Original Article

Time-related intervention efficacy, serum ferritin levels, and prognosis in patients with aneurismal subarachnoid hemorrhage

Xinmin Zhou, Yu Xu, Jianfeng Jiang, Wangchen Zhou

Department of Neurosurgery, The Jiangyin Clinical College of Xuzhou Medical University, Jiangyin 214400, Jiangsu, China

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Abstract: Objective: This study sought to investigate the effects of interventional therapy on therapeutic efficacy, ferritin and prognosis of patients with aneurismal subarachnoid hemorrhage at different time points. Methods: A total of 78 patients with aneurismal subarachnoid hemorrhage treated in the hospital of Xuzhou Medical University from August 2015 to August 2017 were selected and divided into an ultra-early stage group (the duration from the occurrence of hemorrhage to the interventional therapy was within 24 h) (n=21), early stage group (the duration from the occurrence of hemorrhage to the interventional therapy was within 24-72 h) (n=32) and late stage group (the duration from the occurrence of hemorrhage to the interventional therapy was more than 72 h) (n=25) according to the timing of interventional embolization therapy. After intervention, venous blood was taken to detect the serum ferritin content. The postoperative complications were recorded. The followed up lasted for 90 d. The prognosis of patients was evaluated using the Glasgow outcome scale (GOS), and the postoperative cognitive function was evaluated using the Montreal cognitive assessment (MoCA) scale. Pearson analysis was performed for the correlation analysis between serum ferritin, prognosis and time of interventional therapy. Results: The incidence rates of postoperative adverse reactions and serum ferritin content after operation in the ultra-early stage group and the early stage group were significantly lower than that in the late stage group, along with significant elevation of GOS and MoCA scores (P<0.05). Timing of interventional therapy was significantly correlated with the prognosis, cognitive function and serum ferritin in patients (P<0.01). Conclusion: The time of interventional therapy for patients with aneurismal subarachnoid hemorrhage can significantly affect the serum ferritin, therapeutic effect and prognosis of patients.

Keywords: Aneurismal subarachnoid hemorrhage, interventional therapy, ferritin, prognosis

Introduction

As the most common kind of acute hemorrhagic cerebrovascular disease in neurosurgery, subarachnoid hemorrhage (SAH) refers to the hemorrhage flowing into the arachnoid space due to vascular rupture at the base of the brain, which leads to high mortality and disability rates. It therefore results in great psychological and economic burden to the patient's family and society [1, 2]. Intracranial aneurysm represents one of the most common causes of subarachnoid hemorrhage, accounting for more than 60%, and aneurismal subarachnoid hemorrhage generally give rise to vasospasms and large-area brain tissue ischemia, as the major cause of brain injury [3, 4]. The accumulation of inflammatory factors and toxic substances in the blood vessel in aneurismal subarachnoid hemorrhage can further worsen brain injury [5]. Generally, the diagnosis of subarachnoid hemorrhage includes CT scan, MRI and cerebral angiography. The various kinds of imaging test facilitate the view of blood vessels in detail and detect bleeding in the brain. Surgery can be conducted based on a definitive diagnosis. The cerebrospinal fluid has been valued for its role in rapid differential diagnosis between subarachnoid hemorrhage and traumatic lumbar puncture by D-dimer immunoturbidimetric assay [6].

Ferritin exists in almost all living organisms, including archaea, bacteria, algae, higher plants, and animals. In humans, it functions as a buffer against iron deficiency and iron overload, ensuring that red blood cells are able to supply enough oxygen. It has been shown that
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plasma ferritin can act as an indirect marker of the total amount of iron stored in the body while serum ferritin can be used as a diagnostic test for iron-deficiency anemia. According to a large amount of evidence from research, ferritin is closely related to cognitive impairment after trauma. In addition, Cesare et al [7] studied and found that the ferritin content in the peripheral blood of patients with subarachnoid hemorrhage was abnormally and significantly increased. The study illustrated that patients who subsequently had chronic hydrocephalus requiring CSF shunting were associated with higher CSF levels of ferritin in the acute stage of SAH. Higher CSF ferritin levels may not reflect the amount of blood in the subarachnoid space that was intracranially metabolized, but rather more intense subarachnoid inflammatory reactions which may cause chronic hydrocephalus after SAH [8]. The evidence from clinical data suggest that CSF ferritin levels may be an important additional laboratory test in the diagnostic work-up of patients with suspected SAH. CSF ferritin levels may prove particularly helpful in cases with late presentation if the CT brain scan is normal and CSF bilirubin level is undetectable [9].

Serum ferritin levels have been related to adverse cardiovascular and stroke outcomes. It has been shown that elevated ferritin levels, ICH volume together with decreased GCS, were characterized among groups with adverse prognosis. In addition, serum ferritin was moderately correlated with GCS ($r=-0.643$), ICH volume ($r=0.562$), and had significantly higher correlation with long-term prognostic scores on the 7th day mRS ($r=0.802$) and 30th day mRS ($r=0.916$), presenting as a possible prognostic index for Acute Hemorrhagic Stroke [10]. It has been revealed that baseline serum ferritin level at admission may predict the short-term prognosis of patients with ICH, and may provide a new target for intracerebral hemorrhage therapy [11], while a combination of serum iron, ferritin and transferrin, is suggested to predict outcome in patients with intracerebral hemorrhage [12].

Currently, early repair of an aneurysm is the most important therapeutic measure for aneurismal subarachnoid hemorrhage, in which surgical clipping and interventional embolization therapy can effectively prevent recurrence of hemorrhaging and cerebral vasospasms [13]. It has been demonstrated that the 5-year survival rate of patients after interventional therapy is significantly improved compared to that of patients receiving surgical clipping; indicating the potential of interventional embolization therapy after hemorrhage [14]. Rong et al [15] reported that minimally-invasive intravascular interventional therapy combined with drug therapy can effectively improve the prognosis of patients with aneurismal subarachnoid hemorrhage. The development of minimally-invasive endovascular techniques dramatically elevated the treatment rate of patients with aneurismal subarachnoid hemorrhage. Moreover, Patil et al [16] suggested that the time of interventional therapy for subarachnoid hemorrhage was closely related to the prognosis of patients and underscored that the appropriate time of treatment was of great importance. In this study, the influence of different intervention times on the therapeutic effect and the indicator value for prognosis were evaluated among patients with aneurismal subarachnoid hemorrhage.

Patients and methods

Research subjects and grouping

Initially, 384 patients with aSAH treated in The Jiangyin Clinical College of Xuzhou Medical University from August 2015 to August 2017 were screened. Inclusion criteria: 1) patients were diagnosed with spontaneous subarachnoid hemorrhage by imaging examination or lumbar puncture, 2) patients were diagnosed with aneurysm by digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or surgery and SAH caused by the aneurysm, 3) patient, or the patient’s legally authorized representative consented to the treatment on the patient’s behalf, signed and dated the informed consent documents, agreed with the interventional therapy and conformed to the diagnosis, and 4) clinical data was completed. Exclusion criteria: 1) patients who were not definitely diagnosed with intracranial aneurysm, 2) patients whose SAH was not caused by aneurysm, 3) patients with other severe diseases seriously affecting their survival time, or 4) patients who didn’t agree with the interventional therapy. Finally, a total of 78 patients who met the criteria were selected, including 36 male patients aged 42-76 years old and 42 female patients aged 45-73 years old. All subjects signed the informed consent, and this
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clinical trial was approved by the Ethics Committee of The Jiangyin Clinical College of Xuzhou Medical University.

Grouping

The patients were divided into the following groups based on the time from the occurrence of SAH to the treatment intervention: the ultra-early stage group (the time from the occurrence of hemorrhage to the interventional therapy was within 24 h) including 21 cases, the early stage group (the duration from the occurrence of hemorrhage to the interventional therapy was within 24-72 h) including 32 cases, and the late stage group (the duration from the occurrence of hemorrhage to the interventional therapy was more than 72 h) including 25 cases. All the patients were subjected to embolization treatment, as well as received the same maintenance treatment and care after operation.

Evaluation of therapeutic effect

The patients were followed up for 90 d. The incidence rate of postoperative complications in patients and the therapeutic effects were evaluated as previously reported, by examinations including corresponding cerebral angiography and brain CT [17]. The side effects or complications included intracranial hematoma, cerebral hernia, cerebral vasospasm, brain swelling and massive cerebral ischemia.

Detection of serum ferritin levels

Fasting venous blood was drawn from patients at 30 d, 60 d and 90 d after treatment. The content of serum ferritin was detected by using Ferritin ECLIA (Roche E-170). The value of ferritin levels was automatically read and all calculations were performed by the Hitachi Mod PE® Software system using a machine-stored calibration curve.

Prognosis evaluation of patients

The prognosis of patients was evaluated by Glasgow Outcome Scale (GOS), along with result of cerebral angiography and brain CT, at 30 d, 60 d and 90 d after operation. Full recovery or mild disability in patients indicated good prognosis (5-4 points), severe disability or vegetative status indicates poor prognosis (3-2 points). One point meant the patients died.

The postoperative cognitive function of patients was evaluated by Montreal cognitive assessment (MoCA), at 30 d, 60 d and 90 d after operation: The full score was 30 points (26 points or more for normal cognitive function, 14-26 points for the mild cognitive impairment, 9-14 points for the moderate cognitive impairment and 0-9 points for the severe cognitive impairment). A low score suggested the severe cognitive impairment.

Statistical analysis

The data were analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The measurement data of this study were expressed as mean ± standard deviation. Continuous data from multiple groups at the same time point were analyzed by using one-way ANOVA, with the Tukey’s post hoc test. Chi-square test was used for enumeration data. Pearson analysis was conducted for the correlation analysis between serum ferritin levels, prognosis and the time of interventional therapy. P<0.05 suggested that the difference was statistically significant.

Results

General data analysis

General data of patients enrolled in each group were recorded and analyzed. Results revealed that there were no statistically significant differences in age, gender, history of hypertension and diabetes mellitus, amount of bleeding and aneurysm site in patients among the ultra-early stage group, early stage group and late stage group (P>0.05), but significant difference was found in the timing of the treatment (P<0.01). The period from hemorrhage to treatment was (15.8±5.6) h in ultra-early stage group, (53.8±11.5) h in early stage group and (138.6±15.9) h in late stage group, respectively (Table 1).

The incidence rate of adverse reactions after treatment

We found that the incidence rate of adverse reactions in patients in the ultra-early stage group and early stage group were markedly lower than that in the late stage group (P<0.05). The rate of the ultra-early stage group was significantly reduced compared to that in the early stage group (P<0.05) (Figure 1).
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Comparison of serum ferritin content after operation among groups of patients

Serum ferritin was detected in each group of patients at 30 d, 60 d and 90 d after operation. Results demonstrated that the serum ferritin content in patients in the ultra-early stage group and early stage group at 30 d, 60 d and 90 d after operation were significantly decreased compared to that in the late stage group (P<0.05). The contents in the ultra-early stage group were statistically lower than that in the early stage group (P<0.05) (Figure 2).

Comparison of prognosis among groups of patients

The prognosis of patients in each group was evaluated using GOS at 30 d, 60 d and 90 d after operation, and the cognitive impairment of patients in each group was evaluated using the MoCA scale. Of note, the GOS and MoCA scores of patients in the ultra-early stage group and early stage group at 30 d, 60 d and 90 d after operation were remarkably higher than those in late stage group (P<0.05). Especially, the scores in the ultra-early stage group were even significantly reduced compared to those in the early stage group (P<0.05) (Figure 3).

Correlation analysis between time of interventional therapy and serum ferritin

We further assessed the correlation between the duration time from the occurrence of hemorrhage to the interventional therapy (time of interventional therapy) and serum ferritin content via Pearson analysis. The data revealed that the in-time interventional therapy was implicated with low levels of serum ferritin content. Furthermore, the time of interventional therapy had a significantly positive correlation with serum ferritin content (P<0.05, r²=0.395) (Figure 4).
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The correlation between time of interventional therapy and prognosis was evaluated. Results revealed that timeliness of interventional therapy ensured good prognosis. Moreover, the time of interventional therapy presents as a negative correlation with GOS score (P<0.05, r²=0.482) and MoCA score (P<0.05, r²=0.468) (Figure 5).

Discussion

The most common cause of subarachnoid hemorrhage is a hemorrhage from an aneurysm, which results in an important correlation to death and disability. The prognosis of patients with aneurismal subarachnoid hemorrhage is often unfavorable, and adverse reactions after treatment present as main factors leading to death [18]. Kożba-Goszyńska et al [19] revealed that vasospasm and intracranial hematoma after treatment of patients with aneurismal subarachnoid hemorrhage were significantly associated with the prognosis and cognitive function of patients. Notably, the development of interventional therapy has significantly improved the survival rate and reduced the poor prognosis ratio among patients with aneurismal subarachnoid hemorrhage [20]. Moreover, Petersmann et al [21] illustrated that the serum ferritin content in patients with subarachnoid hemorrhage was significantly increased within 2 weeks and gradually declined after treatment. Subarachnoid hemorrhage leads to local ischemia and hypoxia in brain tissues, and the subsequent accumulation of a large number of inflammatory mediators and macrophages in the body that destroy red blood cells, resulting in the release of a lot of iron ions. These iron ions will produce a great deal of ferritin and hydroxyl radicals with strong toxicity, both of which further cause damage in neurons [22]. Importantly, subarachnoid hemorrhage can deconstruct the blood-brain barrier, and enable ferritin from brain tissues into the peripheral blood through the

Figure 2. Comparison of serum ferritin content among groups of patients. The serum ferritin content in patients in the ultra-early stage group and early stage group at 30 d, 60 d and 90 d after operation was significantly lower than that in the late stage group. In the ultra-early stage group, it was also significantly lower than that in the early stage group (**P<0.01, comparison between two groups).

Figure 3. Comparison of prognosis among groups of patients. (A) GOS score, (B) MoCA score. The GOS and MoCA scores of patients in the ultra-early stage group and early stage group at 30 d, 60 d and 90 d after operation were significantly higher than those in late stage group. In the ultra-early stage group, they were also significantly higher than those in the early stage group (**P<0.01, comparison between two groups).
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blood-brain barrier. Previous evidence revealed that the ferritin content in the peripheral serum has a positive correlation with that in the cerebrospinal fluid. As the ferritin content in the peripheral serum of patients with subarachnoid hemorrhage is abnormally and significantly increased, it is suggested to predict the ferritin content in brain tissue by measuring the levels in the peripheral serum [23]. In this study, our data further reveal that the time of interventional therapy had a weak and positive correlation with serum ferritin content but shared a weak negative correlation with GOS and MoCA score; which refers to a bad prognosis if the score decreases. Similarly, in the study of iron overload measurement by means of exfoliative cytology, a weak positive correlation between positivity of buccal smears for Perl’s Prussian blue staining and respective serum ferritin levels, was found from 50 thalassemic patients [24]. In a study of 85 hemodialysis patients, a weak association was indicated between serum ferritin and serum iron [25]. We therefore propose that a larger sample size may be required in further study to evaluate the value of serum ferritin and prognosis on the interventional therapy based on our preliminary data regarding a weak correlation between serum ferritin, prognosis and the time of therapy.

In this study, patients with aneurismal subarachnoid hemorrhage receiving interventional therapy were selected to evaluate the effects of the therapy at an ultra-early, early and late stage to measure the therapeutic effect, serum ferritin and prognosis. Our results revealed that the incidence rate of postoperative adverse reactions was significantly reduced in patients receiving interventional therapy sooner. Previous study on the safety and efficacy of ferric carboxymaltose in the treatment of iron deficiency anemia in patients with Inflammatory Bowel Disease present that rapid application of relevant therapy was convenient for physicians and reduced patients’ time lost from work [26]. We propose that the timing interventional therapy can greatly alleviate the damage to red blood cells during hemorrhage due to the production of a large number of inflammatory factors and macrophages, and reduce the occurrence of intracerebral edema as well as cerebrovascular injury. In addition, Hu et al [27] suggested, based on a study in a rat model, that the sooner the rats with subarachnoid hemorrhage received interventional therapy, the lower the incidence rate of intracranial hematoma. In line with the previous findings regarding the reliability of the rise of ferritin in the evaluation of CNS severity [28], we observed that the ferritin content was also increased.

Figure 4. Correlation analysis between time of interventional therapy and serum ferritin. The time of interventional therapy presents a positive correlation with the serum ferritin content in patients.

Figure 5. Correlation analysis of time of interventional therapy with GOS score and MoCA score of patients. A. Correlation analysis between time of interventional therapy and GOS score. B. Correlation analysis between time of interventional therapy and MoCA score. The time of interventional therapy is negatively correlated with the GOS score and MoCA score of patients.
among patients from different groups. Notably, its content in the ultra-early stage group was statistically lower than that in early or late stage group, suggesting the necessity of the therapy over time. Besides, as Glasgow Outcome Scale and Montreal Cognitive Assessment are generally employed in the efficacy evaluation of medicine on patients with Aneurysmal Subarachnoid Hemorrhage (aSAH), we also adopted GOS and MoCA to test the impact on aSAH [29]. The results of GOS and MoCA further validated the rapid interventional therapy denoted a more favorable outcome.

According to the study of Watson et al [33], the ferritin content in brain tissue is closely related to the cognitive impairment of patients with hemorrhagic brain injury, and the decline in serum ferritin effectively displays a decrease in the ferritin content in the brain, which can obviously reduce the damage of iron ions to nerve function, effectively improve the prognosis and alleviate the cognitive impairment of patients. Similar to that, our study also revealed that the sooner the interventional therapy was given, the better the prognosis and the milder the postoperative cognitive impairment of patients. Also, it has been indicated that the cognitive impairment gradually deteriorates in patients with the delay of interventional therapy [31]. Our data showed embolization therapy can effectively control the risk of poor prognosis, which is consistent with previous evidence of embolization in prevention of the recurrence of hemorrhage [32].

The results at 30 d, 60 d and 90 d after operation indicated that the level of serum ferritin presents a decreasing trend, which was in line with previous data on iron chelation therapy that at 6 months, participants exhibited a clinically relevant decrease in serum ferritin, which trended toward statistical significance [30]. However, the limitation in this study still exists that the observation duration of the post-operation should be extended from 90 days, within a larger number of patients, which may provide comprehensive views and evaluations on the value of ferritin towards the prognosis of SAH after the interventional therapy.

**Conclusion**

In conclusion, our data demonstrated that the different time of interventional therapy for patients with aneurismal subarachnoid hemorrhage can significantly affect the therapeutic effect and prognosis of patients, which provides insights that patients with aneurismal subarachnoid hemorrhage should be treated with interventional therapy as soon as possible, in order to reduce the poor prognosis and risk of cognitive impairment of patients.

**Disclosure of conflict of interest**

None.

**Address correspondence to:** Dr. Xinmin Zhou, Department of Neurosurgery, The Jiangyin Clinical College of Xuzhou Medical University, No.3 Yingrui Road, Jiangyin 214400, Jiangsu, China. Tel: +86-0510-88017063; Fax: +86-0510-88017063; E-mail: xinminzhou940@163.com

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