European Review for Medical and Pharmacological Sciences 2014; 18: 3653-3658

Sequential therapy for non-thalamus supratentorial hypertensive intracerebral hemorrhages

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Abstract. – OBJECTIVE: We sought to assess the effectiveness of sequential therapy for non-thalamus supratentorial hypertensive intracerebral hemorrhage (NTS-HICH).

PATIENTS AND METHODS: We retrospectively analyzed clinical data of 110 patients with HICH. The patients were admitted 72 hours after disease onset, and 43 patients received sequential therapy. The length of hospital stay, treatment costs, incidence of pulmonary infections, mortality rates and Modified Rankin Score (mRS) 1 and 3 months after NTS-HICH were compared between patients who received sequential or non-sequential therapies.

RESULTS: The length of hospital stay, treatment costs, and 1-month mortality rates were not significantly different between both groups. However, mortality rates at 3 months, incidence of pulmonary infection, and mRS at both 1 and 3 months were significantly better in patients who received sequential therapy.

CONCLUSIONS: Sequential therapy significantly improves the prognosis for patients with NTS-HICH.

Key Words:
Non-thalamus supratentorial cerebral hemorrhage, Hypertension, Sequential therapy, Modified Rank score, Drainage.

Introduction

Hypertensive intracerebral hemorrhages (HICH) account for 10-15% of acute cerebrovascular diseases and have been recognized as a major cause of mortality and disability in patients with stroke[1-3]. There are no established recommendations for the treatment. In this study, we evaluated the effectiveness of sequential therapy which is a standard procedure in the treatment of patients with HICH. Sequential therapy was based on recent publications on HICH[4-10]. Our findings demonstrate that sequential therapy has an important factor in the management of HICH, and improves prognosis and reduces occurrence of pulmonary infection.

Patients and Methods

Patients

We retrospectively evaluated clinical data of patients with HICH whose disease onset was less than 72 hours before hospitalization and whose diagnosis was confirmed by head CT imaging. The diagnosis of HICH was made according to the diagnostic criteria of Guidelines for the primary prevention of stroke in American Heart Association Stroke Council the 5th National Academic Conference of Cerebrovascular Disease.[11]. The patients were part of the HICH database.

Patients were excluded if they had the following: (1) cerebral hemorrhage induced by intracranial aneurysms, arteriovenous malformations, tumors, trauma or general conditions, such as blood disorders; (2) hemorrhages following cerebral infarction; (3) concomitant serious conditions, such as severe heart, liver, kidney, lung disorders or dysfunctions; (4) prior history of ipsilateral stroke and sequelae (e.g., limb dysfunction); (5) unknown medical histories prior to admission; (6) untreated and discharged patients or patients died after admission; (7) intraventricular, thalamus or subtentorial hemorrhages.

A hundred and ten patients were included in this study and comprised 72 (65.5%) male and 38 (34.5%) female patients, aging from 27-81 ([mean ± SD] 52.39 ± 11.74 years). Based on cerebral hemorrhage site, there were 102 cases of basal ganglia hemorrhages and 8 cases of lobar hemorrhages. Forty-three patients received sequential therapy, while 65 patients underwent

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non-sequential therapy. Both groups were comparable for age, gender, bleeding volume, bleeding site, and the Glasgow Coma Scale (GCS) scores at admission (Table I). Sequential therapy was administered as described below.

Procedures

The following procedures were used for the treatment of HICH:

1. In patients with the disease onset of < 24 hours and state of consciousness of up to light coma, blood pressure control and hemostasis were administered. Dehydration measures were not considered, and changes in consciousness were closely monitored.
2. In patients with the disease onset of < 24 hours and state of consciousness of more than light coma, a half dose of 20% mannitol was prescribed. In addition, a full dose of 20% mannitol, alone or in combination with other dehydration therapies, could also be administrated. The changes in consciousness were closely monitored. In case of improvement in consciousness, continuation of above interventions was consid-

Table I. Clinical parameters.

Clinical parameters	Sequential therapy	Non-sequential therapy	Chi-square	Z (t)	p
Number	43	67			
Male	27	45	0.222		0.638
Female	16	22			
Age (yrs)	51.49 ± 11.19	52.97 ± 12.13		-0.644*	0.521
Volume (ml)	36.42 ± 22.50	34.53 ± 20.54		-0.332	0.740
Locations					
Basal ganglia	41	61	0.719		0.396
Lobes of the brain	2	6			
Hospital awareness					
I	14	20	1.407		0.843
II	3	2			
III	5	9			
IV	18	29			
V	3	7			
Outcomes					
Hospitalization length (days)	12.99 ± 6.63	14.06 ± 7.40		-0.021	0.983
Treatment costs (USD)	5144.21 ± 3076.77	5135.52 ± 1991.35		-1.302	0.193
Mortality (1 month)	2 (4.65%)	9 (13.43%)	FET		0.196
Mortality (3 month)	2 (4.65%)	12 (17.91%)	FET		0.046
mRS (1 month)					
0	1	1	12.025		0.034
1	5	4			
2	6	3			
3	4	2			
4	20	24			
5	5	24			
mRS (3 months)					
0	3	4	13.322		0.021
1	5	6			
2	12	9			
3	16	11			
4	4	17			
5	1	8			
Pneumonia					
Yes	7 (16.30%)	23 (35.40%)	4.709		0.030
No	36 (83.70%)	42 (64.60%)			

Footnote: *t-test. FET: Fisher's Exact Test. mRS: Modified Rankin Scale: 0, no symptoms at all; 1, no significant disability, despite symptoms, able to carry out all usual duties and activities; 2, slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance; 3, moderate disability, requiring some help, but able to walk without assistance; 4, moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5, severe disability, bedridden, incontinent and requiring constant nursing care and attention. Comparison of the GCS scores and consciousness ratings: 14-15, level 1; 13, level 2; 10-12, level 3; 6-9, level 4; 3-5, level 5.

ered. However, in patients with no improvement, or those exhibiting deterioration of the state of consciousness, extracranial drainage against hematoma could be performed. If any post-operative improvement in consciousness was observed within 6 hours, urokinase(UK) (2-3 million units 25000IU to 30000IU, q.i.d.) was administered through the incranial infusion line for 3 hours at a time, with a 3 hour break between sessions, in order to drain 90% of hematoma within 48-72 hours. If there was no improvement, or deterioration was observed after this intervention, patients were subjected to craniotomy surgery in emergency.

3. In patients with the disease onset of > 24 hours, the state of consciousness below light coma, and bleeding volume of < 20 ml, conservative interventions, such as hemostasis, blood pressure control, and neurotrophic medications were undertaken. In patients with the bleeding volume of > 20 ml, a minimally invasive hematoma aspiration (MIHA) was applied, and post-operative treatments within 24 hours of the onset were administered as shown in Figure 1.

The evaluated patient data included average duration of hospitalization, cost, post-attack mortality at months 1 and 3, and modified Rankin score (mRS).

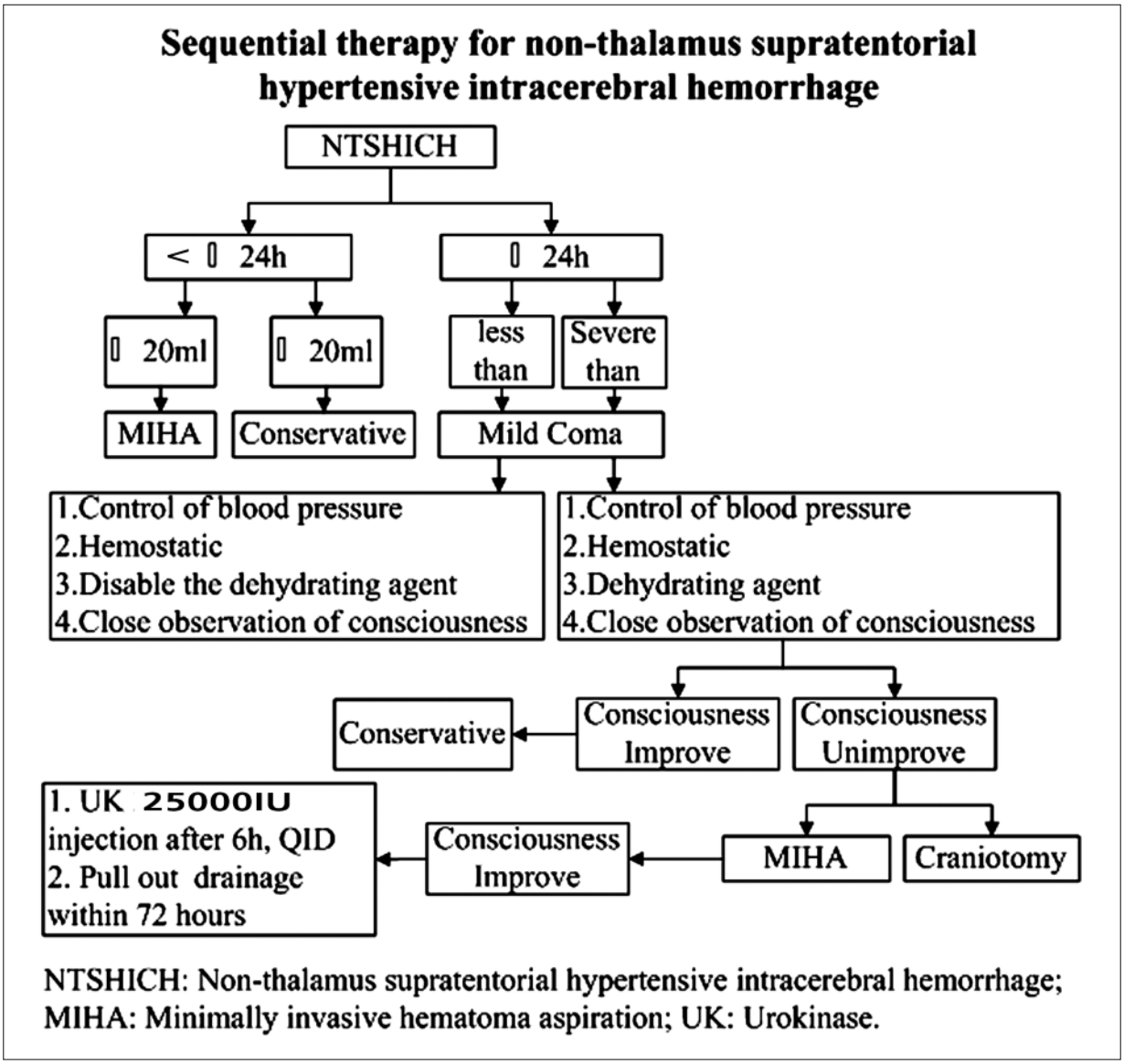

Figure 1.

Statistical Analysis

All statistical analyses were done using SPSS 13.0 software package (SPSS Inc., Chicago, IL, USA). Values are expressed as the mean ± SD. Quantitative data were analyzed by the *t*-test or nonparametric rank-sum test, while categorical data were compared using the chi square or Fisher exact tests. $p < 0.05$ was considered statistically significant.

Results

Both study groups were comparable for age, gender, bleeding volume, bleeding sites and GCS at admission (Table I). Further, there were also no statistically significant differences in hospitalization days, total expenditure, or one month mortality rates between both study groups (Table I). However, mortality at month 3, mRS scores at both month 1 and 3, and prevalence of pulmonary infection were significantly lower in patients who received sequential therapy (Table I). Specifically, with regard to pulmonary infection, there were 7 (16.30%) patients with pneumonias in the sequential therapy group and 23 (35.40%) patients in the non-sequential therapy group (Table I).

Discussion

Our basic principles of sequential therapy for HICH include prevention of hematoma expansion and reduction of secondary neurological damage. There is a correlation between hematoma expansion and deterioration of the early condition[12]. It was found that early disease deterioration is caused by hematoma enlargement, while deterioration 48 hours later is mainly caused by brain edema[12]. However, disease progression after 48 hours is mainly affected by cerebral edema. Therefore, an early prevention of hematoma expansion is a critical predictor of prognosis[12].

There are several approaches to control early hematoma expansion. First, intensive blood pressure control should be applied to prevent significant fluctuations in blood pressure. The target systolic blood pressure of < 140 mm Hg was suggested[6]. It was shown that intensive measures to lower blood pressure are associated with decreased prevalence of hematoma expansion[6]. As blood pressure controlling drugs, nimodipine or nicardipine can be considered, since these drugs prevent vasospasm, suppress regional cerebral edema, reduce secondary brain damage, and prolong antihypertensive effect[7]. Second, intracranial pressure-lowering agents can be used according to a specific protocol. Early interventions are often done with mannitol. However, the use of mannitol remains controversial, since this drug increases the pressure difference between inner and outer vessel walls of bleeding sites, and may thus lead to hemorrhage recurrence, acceleration of bleeding, or even hematoma expansion. Some reports indicate that the use of mannitol during the early stages of HICH is associated with an increased risk of hematoma expansion[4,13]. Therefore, the use of mannitol during early intervention depends on the state of consciousness. For patients within 24 hours after the onset and with the state of consciousness of up to light coma, the use of mannitol should be avoided. As an alternative, the blood pressure lowering therapies and hemostasis should be applied, while changes in the state of consciousness closely monitored. In patients with light coma, a half dose of 20% mannitol can be administrated. Furthermore, in moderate or severe coma, full dose of mannitol or a combination of mannitol with other dehydration drugs should be administrated. Third, hemostatic agents can be used early. There was no conclusive evidence demonstrating that early intervention is capable of effectively reducing hematoma expansion. Yet, hemostatic agents should be administered as early as possible, once the diagnosis of cerebral hemorrhage is confirmed.

Prevention of hematoma expansion may also attenuate secondary cerebral tissue damages. Patients with hematomas of > 20 ml are potential candidates for surgical interventions. The use of a minimally invasive hematoma aspiration at 24 hours is preferred in patients with a state of consciousness up to light coma, and UK is administrated at 24 hours after disease onset. In case of disease onset of more than 24 hours ago, UK is administrated every 6 hours after the puncture for three or four times, such as done in our study (infusion for 3 hours-5 hours with a break for 3 hours in-between). The hematoma should be removed by 90% within 72 hours of the puncture. Early extubation is done to minimize the chance for intracranial infections. If no change in the state of consciousness was observed after the puncture, craniotomy for hematoma removal is recommended. In patients

with the state of consciousness of up to light coma, vital signs should be closely monitored, and blood pressure should be within the target values. In patients with dysphoria, sedative agents may be prescribed. After 24 hours of disease onset, external drainage of hematoma should be conducted for hematoma of > 15 ml. In case of recurrent bleeding, craniotomy for hematoma removal should be performed. In patients with less than light coma lasting more than 6 and less than 24 hours, early intervention is not recommended without considering the size of hematoma and the time of disease onset.

The choice of early intervention procedure (i.e., within 24 hours after disease onset) should be based on the extent of consciousness change, rather than on the size of supratentorial non-thalamus hematoma. An application of ultra-early (within 6 hours of disease onset) intervention in conscious patients was not proved effective in clinical trials. On the contrary, this intervention was associated with a high rate of rebleeding.

The risk of recurrent hemorrhage from intracerebral infusion of UK has been estimated by previous authors[14] to range from 7% to 15% of treated patients. Because the rebleeding risk can potentially be increased by early aspiration, several authors[14,15] have suggested avoiding aspiration and thrombolysis in the initial 6 to 24 hours after ICH onset which is the same point with us. The risk of hematoma expansion during treatment must be closely monitored in future studies, including any associated untoward clinical sequelae.

Gaberel et al[16] report a meta-analysis of intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage (IVH), which find a obvious beneficial effect on survival in the UK group compared to the rtPA group. They didn't find a statistically significant differernce in terms of complications between the 2 therapeutic types. The fibrinolytic agent UK is more cheaper compared with rtPA in developing countries. There are many publications on UK around Asian countries like China, Kroean, Japan. However, we also find UK therapy on ICH in Europe and America. The prevalence of rebleeding occurs on young patients who have history of hypertension after recheck the rebleeding patients with HICH. An increased blood pressure may increase the risk of hematoma enlargement. Some authors think about the phenomena may due to a different toxicity potential or the result of "small study effect" and the possible occurrence of publication bias. The mean patient sample size is not similar between the rtPA and UK groups. Ziai et al[17] performed a secondary longitudinal exploratory data analysis of a randomized multicenter trial of UK versus placebo as a treatment for IVH. They find apparent beneficial effect of intraventricular UK on ICP, duration of external ventricular drain use, and tolerance to EVD closure implies a therapeutic advantage in the management of severe IVH. There are Multicenter Randomized Controlled Trials[18,19] showing that intraventricular UK may significantly improve 30-day survival and effectively reduces ICH volume.

Conclusions

Due to the retrospective nature of this study, it is important that the findings be further confirmed by prospective studies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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