

Early tracheostomy is associated with better prognosis in patients with brainstem hemorrhage

Wei-Long Ding¹, Yong-Sheng Xiang¹, Jian-Cheng Liao¹, Shi-Yong Wang¹ and Xiang-Yu Wang^{1,*}

¹Department of Neurosurgery, The First Affiliated Hospital of JiNan University, Guangzhou, Guangdong Province, 510632, P. R. China

*Correspondence: wangxy123@jnu.edu.cn (Xiang-Yu Wang)

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Brainstem hemorrhage is presumed to be invariably associated with a poor prognosis in people with spontaneous hypertensive cerebral hemorrhage. The optimal timing of tracheostomy placement in brainstem hemorrhage patients, who generally require endotracheal intubation for airway protection, remains uncertain. Our research aim was to analyze the impact of early tracheostomy versus late tracheostomy on brainstem hemorrhage patients related outcomes and prognostic factors at 30 days. We identified early tracheostomy and how it could benefit the patients with brainstem hemorrhage and ameliorate the predictors of functional recovery at 30 days. Data on 136 patients with brainstem hemorrhage and Glasgow Coma Scale score ≤ 8 , were retrospectively collected from 2012 to 2019. Patients were divided into the early tracheostomy group and the late tracheostomy group. Patients in the early tracheostomy group had a significantly lower neurosurgical intensive care unit stay (both overall and survival) compared with the late tracheostomy group (15.6 days vs. 19.0 days, $P = 0.041$, overall and 14.5 vs. 19.5 days, $P = 0.023$, survival). Also, the good outcomes (modified Rankin Score ≤ 3) were higher in the early tracheostomy group ($P = 0.036$). Multivariate analysis demonstrated that less hemorrhagic volume, high Glasgow Coma Scale score on admission, young age, and early tracheostomy were significantly associated with a better 30-day functional outcome. In conclusion, an early tracheostomy in patients with brainstem hemorrhage can reduce neurosurgical intensive care unit stay, and in addition to improvements in prognosis at 30 days.

Keywords

Brainstem hemorrhage; tracheostomy; statistical analysis; neurology; Glasgow coma scale

1. Introduction

Brainstem hemorrhage (BSH) is a rare neurological illness that accounts for approximately 5~10% of all spontaneous intracranial hemorrhages, the overall mortality rate is high, with a range from 30% to 70%, resulting in survivors with long-term neurological deficits (Dziewas et al., 2003; Jeong et al., 2002; Wessels et al., 2004;

Wijdicks and St. Louis, 1997). The disease often causes disturbance in consciousness, tetraparesis, severe hyperthermia, and respiratory failure. With the development in the microsurgery and stereotactic surgery field, the outcome of patients with BSH has been undoubtedly improved (Hara et al., 2001). Observational studies identified poor outcomes such as coma on admission, large hematoma, abnormal respiration, and pupil abnormalities as prognostic indicators (Arabi et al., 2004; Murata et al., 1999; Wijdicks and St. Louis, 1997).

BSH patients in a coma need to maintain a secure airway, especially in the acute period, severe BSH patients always need airway management and mechanical ventilation. An endotracheal tube may be used, but it is usually poorly tolerated and requires oral care and challenging feeding. Thus, tracheostomy is preferred, since benefits of this procedure have been reported, such as improved pulmonary hygiene, enhanced comfort, and a more precocious removal of the mechanical ventilator (McCredie et al., 2017).

Percutaneous tracheostomy is a common procedure in intensive care units. Some studies are available on patients who potentially benefit from undergoing early tracheostomies, such as patients with spinal cord injury (Flanagan et al., 2018), patients with traumatic brain injury (Cai et al., 2017), or patients after cardiac surgery (Devarajan et al., 2012). Tracheostomy timing will affect stroke recovery as well. Villwock et al. (2014) examined the timing of tracheostomy on the outcome of over ten thousand stroke patients they concluded that early tracheostomy in stroke patients could reduce the incidence of ventilator-associated pneumonia, shorten hospital stay, and lower total hospital costs.

A retrospective study performed by Chen et al. (2019) evaluated the timing and outcome in patients with hemorrhagic stroke who received a tracheostomy, and their results also revealed that patients subjected to early tracheostomy have a higher rate of neurosurgical operation than patients subjected to late tracheostomy. They also found that patients who underwent early tracheostomy are associated with a shorter hospital stay and reduced hospital costs than those who underwent late tracheostomy.

Patients with BSH are certainly candidates for prolonged invasive mechanical ventilation and difficult weaning. Thus, there is no reason to prolong translaryngeal intubation. However, the tracheostomy also has some risks, which may induce airway or esophageal injury, tracheomalacia, and tracheoinnominate fistula, and some evidence

suggested that early tracheostomy does not improve the outcome. Kleffmann et al. (2020) found that percutaneous tracheostomy in patients led to a significant increase in intracranial cerebral pressure during the procedure, patients with a baseline intracranial pressure more than 15mmHg are at risk to develop harmful intracranial pressure crises. As a result, the optimal time for performing this procedure remains controversial (Ahmed and Kuo, 2007; Huang et al., 2013), and no evidence is available comparing the influence of early tracheostomy (ET) or a late tracheostomy (LT) in the prognosis of BSH patients.

Previous studies focused their attention on the evaluation of the effect of ET on patients with traumatic brain injury (TBI), including three randomized trials (Ahmed Boudierka et al., 2004; Dunham et al., 2014; Sugerma et al., 1997). More recently, Dunham et al. (2014) performed a comprehensive systematic review to evaluate all randomized controlled trials to assess the impact of ET on the outcome of patients with TBI. They found that ET does not decrease the VAP rate, but it reduces mechanical ventilator. Furthermore, the study demonstrated that ET increases the risk of hospital death.

Another systematic review conducted by McCredie et al. (2017) compared the effect of ET versus LT or prolonged intubation in critically ill patients with acute brain injury. Ten trials (with 503 cases in total) were analyzed. The study demonstrated that ET reduces the long-term mortality rate, length of ICU stays, and duration of the mechanical ventilator. However, ET fails to reduce short-term mortality. Furthermore, it increases the probability of ever receiving a tracheostomy.

Shamim et al. (2015) evaluated the effects of ET in 100 ICU patients with isolated TBI who required mechanical ventilation. Tracheostomy performed within 7 days of TBI was defined as ET. Forty-nine patients out of 100 underwent ET, while the others were subjected to prolonged endotracheal intubation (EI). They concluded that the frequency of VAP was higher in the EI group compared to the ET group (45% vs. 63%, $P = 0.09$). Also, the ET group showed significantly less ICU stay (11 days vs. 13 days, $P = 0.03$), fewer days under mechanical ventilator (10 days vs. 13 days, $P = 0.031$), less mortality rate (8.2% vs. 17.6%) and less complication rate (14% vs. 18%). The clinical outcome evaluated by the Glasgow Outcome Scale was better in the ET group, and the total cost in the hospital was considerably less in the ET group compared with the cost of the EI group.

Previous studies were focused on the impact of ET on TBI patients, not on patients with BSH (Ahmed and Kuo, 2007; Arabi et al., 2004; Ahmed Boudierka et al., 2004; Pinheiro et al., 2010). Some aspects of TBI and BSH patients were similar. For instance, in the acute phase of the onset, BSH and TBI patients show the recognizable obstacle at different levels, lost airway protection. Thus, they required the prevention of obstruction resulted from tongue depression and accumulation of secretion. For most patients with severe BSH and TBI, mechanical ventilator and continuous monitoring at Intensive care unit (ICU) are essential due to some possible symptoms such as hyperthermia, ventilator-associated pneumonia, and deep venous thrombosis.

It remains controversial whether BSH should be promptly treated through the surgical evacuation of the hematoma or managed conservatively (Manno et al., 2005). Several studies supported the conservative management in patients with BSH (Grotta, 2004; Komiyama

et al., 1989), although a growing number of studies report the efficacy of the surgical treatment (Hara et al., 2001; Ichimura et al., 2018; Takahama et al., 1989). Ichimura et al. (2018) believed that the surgical strategy could be encouraged with exclusion criteria for early initiation of rehabilitation strategies and Shrestha et al. (2015) also indicated that patients with BSH resulting in severe brainstem compression and progressive deterioration of the clinical status should be subjected to prompt surgical removal of the hematoma.

It remains questionable whether ventricular hemorrhage affects the outcome of patients with BSH. Jang et al. (2011) concluded that ventricular hemorrhage was not a predictor of 90 days of functional recovery. However, Huang et al. (2013) suggested that ventricular hemorrhage is an independent predictor of patients' outcomes. Probably the ventricular extension of hemorrhage may reduce the oppression of parenchyma.

Both BSH and TBI patients exhibited a poor prognosis, representing a heavy burden for their families and society as well (Hara et al., 2001; Kahn, 2010; Rabinstein et al., 2004). The benefit of ET on BSH patients is not yet defined. And no evidence is available comparing the influence of ET or a LT in the prognosis of BSH patients. Our research aim was to analyze the impact of ET versus LT on BSH patients' related outcomes and prognostic factors at 30 days.

2. Subjects and methods

2.1 Subjects

We performed a retrospective observational cohort study with the raw data used coming from a single institution. A total number of 291 patients with a diagnosis of BSH were admitted to the First Affiliated Hospital of JiNan University from September 1st, 2012 to March 31st, 2019. The protocol and all modifications were approved by the Institutional Review Board and Ethics Committee of the University. Only 136 patients out of these 291 met our inclusion criteria that were the following: (1) age more than or equal to 18 years old, (2) Glasgow Coma Scale (GCS) score less than or equal to 8; (3) diagnosis of BSH verified by computed tomography (CT) within 24 hours of the symptom onset, (4) patients without hemorrhage secondary to a ruptured cerebral aneurysm, head trauma, tumor, arteriovenous malformation, or cavernous malformation excluded by CT angiography. Patients who died within the first day, with brain death on admission, contraindications on performing tracheostomy, and disagreed with filling the consent form for the procedure were excluded from our study.

Baseline variables were collected, such as patient age, gender, GCS on admission, the primary location of hemorrhage, volume of hemorrhage, hydrocephalus, smoking history, alcohol consumption, pupillary reflex, a ventricular extension of hemorrhage, and stroke history. If the CT scan showed the presence of hydrocephalus or the hematoma rupture within the ventricles, external ventricular drainage was performed by neurosurgeons. The type of dorsally exophytic hematoma was treated by craniectomy and hemorrhage removal. Data associated with the hospital stay, neurosurgical intensive care unit (NICU) stay, the mortality rate in the hospital, Ventilator-associated pneumonia (VAP) rate, hyperthermia ($> 39^{\circ}\text{C}$) rate, and modified Rankin Score (mRS) at 30 days were evaluated. The hemorrhagic volume was measured by the ABC method on CT brain scan, in which A means the maximum width in cm assessed on the slice through the most substantial portion of hematoma, B means the maximum length in cm assessed by a line perpendicular to

Table 1. Patients' baseline characteristics

Variables	Early tracheostomy (n = 77)	Late tracheostomy (n = 59)	Total (n = 136)	P-value
Gender; n (%)				0.962
male	59 (76.6)	45 (76.3)	104 (76.5)	
female	18 (23.4)	14 (23.7)	32 (23.5)	
Age (year); mean (± SD)	51.47 ± 11.18	50.97 ± 11.37	51.25 ± 11.22	0.797
GCS on admission; mean (± SD)	5.23 ± 1.70	5.36 ± 1.67	5.29 ± 1.68	0.676
Main location of hemorrhage; n (%)				0.362
pons	64 (83.1)	44 (74.6)	108 (79.4)	
midbrain	6 (7.8)	9 (15.3)	15 (11.0)	
Medulla	7 (9.1)	6 (10.1)	13 (9.6)	
Volume of hemorrhage; n (%)				0.824
≤ 10ml	26 (33.8)	21 (35.6)	47 (34.6)	
> 10ml	51 (66.2)	38 (64.4)	89 (65.4)	
Hydrocephalus; n (%)				0.16
Present	38 (49.4)	22 (37.3)	60 (44.1)	
Absent	39 (50.6)	37 (62.7)	76 (55.9)	
Operation; n (%)				0.362
Yes	45 (58.4)	39 (66.1)	84 (61.8)	
No	32 (41.6)	20 (33.9)	52 (38.2)	
smoking; n (%)				0.503
yes	41 (53.2)	28 (47.5)	69 (50.7)	
no	36 (46.8)	31 (52.5)	67 (49.3)	
Habitual alcohol consumption; n (%)				0.982
yes	38 (49.4)	29 (49.2)	67 (49.3)	
no	39 (50.6)	30 (50.8)	69 (50.7)	
Pupil; n (%)				0.503
reactive	56 (72.7)	41 (69.5)	97 (71.3)	
pinpoint	15 (19.5)	12 (20.3)	27 (19.9)	
dilated	6 (7.8)	6 (10.2)	12 (8.8)	
Ventricular extension; n (%)				0.608
yes	28 (36.4)	24 (40.7)	52 (38.2)	
no	49 (63.6)	35 (59.3)	84 (61.8)	
Previous stroke; n (%)				0.543
yes	9 (11.7)	9 (15.3)	18 (13.2)	
no	68 (88.3)	50 (84.7)	118 (86.8)	

GCS, Glasgow Coma Scale; SD, standard deviation; BSH, brainstem hemorrhage.

line A, C means the number of slices involving the hematoma x slice thickness in cm. VAP diagnosis was confirmed by the radiographic imaging of pneumonia, clinical examination, clinical laboratory test, and positive sputum culture for bacterial growth.

Percutaneous tracheostomy was performed by the neurosurgeons in the NICU of our center. Neurosurgeons informed patients' relatives about the risks of this procedure before performing it, and they needed to fill the informed consent in case of acceptance. Patients were categorized according to the date in which tracheostomy was performed. Patients who were subjected to tracheostomy within (less than or equal to) seven days of admission were included in the ET group, and those who were subjected to tracheostomy after seven days of admission were included in the LT group.

2.2 Evaluation and statistical analysis

BSH patients had their functional status evaluated after 30 days using the modified Rankin Score (0 = no symptoms at all, 1 = no significant disability and able to perform usual activities, 2 = slight disability--unable to do previous activities but able to manage their

affairs, 3 = moderate disability--needs help but walks unaided, 4 = moderately severe disability--unable to walk and daily life help required, 5 = severe disability--bedridden and constant attention and care required, 6 = dead), Scores were reported in the medical record. Patients were divided into two groups according to the scores. The good-outcome group included patients with a score from 0 to 3, and the poor-outcome group included patients with a score from 4 to 6 (Kilincer et al., 2005; Rankin, 1957).

Statistical analysis was performed using SPSS software Version 24 for Windows (SPSS Institute, Inc., Chicago, IL, USA). Results are expressed as mean ± SD or number of patients (%), as appropriate. The mean of the results of the two groups was compared using the Student *t*-test. The Chi-square test and Fisher's exact test were used for comparison of qualitative variables. A multivariate logistic regression analysis was used to identify those variables that were independently associated with 30-day functional recovery (good outcome vs. poor outcome). A value of *P* < 0.05 was considered statistically significant.

Table 2. Comparison of the outcomes between early tracheostomy group and late tracheostomy group

Variables	Early tracheostomy (n = 77)	Late tracheostomy (n = 59)	Total (n = 136)	P-value
ICU stay-overall (days); mean (± SD)	15.55 ± 8.81	19.00 ± 10.67	17.04 ± 9.78	0.041
ICU stay-survival (days); mean (± SD)	14.52 ± 8.63	19.48 ± 13.25	16.55 ± 10.95	0.023
Hospital stay (days); mean (± SD)	24.62 ± 12.81	29.17 ± 17.69	26.60 ± 15.23	0.084
Death-in hospital; n (%)				0.192
Yes	37 (48.1)	35 (59.3)	72 (52.9)	
no	40 (51.9)	24 (40.7)	64 (47.1)	
mRS at 30 days; mean (± SD)	4.74 ± 1.30	4.97 ± 1.26	4.84 ± 1.28	0.311
Outcome; n (%)				0.036
Good-outcome	22 (28.6)	8 (13.6)	30 (22.1)	
Poor-outcome	55 (71.4)	51 (86.4)	106 (79.9)	
VAP; n (%)				0.288
Yes	44 (57.1)	39 (66.1)	83 (61.0)	
No	33 (42.9)	20 (33.9)	53 (39.0)	
Hyperthermia; n (%)				0.42
Yes	43 (55.8)	37 (62.7)	80 (58.8)	
no	34 (44.2)	22 (37.3)	56 (41.2)	

NICU, neurosurgical intensive care unit; mRS, modified ranking score; VAP, ventilator associated pneumonia; SD, standard deviation.

3. Results

Only 136 patients out of 291 patients were analyzed, thus representing the final number of the enrolled ones. 104 out of the 136 (76.5%) were male, and 32 (23.5%) were female. Overall, 77 patients underwent ET, and 59 patients underwent LT. The mean age was 51.25 ± 11.22 years (range from 22 to 79 years). The mean GCS on admission was 5.29 ± 1.68. The baseline characteristics of the two groups are listed in (Table 1).

The comparison between the ET group and LT group revealed that patients who were subjected to early tracheostomy had a significantly lower NICU stay-overall (15.55 vs. 19.00 days, $P = 0.041$). When the patients who died in NICU were excluded, the NICU stay-survival was also lower in the ET group (14.52 vs. 19.48 days, $P = 0.023$). The mortality rate in the hospital and VAP rate was not significantly different between the two groups. Next, on the 30th day after BSH, patients were divided into two groups, one group with mRS 0-3 (good outcome group), and the other with mRS 4-6 (poor outcome group). Thirty (22.1%) patients belonged to the good-outcome group, and 106 (79.9%) patients belonged to the poor-outcome group. ET patients were associated with good outcomes ($P = 0.036$). These results are shown in (Table 2).

In addition, multivariate logistic regression analysis showed that undergoing early tracheostomy in comparison to late tracheostomy, significantly improved the 30-day prognosis (good outcome) (adjusted odds ratio [OR] 0.083, 95% confidence interval [CI] 0.010-0.702, $P = 0.022$). GCS score on admission (adjusted odds ratio [OR] 3.226, 95% confidence interval [CI] 1.237-8.412, $P = 0.017$), hematoma volume (adjusted odds ratio [OR] 0.023, 95% confidence interval [CI] 0.001-0.394, $P = 0.009$) and patients' age (adjusted odds ratio [OR] 0.901, 95% confidence interval [CI] 0.817-0.994, $P = 0.038$) were independent factors affecting the 30-day functional outcomes. These results are shown in (Table 3).

4. Discussion

This is the first study comparing the effect of ET and LT on patients with BSH. BSH is the devastating type of intracerebral hemor-

rhage, and the patients who survive are often affected by long-term neurological deficits. Therefore, a thorough understanding of BSH epidemiology, surgical operation, pathology, and outcomes is of utmost importance to communicate to patients' relatives the actual expectations and the most appropriate therapeutic strategies. In our cohort, ET resulted as a significant predictor of 30-day prognosis. It can lower the overall NICU stay, and when the dead patients in NICU were excluded, the overall stay was also significantly lower in the ET group. Also, ET patients tended to have a good outcome on the 30th day after BSH. However, ET did not reduce the mortality rate and VAP rate. To determine the prognostic factors of mortality in patients with BSH, our study revealed that patients with early tracheostomy, high GCS on admission, hemorrhagic volume less than 10 mL, and young age were associated with a better outcome at 30 days. Although the prognosis of patients with BSH remained poor in most cases, our study indicated that the patients could benefit from early tracheostomy.

Severe BSH puts the patients at risk for neurological complications and in need of airway protection. In such cases, treatment strategies may differ, with an increased focus on airway management, blood pressure management, and blood oxygen saturation monitoring, to ensure the arrival of an adequate amount of oxygen to the brain tissues. Our data showed that the ET group had a significantly lower overall NICU stay (15.55 vs. 19.00 days, $P = 0.041$) and survival NICU stay (14.52 vs. 19.48 days, $P = 0.023$) compared with the LT group. Long-term endotracheal intubation may result in the accumulation of secretions above the endotracheal cuff in patients undergoing translaryngeal ventilation, together with a reduced level of consciousness with high sedation, constant opening of the vocal cords by the tube and high rate of aspiration into the distal airways. These disadvantages put patients at high risk of developing VAP. Therefore, the ET tube resulted as a vital asset in these circumstances because it can be regularly and easily cleaned, thus preventing the buildup of the biofilm. Also, the reduction of the length of NICU stay is essential for the financial benefits, because the NICU treatment is the most expensive part of the treatment.

Table 3. Multivariable logistic regression analysis for evaluating 30-day functional outcomes in patients with BSH

characteristic	Odd ratio (95% confidence interval)	P-value
Gender		
male versus female	0.960 (0.053-17.274)	0.978
Age	0.901 (0.817-0.994)	0.038
GCS on admission	3.226 (1.237-8.412)	0.017
Main location of hemorrhage		
pons	6.691 (0.022-2028.555)	0.514
midbrain	0.315 (0.001-96.339)	0.692
medulla	Reference	
Volume of hemorrhage		
≤ 10 ml versus > 10 ml	0.023 (0.001-0.394)	0.009
Hydrocephalus		
present versus absent	0.446 (0.071-2.795)	0.388
Early versus late tracheostomy	0.083 (0.010-0.702)	0.022
Operation		
yes versus no	3.042 (0.427-21.657)	0.267
Smoking		
yes versus no	0.129 (0.016-1.023)	0.053
Habitual alcohol consumption		
yes versus no	0.892 (0.146-5.449)	0.901
Ventricular extension		
yes versus no	0.203 (0.027-1.549)	0.124
Previous stroke		
yes versus no	11.635 (0.317-427.598)	0.182
VAP		
yes versus no	0.245 (0.024-2.499)	0.235
Hyperthermia		
yes versus no	1.136 (0.071-18.120)	0.928

GCS, Glasgow Coma Scale; VAP, ventilator associated pneumonia.

Exercising patients with an endotracheal tube has been demonstrated as safe and feasible, and an endotracheal tube alone is not a contraindication in patients during their early rehabilitation. However, mobility and "out-of-bed exercises" commonly do not occur in these patients' cohort. The vast majority of patients tend to rest in bed until they received a tracheostomy. Therefore, reduced rehabilitation is performed before the tracheostomy tube insertion. Early transfer from ICU also means earlier inpatient rehabilitation, which can improve patients' functional recovery. According to a recent study, early stomacher is associated with a timelier achievement of patient-centered outcomes (Sutt et al., 2020). Patients who underwent ET return to their usual daily activities such as eating, drinking, out-of-bed mobility and talking significantly earlier compared with patients who underwent LT.

Matsukawa et al. (2015) concluded that GCS with a score of less than 9, hyperthermia (a core temperature $\geq 39^{\circ}\text{C}$), maximum hematoma diameter ($> 27\text{ mm}$), and hemorrhage extension to midbrain or thalamus were significantly related to death. Hyperthermia had an impact on the outcome of patients with BSH, especially in central hyperthermia that does not respond to conventional antipyretic treatments. Patients with high fever ($> 39^{\circ}\text{C}$) and tachycardia are related to high risk of death and severe disability state (Lee et al., 2014; Sung et al., 2009). However, our study showed that ET

failed to decrease the hyperthermia rate, and the hyperthermia rate was not significantly related to the outcome after 30 days. As regard hyperthermia, the reason might be the direct pontine destruction or infection, and some studies reported that hyperthermia is induced by acute hydrocephalus.

In our study, we revealed that GCS on admission and hemorrhagic volume had significant effects on the 30-day outcomes of patients with BSH. Patients with a hemorrhagic volume of $\leq 10\text{ mL}$ and a high GCS score on admission had a good outcome after 30 days. Huang et al. (2017) developed and validated a new grading scale to evaluate mortality at 30 days and the functional outcome after 90 days for patients with primary pontine hemorrhage (PPH). A total of 171 patients in three hospitals were included in their study. GCS score and PPH volume worked as two independent factors to form the new PPH score. Their results showed that patients with a hemorrhagic volume less than 5 mL have a greater chance to survive, while patients with hemorrhagic volume more than 10 mL die at an early stage. Also, patients with a GCS score from 3 to 4 have a higher risk of dying (Huang et al., 2017). Murata et al. (1999) also pointed out that the transaxial size of the hematoma on CT and the initial level of consciousness is strongly associated with the outcome of patients with PPH. Older age is also related to mortality in patients with BSH (Tao et al., 2014). It showed a significant association with the outcome in our study.

5. Conclusions

This retrospective single institution-based analysis of BSH patients demonstrated that early tracheostomy had a significantly lower NICU stay (overall and survival) and a higher rate of good outcomes compared with a late tracheostomy. Factors associated with a good outcome at 30-day were early tracheostomy, high GCS on admission, hemorrhagic volume less than 10 mL, and young age.

Abbreviations

BSH: Brainstem hemorrhage; CT: Computed tomography; ET: Early tracheostomy; GCS: Glasgow Coma Scale; ICU: Intensive care unit; LT: Late tracheostomy; mRS: modified Rankin Score; NICU: Neurosurgical intensive care unit; PPH: Primary pontine hemorrhage; SD: Standard deviation; TBI: Traumatic brain injury; VAP: Ventilator-associated pneumonia.

Author contributions

W. D. and Y. X. conceived and designed the experiments; W. D. and J. L. performed the experiments; W. D. and S. W. analyzed the data; X. W supervised the experiments; W. D. and L. C. wrote the paper.

Ethics approval and consent to participate

The First Affiliated Hospital approved this research of the JiNan University Ethics committee (NO.2019029).

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Conflict of Interest

The authors declare no conflict of interest.

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