J Neurol (2014) 261:324–329
DOI 10.1007/s00415-013-7198-2

ORIGINAL COMMUNICATION

A treatment option for severe cerebellar hemorrhage with ventricular extension in elderly patients: intraventricular fibrinolysis

Jianjian Zhang · Long Wang · Zhongwei Xiong · Qingdong Han · Qidong Du · Shoujia Sun · Yu Wang · Chao You · Jincao Chen

Received: 28 August 2013 / Revised: 14 November 2013 / Accepted: 16 November 2013 / Published online: 3 December 2013

Abstract External ventricular drainage (EVD) combined with intraventricular fibrinolysis (IVF) is rarely used in severe spontaneous cerebellar hemorrhage (SCH) with intraventricular hemorrhage (IVH). Recently, the treatment strategy was repeatedly performed in our hospital to elderly patients with severe SCH + IVH. To analyze its clinical value, we compared it to two treatment strategies which now commonly are used for these patients: conservative management (CM) and clot evacuation (CE). In this study, a total of 118 cases were observed, of which 28 cases received CM, 43 cases received EVD + IVF and 47 cases received CE. The Glasgow Coma Scale score, frequency of complication, mortality in one month, modified Rankin Scale (mRS) at six months, and causes of death were analyzed. The outcomes of patients in the CM group were extremely poor compared to patients undergoing surgery ($P = 0.034$) and the mortality was up to 61.3 % (18/28), which was much higher than those of the two surgical groups ($P = 0.026$). No significant difference was found in mortality and mRS between the two surgical groups ($P > 0.05$). Patients in the CE group mostly died of deterioration of comorbidities and postoperative complications, whereas more deaths occurred in the CM group and the EVD + IVF group due to rebleeding, brainstem compression, perilesional edema and tight posterior fossa (χ^2, $P = 0.006$). It is suggested that EVD + IVF is a treatment option for elderly patients with severe SCH + IVH.

J. Zhang · L. Wang · Z. Xiong · Q. Han · Q. Du · S. Sun · Y. Wang · C. You · J. Chen (✉)
Department of Neurosurgery, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, 1095#, Jiefang Avenue, Wuhan 430030, Hubei, China
e-mail: chenjincao2012@hotmail.com

Keywords Elderly · Intracerebral hemorrhage · Fibrinolysis · Urokinase · Hypertension

Introduction

Spontaneous cerebellar hemorrhage (SCH) comprises about 5 to 10 % of all spontaneous intracerebral hemorrhages [5], which are most commonly caused by hypertension [3]. Because of its close proximity to the fourth ventricle, SCH is frequently complicated by intraventricular hemorrhage (IVH) [2, 13, 14, 18]. The treatment strategies for patients with SCH + IVH reported in previous studies are different. The "sticking points" indicating treatment are based on the hematoma size and absence or presence of hydrocephalus [7–9, 16, 21]. It is commonly advocated that a severe SCH (diameter >3 cm) with obstructive hydrocephalus should be removed surgically as soon as possible [1]. Clot evacuation (CE) has been strongly recommended by most neurosurgeons until now [3, 7, 9, 21], as external ventricular drainage (EVD) alone was found to be ineffective in some cases [3, 6, 9, 19]. However, not all patients are suitable for CE [6–8] such as elderly patients, most of whom have various comorbidities. A previous study showed that the presence of a single general risk factor such as diabetes, arterial hypertension, blood dyscrasia, and liver disease, might affect the survival outcome, and the combination of two or more of these risk factors statistically worsened the outcome [14]. These findings were also reported by other groups [6–8, 10].

As CE, EVD alone and conservative management (CM) are all not very suitable for elderly patients with severe SCH + IVH [1, 3, 6–10, 19], other treatment options are needed. During the past 20 years, intraventricular fibrinolysis (IVF) after EVD was developed to remove primary

IVH or IVH secondary to supertentorial hemorrhage [4]. However, no study concerning IVF for IVH secondary to cerebellar hemorrhage was found. In the present study, we retrospectively analyzed a consecutive series of elderly patients with severe SCH + IVH who were treated by CE, EVD + IVF or CM. To investigate the clinical value of EVD + IVF for elderly patients with severe SCH + IVH, we compared the treatment courses including complications, outcomes, and causes of death to those of patients who treated by CE and CM.

Methods

Patient sample

From June 2007 to March 2013, a sample of patients with first-time spontaneous cerebellar hemorrhage were consecutively admitted to our neurosurgical unit. The basic inclusion criteria of these patients were as follows: (1) age $\geq$65 years; (2) hemorrhage extending to the ventricles; and (3) maximum diameter of the original hematoma $\geq$3 cm. Patients with hematomas from trauma, tumors, vascular malformations, aneurysms, and cerebral infarctions, were excluded from this study. The institutional ethics committee approved our research protocol.

Radiological evaluation

Computed tomography (CT) scan was performed for each patient at admission. All radiographic parameters (location and maximum diameter of the original hematoma, absence or presence of hydrocephalus) were analyzed.

Treatment protocol and methods

All patients were provided three optional treatment protocols: CM, EVD + IVF, and CE. Due to the fact that these patients had severe SCH + IVH, CE was initially recommended. If CE was rejected, EVD + IVF was proposed as the second option. When both surgical protocols were refused, CM was subsequently performed. All surgical patients underwent operations within 8 h after ictus.

Patients who selected EVD + IVF were treated as below. For EVD, according to the IVH volume, a unilateral or bilateral ventricular drainage was performed under local anesthesia and intravenous sedation. Continuous CSF drainage was kept for 6 h after surgery with the rate being strictly controlled. For IVF, a $\sim$5 ml CSF was removed by each catheter followed by 20,000–30,000 U urokinase delivered in 3 ml saline solution, 2 ml saline solution flush and with the catheter(s) clamped for 4 h. The IVF was repeated two or three times a day during the early stage of treatment.

Patients accepting CE were traditionally treated with suboccipital decompression and clot evacuation under general anesthesia with endotracheal intubation.

Outcome assessment

Evaluation of all 118 patients followed a uniform standard. Basic demographic data, clinical and radiological parameters and the clinical course were retrospectively recorded.

All discharged patients were followed up in the outpatient clinic as far as possible. When a patient was lost to follow-up, a telephone interview was performed. Mortality in one month and the modified Rankin Scale (mRS 0–6) scores at six months were applied to estimate outcomes.

To compare curative effects of the three treatment protocols, post-treatment parameters including GCS score, frequency of complication, mortality in one month and mRS at six months were analyzed. A poor outcome was defined as death or the dependency of daily living provided by others (mRS 4–6).

The causes of death, which grouped as directly-related or indirectly related to hematoma, were compared between the three groups. Causes of death including rebleeding, brainstem compression, perilesional edema and tight posterior fossa were generally considered to be directly related to hematoma. On the other hand, death occurring due to a sharp deterioration of co-existing illnesses or the presence of serious complications was thought to be indirectly related to hematoma.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation. One-way ANOVA was repeatedly performed to compare normally distributed continuous variables including age, clot diameter, MABP and GCS score between the three groups. Categorical variables such as gender, hematoma size, acute hydrocephalus, comorbidities, frequency of complication, death, mRS and causes of death were analyzed using Pearson's Chi-square test. All recorded data were statistically analyzed using the SPSS 13.0 software (SPSS Inc). P value <0.05 was considered to be statistically significant.

Results

Baseline characteristics

The baseline characteristics of the three groups including gender, age, hematoma site, diameter of hematoma,

Table 1 Baseline characteristics of the study sample

	CM ($n = 28$)	EVD + IVF ($n = 43$)	CE ($n = 47$)	P value
Gender, male	17 (60.7 %)	24 (55.8 %)	29 (61.7 %)	0.839
Mean age, year	73.11 ± 5.05	72.93 ± 4.80	71.87 ± 4.53	0.499
Hematoma site, *n* (%)				0.988
Vermis	9 (32.1)	15 (34.9)	17 (36.2)	
Hemisphere	15 (53.6)	21 (48.8)	22 (46.8)	
Vermis-hemisphere	4 (14.3)	7 (16.3)	8 (17.0)	
Mean maximum hematoma diameter, cm	3.83 ± 0.53	3.85 ± 0.52	3.97 ± 0.59	0.478
Acute hydrocephalus, *n* (%)	13 (46.4)	25 (58.1)	26 (55.3)	0.615
GCS at admission, *n* (%)				0.942
3–8	8 (28.6)	10 (23.3)	10 (21.3)	
9–12	9 (32.1)	17 (39.5)	19 (40.4)	
13–15	11 (39.3)	16 (37.2)	18 (38.3)	
Initial MABP, mm Hg	131.29 ± 8.26	131.91 ± 9.02	133.39 ± 11.05	0.622
Comorbidities, *n* (%)				
Hypertension	20 (71.4)	32 (74.4)	30 (65.2)	0.535
Coronary heart disease	10 (35.7)	12 (27.9)	14 (30.4)	0.776
Diabetes mellitus	15 (53.6)	19 (44.2)	20 (43.5)	0.629
Chronic bronchitis	8 (28.6)	13 (30.2)	18 (39.1)	0.609

CM conservative management, *EVD* extraventricular drainage, *IVF* intraventricular fibrinolysis, *CE* clot evacuation, *GCS* Glasgow Coma Scale, *MABP* mean arterial blood pressure

hydrocephalus, GCS at admission, initial MABP, and comorbidities are summarized in Table 1. The 118 elderly patients were treated by CM (28 cases), EVD + IVF (43 cases), and CE (47 cases). There was no statistically significant difference seen in baseline characteristics between the three groups.

Comparison of clinical course and outcome between the three groups

Table 2 compares the clinical course and outcome between the three groups. Causes of death are also described in this Table. In order to minimize the impact of anesthesia on consciousness grading in the surgical groups, postoperative GCS scores were evaluated at the first 24 h after surgery.

There were no statistically significant differences for the pretreatment GCS scores of these three groups (χ^2, $P = 0.935$). Because many patients in the CM group deteriorated and most patients in the EVD + IVF and CE groups ameliorated at the first 24 h after treatment, significant differences were found between the GCS scores of the three groups (χ^2, $P = 0.022$). However, the differences mainly were in the comparisons of CM group with the EVD + IVF group or the CE group (both $P < 0.05$, not shown). There was no significant difference between the two surgical groups ($P > 0.05$, not shown).

Data showed that the mortality in one month of the CM group was significantly higher than those of the EVD + IVF group and the CE group (χ^2, $P = 0.026$), but no difference was observed between the latter two groups ($P > 0.05$, not shown). In addition, we found that patients in the CE group mostly died of diseases indirectly related to hematoma, whereas more deaths occurred in the CM group and the EVD + IVF group were directly related to hematoma (χ^2, $P = 0.006$). According to the mRS at six months, patients in the CM group were far more likely to have poor outcomes than those in the EVD + IVF group and CE group (χ^2, $P = 0.034$). No difference emerged when further comparing the mRS of the EVD + IVF group to those of the CE group ($P > 0.05$, not shown).

Although there were no sharp differences in frequency of pulmonary infection (χ^2, $P = 0.057$) and digestive tract hemorrhage (χ^2, $P = 0.156$) between the three groups, patients in the CE group and the CM group more likely presented secondary hospital-acquired pneumonia when compared to those of the EVD + IVF group ($P < 0.05$, not shown).

Discussion

IVH is common in patients with severe SCH [2, 13, 14, 18]. However, independent case series for elderly patients with severe SCH + IVH are scarcely reported. According to the reported studies of severe SCH, three treatment strategies were widely used: CM, EVD alone and CE [6, 9,

Table 2 Comparisons of clinical course, outcome and causes of death between the three groups

	CM ($n = 28$)	EVD + IVF ($n = 43$)	CE ($n = 47$)	P value
GCS score				
At admission	10.46 ± 3.26	10.19 ± 3.38	10.36 ± 3.17	0.935
24 h after treatment	9.04 ± 4.57[a]	11.40 ± 3.63	11.40 ± 3.65	0.022
Frequency of complication, *n* (%)				
Pulmonary infection	13 (46.4)	10 (23.3)[b]	21 (44.7)	0.057
Digestive tract hemorrhage	11 (39.3)	9 (20.9)	10 (21.3)	0.156
Mortality in one month, *n* (%)	18 (61.3)	16 (38.1)[c]	16 (34.0)	0.026
mRS at 6 months, *n* (%)				0.034
0–3	7 (25.0)	21 (48.8)[d]	26 (55.3)	
4–6	21 (75.0)	22 (51.2)[d]	21 (44.7)	
Causes of death, *n* (%)				0.006
Directly-related to hematoma	15 (83.3)	12 (75.0)[e]	6 (37.5)	
Indirectly-related to hematoma	3 (16.7)	4 (25.0)[e]	10 (62.5)	

EVD extraventricular drainage, *IVF* intraventricular fibrinolysis, *CE* clot evacuation, *GCS* Glasgow Coma Scale, *mRS* modified Rankin Scale

[a] Compared to EVD + IVF or CE $P < 0.05$

[b] Compared to CM or CE $P < 0.05$

[c,d] Compared to CM $P < 0.05$; compared to CE $P > 0.05$

[e] Compared to CM $P > 0.05$; compared to CE $P < 0.05$

17, 19]. As is known, CM is critical in conscious patients without progressive neurological deterioration [2, 6, 7, 13, 14, 18]. EVD is the treatment of an option for obstructive hydrocephalus in the setting of an IVH [6, 16], but it loses its effectiveness when the cerebrospinal fluid pathway and ventricular catheters are obstructed by clots. For a severe SCH with or without IVH, CE is still the most effective treatment until now. However, most elderly people, especially those with various comorbidities, are unable to tolerate CE [6, 18]. As reported in the latest research, high age was considered to be the strongest prognostic factor for an unfavorable outcome [18]. Due to the fact that beneficial effects of the three treatments for elderly patients with severe SCH + IVH are unresolved, other treatment selections are needed.

EVD + IVF could be the fourth strategy. Compared to EVD alone for IVH, EVD + IVF can hasten the resolution of intraventricular blood clots, improve the cerebrospinal fluid circulation and provide a faster control of intracranial pressure [4, 11]. In our study, we retrospectively compared the clinical courses and outcomes of patients accepting EVD + IVF to those of patients who were treated by CE and CM. Although the consciousness status of most patients deteriorated after admission ($P < 0.001$, not shown in the table), the GCS scores at the first 24 h after operation for the EVD + IVF group and the CE group were not significantly different ($P > 0.05$). These results indicated that deterioration in these patients might be caused mainly by acute hydrocephalus rather than severe brainstem compression [6]. Given that brain atrophy and ventricular enlargement are common in the elderly (Fig. 1), a large hematoma may not exert significant brainstem compression or a severe clinical course in the presence of

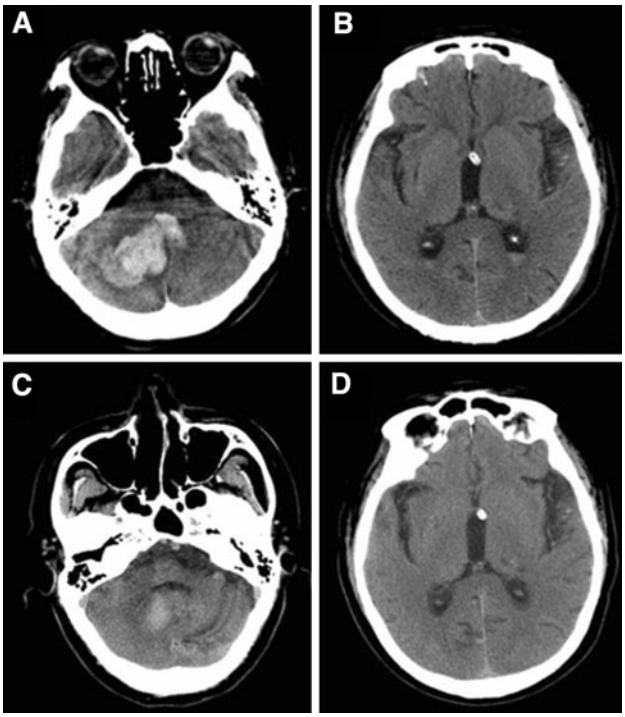

Fig. 1 CT scans of a patient (GCS score 10) with a large hematoma at 12 h after EVD (**a**, **b**), and CT scans of the same patient during consciousness (GCS score 15) one week after EVD + IVF (**c**, **d**). The original hematoma was successfully removed in one week after EVD + IVF and obvious brain atrophy was found from the scans

cerebellar atrophy [6–8]. In this situation, EVD + IVF may be helpful.

CM proved to be ineffective in our study mainly because a hemorrhage in the fourth ventricle was constantly associated with severe obstructive hydrocephalus [6]. Many patients in the CM group deteriorated and presented various complications during their treatment courses. The outcomes were extremely poor compared to patients undergoing surgery ($P = 0.034$) and the mortality was up to 61.3 % (18/28) which was much higher than those of the two surgical groups ($P = 0.026$). As with some previous researches [3, 7, 9, 21], CE was still the most effective treatment in our study. Patients in the CE group had the lowest mortality (34 %, 16/47) and the best outcomes at six months (55.3 %, 26/47). However, after further comparing the mortality and mRS of the CE group to those of the EVD + IVF group, we found no sharp difference between these two groups ($P > 0.05$, not shown). To clarify the reason, frequency of complication and causes of death were analyzed. As a result, we found CM and EVD + IVF tended to lose their effectiveness in the cases with severe brainstem compression and tight posterior fossa in the acute phase, compared to CE ($P = 0.006$). On the contrary, patients of the CE group were more likely to die from the sharp deterioration of comorbidities and serious complications such as pulmonary infection (compared to EVD + IVF, $P < 0.05$).

Similar to previous reports [11, 12, 15], IVF was found to be safe and effective in our study. Only two cases of ventriculitis, two episodes of re-bleeding and one upward herniation, were presented in the EVD + IVF group. Interestingly, as reported in a recent article [20], blood in the third and fourth ventricles cleared quickly after initiation of IVF. Furthermore, during the IVF courses, a rapid resolution of the original hematoma was unexpectedly observed in the first week following IVH clearance in most survivors (Fig. 1).

Conclusion

CE is still the most effective treatment for elderly patients with severe SCH + IVH, whereas CM is not recommended according to our study. However, when the patients considered can not tolerate CE due to their serious comorbidities, EVD + IVF may be another treatment option. It must be clarified that our research is only a retrospective study and has many limitations. For example, the treatment selection is easily influenced by the ideas of the legal deputies or the doctors. To more objectively evaluate the curative effects of EVD + IVF for this kind of patients, large randomized trials are required. We think high age and various comorbidities may be the most important factors that need to be studied in the further researches.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, Mayberg M, Morgenstern L, Ogilvy CS, Vespa P, Zuccarello M (2007) Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke 38:2001–2023
2. Dammann P, Asgari S, Bassiouni H, Gasser T, Panagiotopoulos V, Gizewski ER, Stolke D, Sure U, Sandalcioglu IE (2011) Spontaneous cerebellar hemorrhage–experience with 57 surgically treated patients and review of the literature. Neurosurg Rev 34:77–86
3. Ferro JM (2006) Update on intracerebral haemorrhage. J Neurol 253:985–999
4. Gaberel T, Magheru C, Parienti JJ, Huttner HB, Vivien D, Emery E (2011) Intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage: a meta-analysis. Stroke 42:2776–2781
5. Heros RC (1982) Cerebellar hemorrhage and infarction. Stroke 13:106–109
6. Kirollos RW, Tyagi AK, Ross SA, van Hille PT, Marks PV (2001) Management of spontaneous cerebellar hematomas: a prospective treatment protocol. Neurosurgery 49:1378–1386 (discussion 1386–1377)
7. Kobayashi S, Sato A, Kageyama Y, Nakamura H, Watanabe Y, Yamaura A (1994) Treatment of hypertensive cerebellar hemorrhage–surgical or conservative management? Neurosurgery 34:246–250 (discussion 250–241)
8. Koziarski A, Frankiewicz E (1991) Medical and surgical treatment of intracerebellar haematomas. Acta Neurochir 110:24–28
9. Lui TN, Fairholm DJ, Shu TF, Chang CN, Lee ST, Chen HR (1985) Surgical treatment of spontaneous cerebellar hemorrhage. Surg Neurol 23:555–558
10. Morioka J, Fujii M, Kato S, Fujisawa H, Akimura T, Suzuki M, Kobayashi S, Japan Standard Stroke Registry G (2006) Surgery for spontaneous intracerebral hemorrhage has greater remedial value than conservative therapy. Surg Neurol 65:67–72 (discussion 72–63)
11. Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A (2000) Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. J Neurol 247:117–121
12. Nyquist P, Hanley DF (2007) The use of intraventricular thrombolytics in intraventricular hemorrhage. J Neurol Sci 261:84–88
13. Pong V, Chan KH, Chong BH, Lui WM, Leung GK, Tse HF, Pu JK, Siu CW (2012) Long-term outcome and prognostic factors after spontaneous cerebellar hemorrhage. Cerebellum 11:939–945
14. Salvati M, Cervoni L, Raco A, Delfini R (2001) Spontaneous cerebellar hemorrhage: clinical remarks on 50 cases. Surg Neurol 55:156–161 (discussion 161)
15. Shen PH, Matsuoka Y, Kawajiri K, Kanai M, Hoda K, Yamamoto S, Nishimura S (1990) Treatment of intraventricular hemorrhage using urokinase. Neurol Med Chir 30:329–333
16. Shenkin HA, Zavala M (1982) Cerebellar strokes: mortality, surgical indications, and results of ventricular drainage. Lancet 2:429–432

17. St Louis EK, Wijdicks EF, Li H, Atkinson JD (2000) Predictors of poor outcome in patients with a spontaneous cerebellar hematoma. Can J Neurol Sci 27:32–36
18. Tsitsopoulos PP, Tobieson L, Enblad P, Marklund N (2012) Prognostic factors and long-term outcome following surgical treatment of 76 patients with spontaneous cerebellar haematoma. Acta Neurochir 154:1189–1195
19. van Loon J, Van Calenbergh F, Goffin J, Plets C (1993) Controversies in the management of spontaneous cerebellar haemorrhage. A consecutive series of 49 cases and review of the literature. Acta Neurochir 122:187–193
20. Webb AJ, Ullman NL, Mann S, Muschelli J, Awad IA, Hanley DF (2012) Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic: the clot lysis: evaluating accelerated resolution of IVH (CLEAR IVH) program. Stroke 43:1666–1668
21. Zieger A, Vonofakos D, Steudel WI, Dusterbehn G (1984) Nontraumatic intracerebellar hematomas: prognostic value of volumetric evaluation by computed tomography. Surg Neurol 22:491–494