout the surgery. It often happens that some patients are worried about the risks of wake-up anesthetic craniotomy or misunderstand the steps of the procedure, so they need to be educated in details in advance about what they would see, hear and feel during the surgical operation. It is usually the case that the education of patients would eliminate those worries. Besides the regular assessments, it is important to assess patients' additional capabilities including language, pattern recognition, physical activity and tolerance of the surgical procedures. Those patients unable to cooperate or have language barriers or have mental confusion should not be eligible for the awake anesthetic craniotomy.

Sound monitoring during the surgical operation requires patient to full understand what is going on and to cooperate well, there are currently two methods for sound monitoring, one is to ask patient to continuously count numbers and speak out and the other to recognize certain items. The method of counting numbers is relatively easier to use and to detect the interruption of the language; however, the areas in the brain responsible for these two functions are separately located. Electronic stimulation and functional magnetic resonance imaging techniques have indicated that item recognition is more precisely located in the language areas of brain[21].

Conclusions

In general, the use of remifentanil under the condition of good local infiltrating anesthesia, awake anesthetic craniotomy can be safely performed with stable hemodynamics, few side effects and good patient satisfaction.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Vennila R, Hall A, Ali M, Bhuiyan N, Pirotta D, Raw DA. Remifentanil as single agent to facilitate awake fibreoptic intubation in the absence of premedication. Anaesthesia 2011; 66: 368-372.
2) Del Gaudio A, Ciritella P, Perrotta F, Puopolo M, Lauta E, Mastronardi P, De Vivo P. Remifentanil vs fentanyl with a target controlled propofol infusion in patients undergoing craniotomy for supratentorial lesions. Minerva Anestesiol 2006; 72: 309-319.
3) Sneyd JR, Andrews CJ, Tsubokawa T. Comparison of propofol/remifentanil and sevoflurane/remifentanil for maintenance of anesthesia for elective intracranial surgery. Br J Anaesth 2005; 94: 778-783.
4) Zhang Z, Jiang T, Xie J. Awake craniotomy and intraoperative functional mapping for surgery of gliomas located in language areas. Chin J Neurosurg 2007; 23: 643-645.
5) Olsen KS. The asleep-awake technique using propofol-remifentanil anaesthesia for awake craniotomy for cerebral tumours. Eur J Anaesthesiol 2008; 25: 662-669.
6) Skoglund K, Enblad P, Marklund N. Effects of the neurological wake-up test on intracranial pressure and cerebral perfusion pressure in brain-injured patients. Neurocrit Care 2009; 11: 135-142.
7) Rehberg S, Weber TP, Van Aken H, Theisen M, Ertmer C. Sleep disturbances after posterior scoliosis surgery with an intraoperative wake-up test using remifentanil. Anesthesiology 2008; 109: 629-641.
8) Deipolyi AR, Han SJ, Sughrue ME, Litt L, Parsa AT. Awake far lateral craniotomy for resection of foramen magnum meningioma in a patient with tenuous motor and somatosensory evoked potentials. J Clin Neurosci 2011; 18: 1254-1256.

9) Klimek M, Vincent AJ. Awake craniotomy for brain tumor resection–what does the anaesthesist do? AINS 2011; 46: 386-391.

10) Bonhomme V, Franssen C, Hans P. Awake craniotomy. Eur J Anaesthesiol 2009; 26: 906-912.

11) Zhao GF, Zhang XA, Wu QL. Target- controlled infusion of propofol for TIVA with remifentanil or fentanyl. Guangdong Med J 2004; 25: 765-767.

12) Demirbilek S, Ganidagli S, Aksoy N. The effects of remifentanil and alfentanil-based total intravenous anesthesia (TIVA) on the endocrine response to abdominal hysterectomy. Clin Anesth 2004; 16: 358-363.

13) Park SJ, Shim YH, Yoo JH, Nam SH, Lee JW. Low-dose remifentanil to modify hemodynamic responses to tracheal intubation: comparison in normotensive and untreated/treated hypertensive Korean patients. KJA 2012; 62: 135-141.

14) Ozkan D, Ergil J, Alptekin A, Aktürk N, Gümüs H. Target controlled remifentanil infusion for smooth laryngeal mask airway removal during emergence from desflurane-remifentanil anesthesia. J Anesth 2012; 26: 369-374.

15) Gupta S, Macneil R, Bryson G. Laryngoscopy in conscious patients with remifentanil: how useful is an “awake look”? J Clin Anesth 2012; 24: 19-24.

16) Song JW, Kwak YL, Lee JW, Chang CH, Kim HS, Shim YH. The optimal effect site concentration of remifentanil in combination with intravenous midazolam and topical lidocaine for awake fibreoptic nasotracheal intubation in patients undergoing cervical spine surgery. Minerva Anestesiol 2012; 78: 521-526.

17) Majholm B, Bartholdy J, Clausen HV, Virkus RA, Engbæk J, Møller AM. Comparison between local anaesthesia with remifentanil and total intravenous anaesthesia for operative hysteroscopic procedures in day surgery. Br J Anaesth 2012; 108: 245-253.

18) Natalini G, Di Maio A, Rosano A, Ferretti P, Bertelli M, Bernardini A. Remifentanil improves breathing pattern and reduces inspiratory workload in tachypneic patients. Respir Care 2011; 56: 827-833.

19) Geng ZY, Xu X. Clinical pharmacology of remifentanil. Int J Anesthesiol Resus 2004; 25: 203-206.

20) Renna M, Chung R, Li W, Maguire C, Mullen MJ, Chambers J, Henein MY. Remifentanil plus low-dose midazolam for outpatient sedation in transesophageal echocardiography. Int J Cardiol 2009; 136: 325-329.

21) Petrovich Brennan NM, Whalen S, de Morales Branco D, O'shea JP, Norton IH, Golby AJ. Object naming is a more sensitive measure of speech localization than number counting: Converging evidence from direct cortical stimulation and MRI. Neuroimage 2007; 37: 100-108.