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Evaluation of the Efficacy and Safety of Short-Course Deep Sedation Therapy for the Treatment of Intracerebral Hemorrhage After Surgery: A Non-Randomized Control Study

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Statistical Analysis C
Data Interpretation D
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Background: While mild and moderate sedation have been widely used to reduce sudden agitation in intracerebral hemorrhage (ICH) patients after surgery, agitation is still a frequent problem, which may cause postoperative blood pressure fluctuation. The present study aimed to evaluate the efficacy and safety of short-course deep sedation for the treatment of ICH after surgery.

Material/Methods: A total of 41 ICH patients who received surgery, including traditional craniotomy hematoma removal and decompressive craniectomy, were including in this non-randomized control study. Patients in the deep sedation group received continuous postoperative sedation with a target course for ≤12 hours and reached SAS scores of 1~2. Patients in the traditional sedition group received continuous light sedation and reached SAS scores of 3~4. Additional therapeutic interventions included antihypertensive treatment, mechanical ventilation, tracheotomy, and re-operation.

Results: Patients in the deep sedation group had deeper sedation degree, and lower systolic blood pressure (SBP) and diastolic blood pressure (DBP). Residual hematoma after surgery in patients in the deep sedation group were smaller on the second, seventh, and fourteenth day after surgery (p=0.023, 0.003, 0.004, respectively). The 3-month mortality and quality of life of patients in the deep sedation group were lower and better than that of patients in the traditional sedation group, respectively (p=0.044, p<0.01). No significant difference in the incidence of ventilator-associated pneumonia (VAP) and ICU days were observed between the two groups.

Conclusions: Short-course deep sedation therapy in ICH patients after surgery is efficient in controlling postoperative blood pressure, reducing re-bleeding, and improving clinical prognosis.

MeSH Keywords: Cerebral Hemorrhage • Deep Sedation • Postoperative Care

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Background

Spontaneous intracerebral hemorrhage (ICH) patients are prone to agitation and delirium due to impaired nerve function, increased intracranial pressure, and iatrogenic adverse stimulus such as an operation, establishment of artificial airway, and mechanical ventilation [1]. Agitation and delirium usually lead to increased oxygen consumption, excessive stress, blood pressure fluctuation, and increased intracranial pressure, which may cause re-bleeding, hematoma enlargement, and neurological function deterioration [2–4]. Therefore, reducing agitation and delirium through sedation and analgesia is critically important for the treatment of spontaneous ICH, which has been widely appreciated by neurologists and intensivist staff around the world [5–7]. However, no consistent guidelines and protocols for sedation therapy are available for the treatment of spontaneous ICH patients and patients with severe brain injury. Sedative treatment of spontaneous ICH patients usually refers to sedation therapy guidelines for critically ill patients [3,8]. Traditionally, mild or moderate sedation rather than deep sedation is recommended for spontaneous ICH patients [3,8]. Studies of critically ill patients suggest that excessive sedation leads to a number of complications, including muscle atrophy and weakness, pneumonia, ventilator dependence, thromboembolic diseases, nervous tension, pressure sores and delirium, prolonged mechanical ventilation, and prolonged ICU stays [9–11].

In clinical practice, mild or moderate sedation is not effective for reducing agitation and delirium in spontaneous ICH patients due to significantly impaired cognitive abilities and behavior controls. Agitation is commonly observed in spontaneous cerebral hemorrhage patients who received moderate sedation therapy, causing fluctuation in blood and intracranial pressures, and even significant disease deterioration. In the present study, we evaluated the efficacy and safety of short-course deep sedation therapy in spontaneous ICH after surgery. We also optimized the protocol of short-course deep sedation therapy to reduce the incidence of adverse events and complications caused by deep sedation.

Material and Methods

Research ethic statement

This study was approved and supervised by the Ethics Committee of the Affiliated Hospital of Taishan Medical University. Informed consent was signed by close relatives of all patients.

Patients and surgery

Between March 2011 and July 2013, a total of 41 spontaneous ICH patients, including 28 males and 13 females, who received surgery treatments of traditional craniotomy hematoma removal or decompressive craniectomy were included in this study. Ventricle drainage was conducted at the same time. Patients who received hematoma puncture drainage or separate ventricular drainage were not included in this study.

The ages of the study patients ranged from 30 years to 79 years. Of the 41 patients, 26 patients received deep sedation therapy with target course for ≤12 hours (the deep sedation group), and 15 patients received mild to moderate sedation therapy with target course for ≤12 hours (the traditional sedation group). This was a non-randomized control study, with no randomized groups and no blinded methodology.

Patients whose preoperative GCS score was 3 were excluded from this study. Patients who had respiratory failure, needed ventilator application, or needed vasopressor agents due to hypotension before surgery were not include in this study. Patients with a medical history of cerebral hemorrhage or cerebral infarction, accompanied by obvious dysfunction with mRS score over 3 were excluded from this study. In addition, patients without permission for deep sedation therapy from their families or physicians were excluded from this study. The surgery indications for patients with spontaneous ICH included >30 mL of supratentorial hemorrhage, >10 mL of infratentorial hemorrhage, >1 cm of midline structure shift, anisocoria, or deteriorating consciousness. Re-operation was conducted when postoperative brain CT showed re-bleeding.

Sedation program

Midazolam was used in the sedation program. Sufentanil was used for postoperative analgesic. No postoperative muscle relaxants were used. All patients in the two groups received analgesia with sufentanil at a fixed dose of 0.2 ug/kg/h. Sedation depth was evaluated based on SAS scores [12]. The traditional sedation group received continuous administration of midazolam after loading (0.05~0.1 mg/kg) and reached a SAS score of 3~4 through adjusting the pump rate. The deep sedation group received a larger dose of continuous infusion of midazolam after a larger loading (0.1~0.2 mg/kg) and reached a SAS score of 1~2 through adjusting the pump rate. Sedative and analgesia treatment were terminated in all patients including the traditional sedation and deep sedation groups on the first postoperative day (according to 8:00 AM, not to the natural day). SAS scores were assessed every 4 hours and for a total of 12 hours in the ICU. Sudden agitation was determined if a SAS score suddenly reach 6 or 7, such as the manifestations of biting the tracheal intubation, trying to pull out the

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catheter, or attacking staff. The frequency of sudden agitation 12 hours after surgery was recorded. Surgeons and patients' families were masked to the postoperative sedation therapy before the surgery, but permission for postoperative sedation therapy was obtained from the surgeons and patients' families.

Additional therapeutic intervention

In patients with elevated blood pressure, continuous infusion of antihypertensive drugs, including nitroglycerin and sodium nitroprusside, was administered through adjusting the pump rate to reduce the SBP and DBP to ≤160 and ≤90 mm Hg, respectively. The ventilator was weaned when spontaneous breathing was improved after the termination of sedative drugs. Tracheotomy was conducted in patients with respiratory tract obstruction and long period of coma (>7 days). Patients with airway patency, stable respiratory function, and hemodynamic stability, were moved out of ICU.

Data collection

The demographic data and medical history, such as age, gender, history of hypertension and cerebrovascular diseases, antihypertensive and antiplatelet treatments before admission, were collected from all patients. We also recorded preoperative indicators including conscious status on admission, blood pressure on admission, GCS on admission, hematoma volume, ICH score proposed by Hemphill et al. [13], and postoperative indicators such as blood pressure 12 hours after surgery, blood gas indicators on admittance to ICU and in the first day after surgery, blood cells and coagulation analysis index on the first day after surgery, mechanical ventilation duration, ICU length of stay, postoperative residual hematoma volume, re-bleeding, and reoperation. Patients underwent CT scan at postoperative 48 hours (expressed as postoperative 2nd day), at 5~7 days (expressed as postoperative 7th day), at 12~14 days (expressed as postoperative 14th day) respectively, and residual hematoma volume was calculated. Postoperative less residual hematoma refers to residual hematoma volume in postoperative 2nd day less than 30% of the preoperative volume or less than 10 mL. Re-bleeding refers to postoperative hematoma volume greater than or equal to the volume of hematoma before the surgery. Clinical prognostic indicators included the incidence of ventilator-associated pneumonia (VAP), mortality, and mRS score at 3 months. Good prognosis was determined by the mRS scores of 0~3, and the mRS scores of 4~6 was considered poor prognosis. The diagnosis of ventilator-associated pneumonia was made according to the Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia [14].

Measurement of the volume of cerebral hematoma

The GE LightSpeed 64-Slice CT plain scan and the CTAW4.4 workstation were used to measure the volume of cerebral hematoma. Intracranial hemorrhage was identified through adjusting the CT region threshold, and the volume of cerebral hematoma was defined as the entire region with hemorrhage. Hemorrhage with irregular shape was divided into a number of regular shapes, and the volume of cerebral hematoma was calculated through summing the volumes of all cerebral hematoma of regular shapes.

Statistical analysis

SPSS version 17.0 was used for statistical analyses. Continuous variables first underwent normal distribution testing. Normally distributed data, which were presented as mean ± standard deviation, were then analyzed using one-way ANOVA. Skewed data that were presented as medians and interquartile range (IQR) were analyzed using the Wilcoxon rank sum test. Categorical variables were compared using χ^2 analysis. The risk factors for 3-month poor prognosis were evaluated using univariate and multivariate logistic regression analysis. A p value less than 0.05 was considered statistically significant.

Results

Demographic information, medical history, and preoperative treatment

There was no significant difference in the gender, age, history of hypertension and cerebrovascular diseases, preoperative antihypertensive and antiplatelet therapy, coma, systolic and diastolic blood pressure on admission, the time between onset and surgery, admission heart rate, admission GCS score, hematoma volume, location of the hemorrhage (left or right, supratentorial or infratentorial), ventricular hemorrhage, and ICH score between the deep sedation and traditional sedation groups (p>0.05) (Table 1).

The surgery and other postoperative treatment

There was no significant difference in the time between ICH onset and surgery, and the surgery duration between the deep sedation group and the traditional sedation group. Three patients in the traditional sedation group underwent re-operation due to re-bleeding, and no patients in the deep sedation group received re-operation. The re-operation rate of the deep sedation group was significantly lower than that in the traditional sedation group (χ^2=5.611, p=0.043) (Table 2).

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Table 1. Demographic information, medical history, and preoperative treatments of ICH patients.

	Deep sedation group (n=26)	Traditional sedation group (n=15)	$F(\chi^2)$	*P*
Male/Female	17/9	11/4	0.278	0.734
Age	52.35±9.83	57.47±8.01	2.935	0.095
History of hypertension (Yes/No/Unknown)	19/4/3	10/0/5	4.679	0.096
History of cerebrovascular diseases (Yes/No/Unknown)	9/12/5	3/9/3	1.053	0.591
Previous antihypertensive therapy (Yes/No/unknown)	11/8/7	6/4/5	0.200	0.905
Previous antiplatelet therapy (Yes/No/unknown)	5/15/6	2/7/6	1.340	0.512
Coma, n (%)	19 (73.1)	12 (80)	0.247	0.720
Time between onset and admission (h) (median(IQR))	2.25 (1.5,4.25)	2.5 (1.5,6.0)	–0.559	0.583
Admission SBP (mmHg)	174.85±28.73	179.20±33.90	0.191	0.664
Admission DBP (mmHg)	103.38±15.83	110.13±22.73	1.252	0.270
Admission HR (beats/min)	76.31±11.09	81.00±14.93	1.318	2.58
Admission GCS score	6.77±2.44	6.67±3.13	0.104	0.908
Location of hemorrhage (left/right)	13/13	6/9	0.383	0.536
Location of hemorrhage (supratentorial/infratentorial)	23/3	15/0	1.867	0.287
Hematoma volume (ml)	50.02±30.22	62.10±25.50	1.694	0.201
Ventricular hemorrhage, n (%)	10 (38.5)	10 (66.7)	3.026	0.082
ICH score (median (IQR))	2 (2,3)	3 (2,3)	–1.845	0.091
Hematoma expansion, n (%)	2 (7.7)	1 (6.7)	0.015	1.000

There was no significant difference in postoperative antihypertensive therapy and the choice of antihypertensive drugs between the deep sedation group and traditional sedation group. All the patients in the deep sedation group received mechanical ventilation after surgery, and the rate of mechanical ventilation in the traditional sedation group was significantly lower than that in the deep sedation group (χ^2=5.611, p=0.043). However, no significantly difference in the duration of mechanical ventilation was identified between the two groups. The rate of tracheotomy in the traditional sedation group was significantly higher than that in the deep sedation group (χ^2=7.031, p=0.008) (Table 2).

Postoperative sedation

No significant difference in the depth of postoperative sedation was found between the two groups when patients were administrated into ICU (Z=–1.000, p=0.011). However, significantly deeper sedation within 12 hours after surgery was observed in the deep sedation group compared to the traditional group. The frequency of sudden agitation within 12 hours after surgery in the deep sedation group was significantly lower than that in the traditional sedation group. In addition, sedation duration in the deep sedation group was significantly longer than that in the traditional sedation group (F=7.086, p=0.011) (Table 3).

Blood pressure after operation

While no significant difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at each time point within 12 hours after surgery was identified between the two groups (Figures 1, 2), the mean values of SBP and DBP in the deep sedation group within 12 hours after surgery were significantly lower than that in the traditional sedation group (F=19.748, p=0.000 and F=7.357, p=0.007, respectively). In addition, the ratio of postoperative SBP >160 mm Hg in the deep sedation

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Table 2. Comparison of surgery and other postoperative treatments between the two groups of ICH patients who received deep ans traditional sedation therapy.

	Deep sedation group (n=26)	Traditional sedation group (n=15)	$F(\chi^2)$	*P*
Time between onset and surgery (h)	4.52±3.14	4.67±3.42	0.020	0.889
Operation duration (h)	3.81±0.66	3.43±0.90	2.314	0.136
Reoperation, n (%)	0 (0)	3 (20)	5.611	0.043
Antihypertensive therapy n (%)	21 (81.7)	13 (86.7)	0.234	1.000
Antihypertensive drugs (nitroglycerin/sodium nitroprusside)	20/1	9/4	4.330	0.059
Mechanical ventilation, n (%)	26 (100)	12 (80)	5.611	0.043
Duration of mechanical ventilation (h)	18.62±12.29	13.03±10.75	2.143	0.151
Tracheotomy, n (%)	5 (19.2)	9 (60)	7.031	0.008

Table 3. Comparison of the sedation duration, SAS score, and sudden agitation frequency between ICH patents who received deep and traditional sedation therapy.

	N	Sedative duration (h)	SAS score (median(IQR))				Sudden agitation frequency (median (IQR))
			Admission to ICU	Postoperative 4th hour	Postoperative 8th hour	Postoperative 12th hour	
Deep sedation group	26	13.67±6.72	2 (2, 2)	2 (1, 2)	2 (1, 2)	2 (2, 4)	1 (0, 1.25)
Traditional sedation group	15	7.67±7.36	2 (2, 3)	4 (4, 4)	5 (4, 5)	5 (4, 5)	3 (2, 3)
F(Z)		7.086	–1.000	–5.456	–5.163	–3.983	–4.936
P		0.011	0.461	0.000	0.000	0.000	0.000

group was significantly lower than that in the traditional sedation group (χ^2=14.314, p=0.000). However, no significant difference in the ratio of postoperative DBP >90 mm Hg was identified between the two groups (χ^2=2.135, p=0.114) (Table 4).

Postoperative laboratory tests

There was no significant difference in the levels of arterial blood pH, PaO_2, $PaCO_2$, lactate, and glucose at ICU admission and the first day after surgery between the two groups. In addition, no significant difference in blood white cell count, neutrophil percentage, hemoglobin concentration, platelet count, PT, and APTT in the first day after surgery were identified between the two groups.

Postoperative hematoma volume and clinic outcomes

The volume of residual hematoma in patients in the deep sedation group on the second, seventh, and fourteenth days after surgery were significantly less than that of the traditional sedation group (p=0.023, 0.003, 0.004, respectively). There was no significant difference in the ratio of postoperative less hematoma volume that was <30% of pre-operation hematoma volume or <10 mL on the second day after surgery between the two groups (χ^2=2.754, p=0.097). No re-bleeding after surgery was reported in the deep sedation group patients, which was significantly lower than that in the traditional sedation group (χ^2=6.855, p=0.018) (Table 5).

No significant difference in ICU days and the incidence of VAP were identified between the two groups. The 3-month mortality in the deep sedation group was significantly lower than that of the traditional sedation group (χ^2=5.119, p=0.044). Based on mRS, the 3-month quality of life of the deep sedation group was significantly better than that of the traditional sedation group (Table 5).

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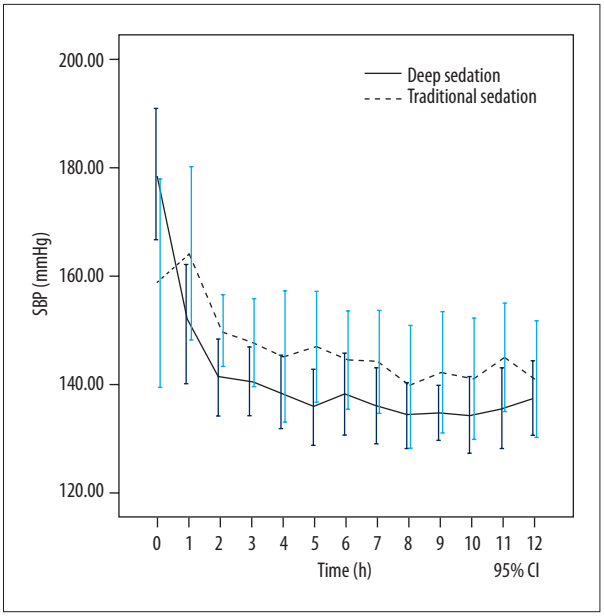

Figure 1. Systolic blood pressure at each time point within 12 hours after the surgery.

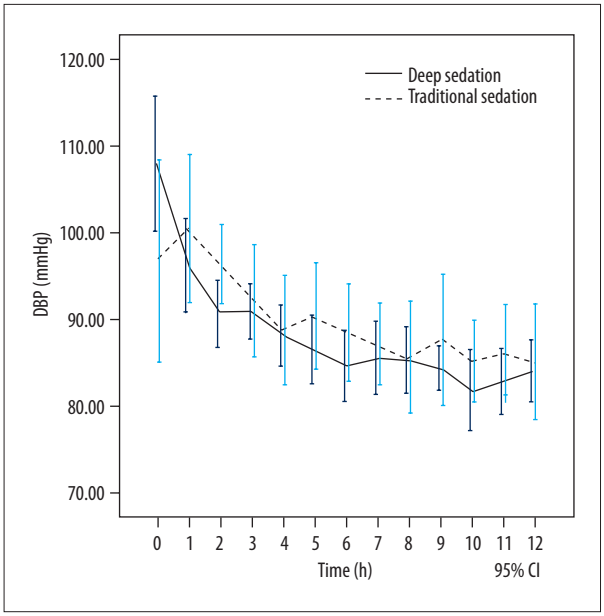

Figure 2. Diastolic blood pressure at each time point within 12 hours after the operation.

Table 4. Blood pressure within 12 hours after aurgery.

	Postoperative SBP (mmHg)	Postoperative DBP (mmHg)	Postoperative SBP >160 mmHg (Yes/No)	Postoperative DBP >90 mmHg (Yes/No)
Deep sedation group	138.30±18.06	86.74±10.34	23/286	103/206
Traditional sedation group	146.59±18.78	89.55±11.29	31/131	65/97
F(Z)	19.748	7.357	14.314	2.135
P	0.000	0.007	0.000	0.144

Risk factors of 3-month poor prognosis

Univariate and multivariate logistic regression analysis revealed that ICH scores and SAS scores in the fourth hour postoperative were independent risk factors for 3-month poor prognosis (p=0.003, p=0.008) (Table 6). The higher SAS score, the lighter sedation, the more likely to lead to a 3-month poor prognosis.

Discussion

Appropriate sedation is an important treatment for critically ill patients in integrated ICUs. Daily interruption of sedation and daily wake-up have been recommended for avoiding long-term deep sedation [3,8]. Generally, mild and moderate sedation are considered to be suitable for most critically ill patients, however, they may not be efficient for patients with some serious diseases. It has been reported that deep sedation is a better choice than mild and moderate sedation for arrhythmia patients undergoing uvulopalatopharyngoplasty, gastrointestinal endoscopy, and pediatrics [15–18]. Several studies have reported that daily wake-up caused brain damage through increasing adrenocorticotrophic hormone and cortisol levels, and fluctuation of blood pressure, ICP, and CPP [19–21]. Therefore, mild and moderate sedation with daily wake-up may not be efficient and safe for the treatment of brain injury.

Our results showed that the frequency of sudden agitation within 12 hours after surgery in the traditional sedation group was significantly higher than that of the deep sedation group. In addition, the SAS scores in the fourth, eighth, and twelfth hours after surgery were significantly higher than in the deep sedation group. We also observed that patients in the traditional sedation group had significantly higher blood pressure within 12 hours after surgery, and a higher ratio of over-targeted blood pressure (SPB 160 and DPB 90 mm Hg) than

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Table 5. Postoperative hematoma volume and clinic outcome.

	Deep sedation group (n=26)	Traditional sedation group (n=15)	$F(\chi^2)$	*P*
Residual hematoma volume on the 2nd day after surgery (ml)	15.78±13.34	41.78±38.52	6.339	0.023
Residual hematoma volume on the 7th day after surgery (ml)	8.72±13.34	22.38±10.02	11.851	0.003
Residual hematoma volume on the 14th day after surgery (ml)	0.87±1.63	5.18±3.34	12.276	0.004
Less hematoma volume after surgery, n (%)	14 (60.9)[a]	5 (33.3)	2.754	0.097
Re-bleeding, n (%)	0 (0)[a]	4 (26.7)	6.855	0.018
VAP, n (%)	4 (15.4)	2 (13.3)	0.032	1.000
ICU days (median(IQR))	2 (1, 3.25)	2 (1, 3.75)	–0.517	0.624
3-month mortality, n (%)	3 (11.5)	6 (42.9)[b]	5.119	0.044
Good/poor prognosis (mRS)	22/4	3/11b	15.502	0.000

[a] N=23, 2 patients didn't undergo CT scan in postoperative 48 h; [b] N=14, one patient was lost to follow-up.

Table 6. Multivariate analysis of 3-month poor prognosis.

Risk factor	Regression coefficient	OR	95% CI	*P*
ICH score	2.411	11.147	2.273–54.660	0.003
SAS score in postoperative 4th hours	1.635	5.127	1.525–17.233	0.008

patients in the traditional sedation group. These results suggest that frequent sudden agitation in patients with traditional sedation led to blood pressure fluctuation, and that deep sedation is better than traditional sedation for controlling the blood pressure of ICH patients after surgery through reducing the frequency of sudden agitation.

Some studies have also suggested that high blood pressure was related to cerebral hemorrhage after craniectomy or enlargement of hemorrhage hematoma [22,23]. Based on a retrospective study including 86 cerebral hemorrhage patients, Basali et al. found that intraoperative and postoperative high blood pressure were more likely caused by postcraniotomy ICH [22]. In addition, a number of studies have reported that early antihypertensive treatment could significantly inhibit hematoma enlargement in ICH patients, and might improve the prognosis of these patients [24–27].

Our results showed that the clinic outcomes of patients in the deep sedation group were better than that of patients in the traditional sedation group. For example, the 3-month mortality and 3-month quality of life of patients in the deep sedation group were significantly lower and better than that of patients in the traditional sedation group, respectively. The positive results of deep sedation therapy on clinical outcomes of ICH patients may be related to several relevant factors. First, the volume of residual hematoma after surgery (including day 2, day 7, and day 14 after surgery) in the deep sedation group was less than that in the traditional sedation group. Less residual hematoma volume likely contribute to the improvement of clinic outcomes. Zuo et al. investigated the clinical outcomes of ICH patients who received sub-total removal of their hematoma. The authors found that patients who had less than 3 mL of postoperative hematoma exhibited lower levels of inflammatory responses and brain edema, and better clinical outcomes than patients with postoperative hematoma >5 mL [28]. Second, in our study, no re-bleeding was found in patients in the deep sedation group. Re-bleeding in ICH patients after surgery is a major factor leading to deterioration, neural function failure, and even death. Morgenstern et al. reported that 3 of 4 ICH patients with re-bleeding after decompressive craniectomy died, suggesting that re-bleeding after surgery was associated with patient death [29]. In our study, that no re-bleeding was found in patients of the deep sedation group may be an important reason for the reduce mortality, and the improved quality of life of the group of patients. Third, the deep sedation group received mechanical ventilation after surgery. Deep sedation plus mechanical ventilation can inhibit tissue damage caused by hypoxemia and increasing oxygen supply and reducing oxygen consumption. Finally,

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most of the patients that survived in our study were admitted to hospital or family rehabilitation therapy. Postoperative systematic, targeted, collaborative rehabilitation treatment can improve the quality of life. Ciccone et al. reported that the collaboration between the physician and care manager and the strong "partnership" between the patient and care manager showed a positive impact on patient health [30].

We also evaluated the safety of deep sedation therapy for ICH patients after surgery. It has been reported that a long course of deep sedation can have a number of adverse events, such as ventilator dependence, ventilator-associated pneumonia, delayed recovery, prolonged ICU days, and pressure ulcer [31]. These adverse events are associated with both the depth and duration of sedation. Therefore, our research emphasized deep sedation, at the same time it also stressed that target course should not be more than 12 hours. No significant difference in ICU days and the incidence of ventilator-associated pneumonia were identified between patients who received short-course deep sedation and traditional sedation. Most ICH patients exhibited different levels of consciousness. Therefore, delayed recovery was not compared between the deep sedation and traditional sedation groups.

A number of limitations in the present study should be discussed. First, a major limitation of this study was the small sample size. Only 41 patients were included. Post-hoc sample size calculation using PASS 11.0 reveals that in order to compare the 3-month prognosis, only 8 patients in each group were required. But in order to accurately compare the 3-month data, the sample size required was 39 cases in each group. Therefore, further research is needed to expand the sample size. Second, random grouping of ICH patients was not conducted in the present study because ICH patients were co-managed by surgeons and ICU physicians who did not reach agreement in the selection of the study sedation plan in some cases. For example, surgeons tended to choose short-course deep sedation rather than the traditional sedation program based on preliminary data showing that short-course deep sedation reduced the rate of re-bleeding and improved the prognosis of ICH patients, resulting in fewer patients receiving traditional sedative. Third, the influence of deep sedation on intracranial pressure and cerebral perfusion was not evaluated in the present study because of the laboratory limitation on available equipment. Finally, nitroglycerin and sodium nitroprusside rather than intravenous calcium antagonists (which is not available in most hospitals in China) were used as antihypertensive drugs in the present study, which was not fully consistent with ICH guidelines.

Conclusions

Our study showed that short-course deep sedation therapy in ICH patients after surgery is efficient in controlling postoperative blood pressure, reducing re-bleeding, and improving clinical prognosis. However, the long-term efficacy and safety of short-course deep sedation therapy in ICH patients need to be further studied.

Competing interests

The authors declare that they have no competing interests.

Trial registration

Chinese Clinical Trial Registry: ChiCTR-OON-15006205.

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