THE SAFETY AND EFECTIVENESS OF EARLY INTENSIVE LOWERING OF BLOOD PRESSURE IN PATIENTS WITH ACUTE INTRACEREBRAL HEMORRHAGE AT DEPARTMENT OF STROKE AT HOSPITAL 103

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SUMMARY

Objective: *To evaluate the safety and beneficial effect of rapid lowering of blood pressure in patients with acute intracerebral hemorrhage.* ***Methods:*** *We randomly assigned 73 patients who had had an acute intracerebral hemorrhage within the previous 6 hours and who had elevated systolic blood pressure to receive intensive treatment to lower their blood pressure (with a target systolic level of <140mmHg within 1 hour) or guideline-recommended treatment (with a target systolic level of <180mm Hg). The primary outcome was death or major disability, which was defined as a score of 3 to 6 on the modified Rankin scale (mRs) (in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death) at 90 days. The rate of serious adverse events was compared between the two groups.* ***Results:*** *Among the 73 patients for whom the primary outcome could be determined, 35 patients (48.0%) receiving intensive treatment, as compared with 38 (52%) receiving guideline-recommended treatment. The ordinal analysis showed significantly lower mRs with intensive treatment ($p<0.05$). Mortality was 2.9% in the group receiving intensive treatment and 2.6% in the group receiving guideline-recommended treatment. Nonfatal serious adverse events occurred in 2.9% and 2.6% of the patients in the two groups, respectively.* ***Conclusion:*** *In patients with intracerebral hemorrhage, intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or severe disability. An ordinal analysis of mRs indicated improved functional outcomes with intensive lowering of blood pressure.*

Keywords*: Blood-Pressure, Intracerebral Hemorrhage, and stroke*

1. INTRODUCTION

Acute intracerebral hemorrhage, which is the least treatable form of stroke, affects more than 1 million people worldwide annually [2] with the outcome determined by the volume and growth of the underlying hematoma [3]. Blood pressure often becomes elevated after intracerebral hemorrhage [4] frequently reaching very high levels, and is a predictor of outcome [5]. In the treatment regimen, adjusting blood pressure has many conflicting ideas. Some authors believe that should not be taken immediately if the average blood pressure <130mmHg will not guarantee blood flow. Some authors argue that the cause of continued bleeding is due to high blood pressure that is not adjusted in time. On the basis of a number of world studies INTERACT1, INTERACT2 initially confirmed the effectiveness of intensive antihypertensive treatment in patients with acute cerebral hemorrhagic stroke [7]. Therefore, we conducted this study to: *determine the safety*

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and effectiveness of early intensive lowering of blood pressure in patients with acute intracerebral hemorrhage.

2. METERIALS AND METHODS

2.1. Research subjects.

73 patients with acute intracerebral hemorrhage within the first 6 hours of hypertension (primary or secondary hypertension), receiving inpatient treatment at the Department of Stroke, Military Hospital 103 from May 2018 to March 2019, were divided into two groups: Intensive Blood-Pressure Lowering (n=35) and Guideline Recommended Blood-Pressure Lowering (n=38).

2.2. Research contents and methods

*** Study design**: a prospective, descriptive, cross-sectional, comparative, intervention study.

*** Research contents**

All patients were included in the study group in two groups and were followed up continuously for up to 3 months.

- In patients who were assigned to receive intensive treatment to lower their blood pressure (intensive-treatment group), intravenous treatment and therapy with oral agents were to be initiated according to prespecified treatment protocols that were based on the local availability of agents, with the goal of achieving a systolic blood-pressure level of less than 140mmHg within 1 hour after randomization and of maintaining this level for the next 7 days [7].

- In patients who were assigned to receive guideline-recommended treatment (standard-treatment group), blood-pressure–lowering treatment was to be administered if their systolic blood pressure was higher than 180mmHg; no lower level was stipulated [10].

All participants were to receive oral antihypertensive agents (or topical nitrates) within 7 days (or at discharge from the hospital if that occurred before 7 days), combination treatment with an angiotensin-converting–enzyme inhibitor and a diuretic was recommended if that treatment was not contraindicated and if no different drugs were specifically required, with the goal of achieving a systolic blood pressure of less than 140 mm Hg during follow-up for the prevention of recurrent stroke.

Demographic and clinical characteristics were recorded at the time of enrollment. Study clinical and subclinical characteristics, image characteristics between two groups and then compare clinical and subclinical indicators to find the effect of positive hypotension. Participants were followed up in person or by telephone at 28 days and at 90 days by doctors who treated directly through mobilphone or social media. Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analyses according to the intention-to-treat principle.

Some diagnostic criteria

- Evaluation of hypertension according to JNC (VII) standard [1].

- The severity of the stroke was assessed with the use of the Glasgow Coma Scale (GCS) [9] and the National Institutes of Health Stroke Scale [9] (NIHSS, on which scores range from 0 to 42, with higher scores indicating a more severe neurologic deficit) at baseline, at 24 hours, and at 7 days (or at the time of discharge, if that occurred before 7 days). Patients were excluded if there was a structural cerebral cause for the intracerebral hemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the GCS [9] in

which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness.

- Major disability was defined as a score of 3 to 5 on the modified Rankin scale at 90 days after randomization. Scores on the mRs range from 0 to 6, with a score of 0 indicating no symptoms; a score of 5 indicating severe disability, confinement to bed, or incontinence; and a score of 6 indicating death. The protocol specified "death or severe disability in patients treated within 4 hours of onset of intracranial hemorrhage" as the key secondary outcome [8].

- Brain CT (or MRI) was performed according to standard techniques at baseline (to confirm the diagnosis) in all patients, and at 24±3 hours in a subgroup of patients who were being treated at sites at which repeat scanning was either part of routine practice. Patients were followed up in person or by telephone at 28 days and at 90 days.

2.3. Data analysis

Data was analyzed by using Medical Statistic method with SPSS 20.0 software. Significant differences were defined at $p<0.05$.

2.4. Ethical research

- Although the study may affect the patient's treatment results between two group, it helped further the treatment, due to the agrreement in adjusting blood pressure is not established.

- The patient and the patient's family members are clearly explained the objectives and research methods, voluntary participation in research and the right to withdraw from research without explanation.

- Information provided by research subjects is kept confidential.

3. RESULTS

3.1. The characteristics of research subjects.

There were no significant differences between the groups in any of the characteristics listed here. ICH denotes intracerebral hemorrhage. Scores on the National Institutes of Heath stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia) Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma). Deep location refers to location in the basal ganglia or thalamus (Table 3.1).

As shown in Table 2, the median time from the onset of the intracerebral hemorrhage to the initiation of intravenous treatment was shorter in the intensive-treatment group than in the standard-therapy group (4.0 hours [interquartile range, 2.8 to 5.2] vs. 4.5 hours [interquartile range, 3.1 to 7.1], $p<0.05$); the median time from randomization to the initiation of treatment was also shorter in the intensive-treatment group (6 minutes [interquartile range, 0 to 38] vs. 20 minutes [interquartile range, 0 to 174]). More patients in the intensive-treatment group than in the standard-treatment group received two or more intravenous agents to lower their blood pressure (91.4% vs. 42.1%, $p<0.05$). The mean systolic blood-pressure levels differed significantly between the two groups from 15 minutes to day 7 after randomization ; at 1 hour, the mean systolic blood pressure was under 140 mm Hg in the intensive-treatment group with 97.1% achieving the target blood pressure of <140 mm Hg) with 32%. As shown in Table 2, there were no significant differences between the two groups with respect to other aspects of medical care during the 7 days after randomization.

3.2. Clinical outcomes and serious adverse events

Table 3.1. Baseline Characteristics of the patients

Characteristic	Intensive Blood-Pressure Lowering (n=35)	Guideline Blood-Pressure Lowering (n=38)
Time from onset of ICH to randomization (hr)		
Median	3.6	3.6
Interquartile range	2.5-4.6	2.6-4.5
Age (yr)	62.0±13.1	63.1±11.6
Number of male patients (%)	22(63)	23(60.3)
Blood pressure (mmHg)		
Systolic	178±16	178±16
Diastolic	102±15	103±15
NIHSS score		
Median	10	11
Interquartile range	6-15	6-16
GCS score		
Median	14	14
Interquartile range	12-15	12-15
Hystory of hypertension	26(74.3)	28(73.7)
Baseline hematoma volume (ml)		
Median	11	11
Interquartile range	6-19	6-20
Intraventricuar extension of hemorrhage - no./total no. (%)	10(28.6)	11(29)
Deep location of hematoma - no./ total no. (%)	29(83)	32(84.2)

Table 3.2. Treatment of Patients with Intracerebral Hemorrhage

Variable	Intensive Blood-Pressure Lowering (n= 35)	Guideline Blood-Pressure Lowering (n= 38)	P
Time from ICH to start of treatment (hr)			
Median	4.0	4.5	
Interquartile range	2.8-5.2	3.1-7.1	<0.05
Time from randomization to start of treatment (hr)			
Median	0.1	0.3	<0.05
Interquartile range	0.0-0.38	0.0-2.9	
Blood-pressure-lowering treatment during first 24 hr - no. (%)			
Any intravenous treatement	32(91.4)	16(42.1)	<0.05
Use of a single intravenous agent	21(60)	11(29)	
The mean systolic blood-pressure levels from 15 minutes to day 7			
At 1 hour			>0.05
<140mmHg	34(97.1)	12(32)	
140- 180 mmHg	1(2.9)	26(68)	
Any surgical intervention - no./total no. (%)			
Evacuation or decompression	1(2.9)	1(2.6)	>0.05
Insertion of a ventricular drain	2(5.7)	2(5.2)	>0.05
Medical treatment during the first 7 days - no./total no. (%)			
Hemostatic therapy	2(5.7)	1(2.6)	<0.05
Use of intravenous manitol	22(63)	23(60.5)	>0.05

Hemostatic therapy included the use of fresh-frozen plasma, vitamin K.

Table 3.3. Primary, Secondary, and Safety Outcomes at 90 Days

Variable	Intensive Blood-Pressure Lowering (n= 35)	Guideline Blood-Pressure Lowering (n= 38)	P
Primary outcome: death or major disability - no./total no. (%)	18(51.4)	21(55.2)	<0.05
Secondary outcome			<0.05
Score on the modified Rankin scale-no./ total no. (%)			
0	3(8.6)	3(7.9)	
1	7(20)	7(18.4)	
2	7(20)	7(18.4)	
3	5(14.3)	6(15.8)	
4	6(17.1)	8(21)	
5	2(5.7)	3(7.9)	
6	4(11.4)	5(13.2)	
Number of death (%)	1(2.9)	1(2.6)	>0.05
Health-related quality of life (problems with mobility, self-care, usual activities, pain or discomfort, anxiety or depression)	21(60)	25(65.8)	<0.05
Duration of hospitalization (day)			
Median	20	19	>0.05
Interquartile range	12-35	11-33	
Safety outcomes			
Severe hypotension including renal failure	1(2.8)	1(2.6)	>0.05
Ischemic or undifferentiated stroke	1(2.8)	1(2.6)	

The mRs evaluates global disability and functioning scores range from 0 (no symptoms) to 6 (death): the primary outcome of death or major disability was assessed as a score on the modified Rankin scale of 3 to 6 at 90 days.

Table 3.4. Effect of Early Intensive Blood-Pressure–Lowering Treatment on the Primary Outcome, According to Prespecified Subgroups

Subgroup	Intensive Blood-Pressure Lowering (n= 35)	Guideline Blood-Pressure Lowering (n= 38)	P
Age			
>70 yr	15(43)	16(42.1)	>0.05
<70 yr	20(57)	22(63.9)	
Time to randomization			
< 4h	19(54.3)	21(55.3)	>0.05
>=4h	16(45.7)	17(44.7)	
Baseline systolic blood pressure			
<180mmHg			
>=180mg	17(48.6)	18(47.4)	>0.05
	18(51.4)	20(52.6)	
History of Hypertension			
Yes	18(51.4)	18(47.4)	>0.05
No	17(48.6)	20(52.6)	
Baseline of NIHSS			
<15	13(37.1)	16(42.1)	>0.05
>=15	22(66.9)	22(63.9)	
Baseline hematoma volume			
<15ml	13(37.1)	16(42.1)	>0.05
>=15ml	22(66.9)	22(63.9)	
Baseline hematoma location			
Deep	17(48.6)	17(44.7)	>0.05
Others	18(51.4)	21(55.3)	
Brain imaging (V – ml)			
First time	15.7±15.7	15.1±14.9	>0.05
Second time	18.2±19.1	20.6±24.9	

Effect of Early Intensive Blood-Pressure–Lowering Treatment on the Primary Outcome, According to Prespecified Subgroups.

At 90 days, 18 of the patients (51.4%) in the intensive-treatment group, as compared with 21 (55.2%) in the standard-treatment group, had a poor outcome ($p<0.05$). The ordinal analysis showed a significant favorable shift in the distribution of scores on the modified Rankin scale with intensive blood-pressure–lowering treatment (pooled odds ratio for shift to higher modified Rankin score, $p<0.05$). Adjusted analyses showed consistency in the treatment effect with respect to the primary and key secondary outcomes in logistic-regression models that included prognostic variables and various cutoff points on the modified Rankin scale

In the Health-related quality of life, patients in the intensive-treatment group reported fewer problems and had significantly better overall health-related quality of life at 90 days than did those in the standard-therapy group (60% vs. 65.8%, respectively).

The rate of death from any cause was similar in the intensive-treatment group and the standard-treatment group (2.8% and 2.6%, respectively) (Table 3). The effects of intensive lowering of blood pressure were consistent across all prespecified subgroups. There were no significant differences between the two groups in any of the other outcomes studied. The numbers of serious adverse events, including episodes of severe hypotension (which occurred in <3% of the patients), were also balanced between the two groups (*Table 3*).

*** Hematoma outcomes**

73 patients who underwent repeat brain imaging for an assessment of the between-group difference in hematoma growth from baseline to 24 hours. The mean hematoma volumes were 15.7±15.7 ml and 15.1±14.9 ml in the two groups, respectively, at baseline and 18.2±19.1 ml and 20.6±24.9 ml, respectively, at 24 hours (Table 4). The difference in hematoma growth between the groups in the 24 hours after baseline was not significant ($p>0.05$), and absolute difference, 1.4 ml ($p<0.05$).

4. DISCUSSION

In our study including patients with intracranial hemorrhage, early intensive lowering of blood pressure, as compared with the more conservative level of blood-pressure control currently recommended in guidelines, did not result in a significant reduction in the rate of the primary outcome of death or major disability. However, in an ordinal analysis of the primary outcome, in which the statistical power for assessing physical functioning was enhanced, there were significantly better functional outcomes among patients assigned to intensive treatment to lower their blood pressure than among patients assigned to guideline-recommended treatment [11]. Furthermore, there was significantly better physical and psychological well-being among patients who received intensive treatment. These results are consistent with observational epidemiologic findings associating high blood-pressure levels with poor outcomes among patients with intracerebral hemorrhage [5] and indicate that early intensive lowering of blood pressure in this patient population is safe.

There was no clear evidence of heterogeneity in the effect of treatment in any subgroup. Moreover, there was no evidence of a significant effect modification according to a history or no history of hypertension, a finding that is relevant because it has been postulated that patients with hypertension have an upward shift in cerebral autoregulation and possibly an increased risk of cerebral ischemia related to intensive lowering of blood pressure [6]. However, given the critical nature and rapid evolution of bleeding in the brain, a somewhat surprising

finding was the absence of a significant difference in the effect of treatment between patients who underwent randomization early (within 4 hours after the intracerebral hemorrhage) and those who underwent randomization later. This could reflect either the limited power of the subgroup analyses or true independence of the effect of the intervention from the time of initiation of treatment. Since early intensive lowering of blood pressure did not have a clear effect on reducing the growth of the hematoma, a key determinant of early death, there may be other mechanisms at play, such as neuroprotection or a reduction in edema, that result in the later positive clinical outcomes with this treatment. The ongoing Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial [12] is expected to provide additional information on the role of intensive lowering of blood pressure within 4.5 hours after the onset of a intracerebral hemorrhage, but future evaluations of the treatment in patients with intracerebral hemorrhage that are conducted in the prehospital setting or at more extended periods after onset than were tested in INTERACT2 may be warranted.

Some limitations should also be noted. First, although the option to use a range of available drug therapies rather than a single agent was a strength of the study, it introduced complexity in assessing the ways in which the effects may have varied across different agents. Moreover, in the open (unblinded) assignment of interventions that led to earlier and more intensive, as compared with less intensive, control of blood pressure, the outcomes may have been confounded by differences in the management strategies that were used for the two groups after randomization, other than those that were documented. Second, although we used established scales and objective criteria, some bias may have been introduced in the assessment of key outcomes. Third, the difference in the blood-pressure levels achieved between the two groups may have been attenuated by the use of an active-comparator control group and the concomitant use of additional agents with blood-pressure–lowering properties (e.g., mannitol) or hemostatic properties (e.g., recombinant tissue factor VIIa); if this is so, however, the magnitude of the benefit of early intensive blood-pressure–lowering treatment could be greater in settings in which only the very highest levels of blood pressure are treated in the hyperacute phase of stroke.

5. CONCLUSION

In summary, early intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or major disability, but an ordinal analysis of scores on the modified Rankin scale did suggest that intensive treatment improved functional outcomes. Intensive lowering of blood pressure was not associated with an increase in the rates of death or serious adverse events.

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TÓM TẮT

HIỆU QUẢ VÀ AN TOÀN CỦA VIỆC KIỂM SOÁT HUYẾT ÁP SỚM TÍCH CỰC Ở BỆNH NHÂN ĐỘT QUỴ CHẢY MÁU NÃO CẤP TẠI KHOA ĐỘT QUỴ BỆNH VIỆN 103

Bùi Văn Nam, Lê Văn Quân

Bệnh viện Quân y 103

Mục tiêu: *Đánh giá tính an toàn và tác dụng có lợi của việc hạ huyết áp nhanh chóng ở những bệnh nhân xuất huyết nội sọ cấp tính.* ***Phương pháp:*** *Chúng tôi lựa chọn ngẫu nhiên 73 bệnh nhân bị xuất huyết nội sọ cấp tính trong vòng 6 giờ đầu có tăng huyết áp tâm thu và được điều trị hạ huyết áp tích cực (với mức tâm thu mục tiêu <140mmHg trong vòng 1 giờ) hoặc theo hướng dẫn điều trị (với mức tâm thu mục tiêu <180mmHg). Kết cục chính là tử vong hoặc khuyết tật nghiêm trọng, được xác định là điểm từ 3 đến 6 trên thang điểm Rankin sửa đổi (mRs) (trong đó điểm 0 cho thấy không có triệu chứng, điểm 5 cho thấy khuyết tật nghiêm trọng và điểm 6 là tử vong) sau 90 ngày. Tỷ lệ các tác dụng phụ nghiêm trọng được so sánh giữa hai nhóm.* ***Kết quả:*** *Trong số 73 bệnh nhân có thể xác định được kết quả chính, 35 bệnh nhân (48,0%) được điều trị tích cực, so với 38 bệnh nhân (52%) được điều trị theo hướng dẫn. điểm mRs thấp hơn đáng kể với điều trị tích cực so với điều trị theo hướng dẫn (p <0,05). Tỷ lệ tử vong là 2,9% trong nhóm được điều trị tích cực và 2,6% trong nhóm được điều trị theo hướng dẫn. Các tác dụng phụ nghiêm trọng chiếm 2,9% và 2,6% bệnh nhân lần lượt ở hai nhóm.* ***Kết luận:*** *Ở những bệnh nhân chảy máu nội sọcấp tính hạ huyết áp tích cực không làm giảm đáng kể tỷ lệ kết cục chính của tử vong hoặc tàn tật nặng. Tuy nhiên phân tích điểm mRs cho thấy kết quả hồi phục chức năng được cải thiện với việc hạ huyết áp tích cực so với nhóm điều trị theo hướng dẫn.*

Từ khóa: *Tăng huyết áp, chảy máu não cấp và đột quỵ*