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Original Research Article

Effect of remifentanil co-administered with propofol on stress response and postoperative complications in patients with cerebral hemorrhage undergoing surgical anesthesia

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Abstract

Purpose: *To determine the anesthetic effect and related indicators following concurrent administration of remifentanil and propofol in cerebral hemorrhage surgery patients.*
Methods: *A total of 88 cerebral hemorrhage patients admitted in Lishui People's District Hospital, Nanjing, China, from December 2019 to December 2020, were assigned to two groups, viz, control group which received fentanyl and propofol for anesthesia, while study group was administered remientanil combined with propofol for anesthesia There were 44 patients in each group. Hemodynamic index, brain injury marker index, stress response index, awakening condition, propofol dosage, anesthetic effect, and adverse reactions were assessed and recorded.*
Results: *Heart rate (HR), diastolic blood pressure (DBP), and systolic blood pressure (SBP) at T2 and T3 of the two groups were less than those at T1. At T3, the study group's HR, DBP, and SBP were substantially higher than those of control group ($p < 0.05$); At 12 and 24 h after operation, brain injury markers and stress response indices in study group were significantly lower compared to control group ($p < 0.05$), while in comparison to control group (79.55 %), the degree of anesthesia in the study group was higher (95.45 %; $p < 0.05$). The incidence of adverse reactions in the study group (15.91 %) was lower than in control group (43.18 %; $p < 0.05$).*
Conclusion: *Remifentanil, when combined with propofol anesthesia, stabilizes hemodynamics, protects against brain injury, and reduces stress reactions in patients undergoing cerebral hemorrhage surgery. The combination is also highly effective and safe. However, validation of these findings in larger clinical trials is required.*

Keywords: *Remifentanil, Propofol, Fentanyl, Cerebral hemorrhage, Anesthesia, Stress response, Adverse reactions, Hemodynamics*

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INTRODUCTION

Cerebral hemorrhage, a prevalent disease which disproportionately affects the middle-aged and elderly population, is characterized by a high rate of disability, high mortality, high morbidity, and poor postoperative prognosis. It is typically treated via surgery [1]. Currently, minimally

invasive cerebral hemorrhage surgery is the primary surgical therapy, as it lowers the risk of brain injury and associated problems by reducing intracranial blood pressure and eliminating hematomas [2,3]. General anesthesia administered safely is essential for the success of surgical treatment and the comfort of the patient during the operation.

Propofol is the standard clinical anesthetic, and is frequently combined with a powerful narcotic analgesic such as fentanyl [4]. However, reports indicate that there are still divergent views in the medical field regarding the clinical effects of both remifentanil and fentanyl, suggesting the need for further research and verification [5].

METHODS

Patient's clinical data

Eighty-eight (88) patients with cerebral hemorrhage who were admitted to Lishui District People's Hospital (Lishui Hospital, Zhongda Hospital, Southeast University) for surgery between December 2019 and December 2020 were recruited for this study. They were assigned to two groups, *viz*, study and control, with 44 patients in each group.

Inclusion criteria

All met the diagnostic criteria for cerebral hemorrhage. These include minimally invasive drainage treatment for cerebral hemorrhage; and the patients fulfilled the relevant clinical indications.

Exclusion criteria

Patients with a history of cerebral infarction or cranial trauma; allergy to the relevant drugs.

Ethical approval

All procedures involving human participants were approved by the Ethics Committee of Lishui District People's Hospital (Lishui Hospital, Zhongda Hospital, Southeast University; approval no. 2019-075) and followed the guidelines the 1964 Helsinki Declaration and its later amendments for ethical research including human subjects [6].

Anesthesia

All patients were given atropine (Henan Runhong Pharmaceutical Co. Ltd; National Medicine Permission no. H41020324; strength: 0.5 mg/mL) 0.5 mg and phenobarbital (Suicheng Pharmaceutical Co. Ltd; National Medicine Permission no. H41025613; strength: 1 ml: 0.1g) 100 mg injection.

A standardized anesthesia protocol was used as follows: The control group was given midazolam (National Medicine Permission no. H20153019; Jiangsu Jiuxu Pharmaceutical Co. Ltd; strength: 3 ml: 15 mg) 0.05~0.08 mg/kg + propofol (Approval No.: H20170310; Imported Sub-Approval No.: National Medicine Permission no. J20171056; Fresenius Kabi Deutschland GmbH; Specification: 50 ml: 0.5 g) 1.5~2.0 mg/kg + vecuronium bromide (approval no.: National Medicine Permission no. H19991172; Zhejiang Xianju Pharmaceutical Co. Ltd; specification: 4 mg) 0.08 - 0.12 mg/kg + fentanyl, National Medicine permission no. H20054171; Yichang Renfu Pharmaceutical Co. Ltd; strength: 1 ml: 50 μg) 2.0~3.0 μg/kg intravenous infusion for induction of anesthesia. In the study group, fentanyl was replaced with remifentanil (National Medicine permission no. H20123421; Sinopharm Group Industry Co. Ltd, Langfang Branch; strength: 2 mg) 1.5 ~ 2.0 μg/kg in the control group.

After the induction of anesthesia, patients were given tracheal intubation and intermittent positive pressure ventilation. Then, the control group received propofol (4.6 - 6 mg/(kg.h)) with fentanyl (0.05 - 0.10 μg/(kg.h)), while the study group accepted propofol (4.6 - 6 mg/(kg.h)) with remifentanil (0.15 - 0.20 μg/(kg.min)) through micropump, respectively; 2 mg of vecuronium bromide was pushed intravenously after an interval of 0.5 to 1 h. During the surgery, the depth of the anesthesia was promptly adjusted according to the patient's vital signs, and the medication was discontinued immediately after the operation.

Evaluation of parameters/indices

Hemodynamic derangement

The SBP, HR, and DBP at T1 (before anesthesia), T2 (after induction of anesthesia), T3 (after intubation), T4 (after puncture drilling), and T5 (after surgery) were measured.

Brain injury markers and stress response indicators

The expressions of Hep, NSE, S100β, Asp, HA, MMP9, OPN, ICAM-1, and Cor were determined by enzyme-linked immunosorbent assay [7]and radioimmunoprecipitation method [8].

Resuscitation and propofol dose

Resuscitation includes autonomous respiratory recovery time and the time to consciousness.

Anesthesia effect

Excellent: Patients behaved quietly during the operation; *good* = patients behaved with mild movement and facial expression changes during the operation; *poor* = patients behaved with obvious agitation during the operation; *excellent* = (excellent + good)/total no. of patients.

Statistical analysis

Using statistical analysis tool SPSS 23.0 software, all data were assessed. Count data were reported as n and %, and comparison between the groups was carried out by χ^2 test. Measurement data were expressed as mean ± SD, and significant differences were determined using Student's t-test. $P < 0.05$ was regarded as statistically significant.

RESULTS

General patient information

Between the two patient groups, there were not any noticeable differences in any clinically relevant clinical data ($p < 0.05$; Table 1).

Hemodynamics

In both groups, HR, DBP, and SBP levels at T2 and T3 were significantly lower than those at T1 ($p < 0.05$). Additionally, as compared to the control group, the HR, DBP, and SBP levels at T3 in the study group was higher ($p < 0.05$; Table 2).

Brain injury markers

Postoperatively, at 12 h and 24 h, the study group had lower levels of brain injury markers than the control group ($p < 0.05$; Table 3).

Stress response indicators

At 12 h and 24 h postoperatively, all stress response indicators were significantly lower in the study group than in the control group ($p < 0.05$; Table 4).

Resuscitation and propofol dose

The time to recovery of spontaneous respiration and time to consciousness were shorter in the study group compared to the control group, and a similar result in the dose of propofol ($p < 0.05$; Table 5).

Table 1: Comparison of clinical data between the two groups

Indicator		Study group (n = 44)	Control group (n = 44)	t/χ^2 value	*P*-value
Gender {(n, %)}	*Male*	28（63.64）	27（61.36）	0.0485	0.8257
	Female	16（36.36）	17（38.64）		
Age (years)		58.34 ± 5.60	57.98 ± 5.71	0.2986	0.7660
Bleeding location (n, %)	*Basal ganglia*	19（43.18）	20（45.45）	0.5166	0.9152
	Thalamic area	14（31.82）	14（31.82）		
	Lobe area	5（11.36）	6（13.64）		
	Others	6（13.64）	4（9.09）		
Drinking history	*Yes*	8（18.18）	7（15.91）	0.0804	0.7768
	No	36（81.82）	37（84.09）		
Smoking history	*Yes*	16（36.36）	17（38.64）	0.0485	0.8257
	No	28（63.64）	27（61.36）		
History of oral antihypertensive drugs	*Yes*	38（86.36）	37（84.09）	0.0903	0.7639
	No	6（13.64）	7（15.91）		
Family history of brain hemorrhage	*Yes*	13（29.55）	14（31.82）	0.0534	0.8172
	No	31（70.45）	30（68.18）		
Complications (n, %)	*Hypertension*	10（22.73）	9（20.45）	0.0759	0.9628
	Hyperlipidemia	21（47.73）	22（50.00）		
	Others	13（29.55）	13（29.55）		
Anemia	*Yes*	4（9.09）	5（11.36）	0.1238	0.7250
	No	40（90.91）	39（88.64）		
Bleeding volume (ml)		18.57 ± 1.82	18.59 ± 1.90	0.0504	0.9599
Registered residence	*Not local*	4（9.09）	5（11.36）	0.1238	0.7250
	Local	40（90.91）	39（88.64）		

Table 2: Comparison of hemodynamics between the two groups (mean ± SD, n = 44)

Indicator	Group	T1	T2	T3	T4	T5
HR (bpm/min)	Study	79.52 ± 4.49	67.91 ± 4.82*	69.52 ± 3.55*	79.89 ± 4.22	78.36 ± 4.14
	Control	80.25 ± 4.33	68.23 ± 4.90*	58.23 ± 3.69*	81.26 ± 4.64	80.36 ± 5.15
t value	——	0.7763	0.3088	14.6257	1.4489	2.0077
P-value	——	0.4397	0.7582	0.0000	0.1510	0.0500
DBP (mmHg)	Study	73.20 ± 4.21	62.26 ± 4.51*	62.50 ± 4.44*	71.39 ± 4.49	71.98 ± 5.62
	Control	72.95 ± 4.25	61.98 ± 4.76*	52.27 ± 4.10*	71.86 ± 4.31	73.14 ± 6.24
t value	——	0.2772	0.3136	11.2283	0.5009	0.9163
P-value	——	0.7823	0.7546	0.0000	0.6177	0.3621
SBP (mmHg)	Study	127.52 ± 11.25	99.43 ± 8.60*	108.25 ± 8.34*	127.30 ± 9.01	129.43 ± 8.36
	Control	126.91 ± 11.31	96.34 ± 9.05*	95.34 ± 7.64*	124.95 ± 9.53	128.95 ± 9.05
t value	——	0.2536	1.6418	7.5714	1.1886	0.2584
P-value	——	0.8004	0.1043	0.0000	0.2379	0.7967

***Note*:** *Differences were significant compared with T1 ($p < 0.05$)

Table 3: Comparison of levels of markers of brain injury between the two groups (mean ± SD, n = 44)

Group	Hep (ng/mL)		NSE (pg/mL)		S100β (pg/mL)		Asp (μmol/L)	
	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h
Study	27.35 ± 2.16	22.16 ± 2.06	15.24 ± 1.64	12.84 ± 1.06	1.43 ± 0.21	1.13 ± 0.18	28.94 ± 4.15	22.35 ± 3.46
Control	38.45 ± 3.46	31.26 ± 3.26	26.35 ± 2.06	22.16 ± 1.98	2.21 ± 0.31	1.87 ± 0.26	40.13 ± 4.23	35.34 ± 3.22
t value	18.0513	15.6529	27.9881	27.5267	13.8181	15.5224	12.5259	18.2303
P value	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 4: Comparison of stress response indicators between the two groups (mean ± SD, n = 44)

Group	HA (μg/mL)		MMP9 (ng/mL)		OPN (ng/mL)		ICAM-1 (μg/mL)		Cor (ng/mL)	
	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h	Postoperative 12h	Postoperative 24h
Study	0.63 ± 0.09	0.50 ± 0.07	103.54 ± 9.35	83.46 ± 7.65	6.43 ± 0.61	5.82 ± 0.56	0.51 ± 0.06	0.36 ± 0.04	221.35± 20.15	205.24±19.65
Control	0.84 ± 0.11	0.74 ± 0.12	163.55 ± 9.42	125.34 ± 9.16	9.22 ± 0.75	8.36 ± 0.96	0.72 ± 0.08	0.57 ± 0.06	314.57± 26.35	252.34±26.34
t value	9.801	11.4593	29.9915	23.2774	19.1433	15.1597	13.9298	19.3172	18.6411	9.5072
P-value	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 5: Comparison of resuscitation and propofol dosage between the two groups (mean ± SD, n = 44)

Group	Time to recovery of spontaneous respiration (min)	Time to consciousness (min)	Propofol dose (mg)
Study	5.54 ± 0.51	13.14 ± 1.34	136.45 ± 13.33
Control	7.20 ± 0.73	15.95 ± 1.63	301.95 ± 19.23
t value	12.3651	8.8335	46.918
P-value	0.0000	0.0000	0.0000

Table 6: Comparison of anesthetic effects between the two groups (n, %)

Group	N	Excellent	Good	Poor	Excellent number
Study	44	23 (52.27)	19 (43.18)	2 (4.55)	42 (95.45)
Control	44	19 (43.18)	16 (36.36)	9 (20.45)	35 (79.55)
χ^2 value					5.0909
p value					0.0241

Table 7: Comparison of adverse reactions between the two groups (n, %)

Group	n	Hypotensive	Tachycardia	Respiratory depression	Bradycardia	Adverse reactions
Study	44	2 (4.55)	1 (2.27)	2 (4.55)	2 (4.55)	7 (15.91)
Control	44	7 (15.91)	3 (6.82)	5 (11.36)	4 (9.09)	19 (43.18)
χ^2 value						7.8610
P-value						0.0051

Degree of anesthetic effect

The degree of anesthesia in the study group was 95.45 %, which was higher than the 79.55 % in the control group ($p < 0.05$; Table 6).

Incidence of adverse reactions

In contrast to the 43.18% incidence in the control group, there were 15.91% fewer adverse events in the study group ($p < 0.05$; Table 7).

DISCUSSION

Cerebral hemorrhage, one of the prevalent critical illnesses, manifests mainly impaired consciousness, sudden headache, aphasia, hemiparesis of one limb, nausea, and vomiting [9]. The pathogenesis of cerebral hemorrhage involves a non-traumatic vascular rupture in the brain parenchyma, which could result in neurological damage, and poses a significant life-threatening risk to patients [10]. Currently, minimally invasive cerebral hemorrhage drainage is the mainstay in the cerebral hemorrhage medical therapy.

Minimally invasive drainage of cerebral hemorrhage may successfully removes the hematoma from the patient's brain, thereby reducing intracranial pressure and decreasing the risk of secondary brain injury. This treatment is simple, minimally invasive, has few complications, and is safe, and it does not cause any significant damage to brain tissue or surrounding blood vessels [11].

The primary steps in minimally invasive drainage for cerebral hemorrhage are: identifying the site of the hemorrhage via cranial CT, selecting a puncture site based on the clinical diagnosis, using urokinase to break up the blood clot in the brain, removing the clot using suction and drainage, and successfully draining the blood out. During minimally invasive drainage of cerebral hemorrhage, patients necessitate general anesthesia with tracheal intubation and stable hemodynamics [12]. Therefore, careful selection of medication is required to achieve the necessary level of anesthesia for performing minimally invasive drainage of cerebral hemorrhage, and to reduce secondary cerebral hemorrhage-related damage to neurological function, ensuring a safe surgical procedure.

Propofol is a short-acting intravenous anesthetic with rapid onset of action, sedative, and hypnotic effects, and can also block chemoreceptors and vagus nerve afferent fibers, thus functioning as an antiemetic, but which may cause discomforts such as eruption and cough [13]. Additionally, fentanyl is an opioid agonist and a strong narcotic analgesic, characterized by rapid analgesia and short duration. It is frequently used as an adjunct to anesthesia, with common adverse effects including nausea and vomiting, cardiac arrhythmias, and depressed respiration [14]. Similarly, remifentanil, a μ-type opioid

receptor agonist of fentanyl, has a rapid onset of action and metabolism and a potent analgesic effect. The main metabolic pathway of remifentanil is rapid hydrolysis by non-specific vinblastine enzymes, and it does not impair liver and kidney functions, and unlike other fentanyl analogs, the analgesic effect of rifentanil and its adverse effects are dose-dependent [15].

The results of the comparative analysis of the anesthetic effects of fentanyl and remifentanil combined with propofol respectively, was conducted in patients undergoing cerebral hemorrhage surgery show that in both groups, HR, DBP, and SBP levels at T2 and T3 were inferior to those at T1 ($p < 0.05$), and in contrast to the control group, the level of HR, DBP, and SBP at T3 in the study group was higher. These findings implied that remifentanil improved the patient's hemodynamic condition and provide adequate regulation for the surgery.

Hep is a peptide that regulates iron transport and inhibits perihematomal iron deposition and iron deposition-mediated damage [16]. The release of Hep into circulation rises as perihematomal cells are destroyed. NSE and s100β are marker molecules in neuronal cells and glial cells, and are involved in the catalysis of gluconeogenesis or the regulation of calcium homeostasis; the destruction of neurons and glial cells during cerebral hemorrhage causes an increased release of NSE and s100β [17]. Asp is a type of excitatory amino acid, and the stimulation of local brain tissue by hematoma results in Asp release, accumulation, and neurotoxicity, as well as a significant amount of blood flow across the blood-brain barrier. Cor, secreted by the adrenal cortex, is increased with the enhancement of adrenal cortical secretion under stress, and in turn, its increase may enhance the body's ability to tolerate traumatic stimuli. HA is a class of microtubule-associated proteins that are secreted in large quantities during stress reaction, and activate inflammatory response and exacerbate brain tissue damage after perihematomal infiltration [18]. MMP9 is a protease involved in extracellular matrix hydrolysis that promotes inflammatory cell infiltration around the hematoma and disrupts the blood-brain barrier, thereby exacerbating brain edema. OPN is a secreted class of extracellular matrix proteins that mediates macrophage infiltration around hematomas, as well as the disruption of the blood-brain barrier. ICAM-1 is a class of intercellular adhesion molecules that mediates the adherence and infiltration of numerous inflammatory cells around hematomas, resulting in damage to brain tissue through the inflammatory activity of inflammatory cells [19].

In this study, at 12 h and 24 h postoperatively, all brain injury markers and stress response indicators in the study group were lower with significant differences. These indicate that patients' brain damage was effectively protected, and stress reaction was effectively controlled after co-administration of remifentanil with propofol compared with fentanyl, which is consistent with other reported results [20]. Furthermore, the degree of anesthesia and lower incidence of adverse reactions in the study group suggest that remifentanil is safer and more effective than fentanyl.

Limitations of the study

This study has certain limitations, being single-centre clinical trial utilizing a relatively small sample size, as well as a relatively short follow-up period for patients.

CONCLUSION

Remifentanil combined with propofol anesthesia creates a more stable hemodynamic state for patients undergoing cerebral hemorrhage surgery. The combination is also a very effective and safe anesthetic. However, further multicenter clinical trials are required prior to application in clinical practice.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Lishui District People's Hospital (Lishui Hospital, Zhongda Hospital, Southeast University, China; approval no. 2019-075).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jiajia Xu and Litian Zhou designed the study and carried them out; Jiajia Xu, Litian Zhou, Jian Hu, Jiao Lei, Pinglai Yang and Litian Zhou supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript. Jiajia Xu and Litian Zhou contributed equally to the work and should be considered co-first authors.

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