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Expansion of recruitment time window in antihypertensive treatment of acute cerebral hemorrhage (ATACH) II trial

AI Qureshi[1,*], **YY Palesch**[2], and **ATACH II Investigators**

[1]*Zeenat Qureshi Stroke Research Centre, University of Minnesota, Minneapolis, MN, USA*

[2]*Division of Biostatistics and Epidemiology, Medical University of South Carolina, Charleston, SC, USA*

Abstract

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial is an ongoing multi-center, randomized phase III trial to determine the efficacy of early, intensive, antihypertensive treatment using intravenous (IV) nicardipine initiated within 3 h of onset of intracerebral hemorrhage (ICH). On March 11th, 2012, the National Institutes of Neurological Disorders and Stroke approved recruitment of patients with ICH within 4.5 h of symptom onset. The expansion of recruitment window was based on the recent ATACH-I study analysis that suggests reduction of hematoma expansion and death, and disability in those subjects who were treated within 4.5 h after symptom onset. Another recent single center study further identified that hematoma expansion, the primary target for systolic blood pressure reduction, appeared to be equally prevalent in subjects who are presenting between 3 and 4.5 h. The expansion has the potential to evaluate the efficacy of the treatment intervention in a larger group of patients with ICH.

Keywords

time window; intracerebral hemorrhage; acute hypertensive response; systolic blood pressure; recruitment

Introduction

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial is an ongoing multi-center, randomized phase III trial to definitively determine the efficacy of early, intensive, antihypertensive treatment using intravenous (IV) nicardipine initiated within 3 h of onset of intracerebral hemorrhage (ICH) and continued for the next 24 h in subjects with spontaneous supratentorial ICH [1]. The primary hypothesis of this large (N = 1,280) trial is that systolic blood pressure (SBP) reduction to <140 mmHg reduces the likelihood of death or disability at 3 months after ICH, defined by the modified Rankin Scale (mRS) score of 4–6, by at least 10% absolute compared to standard SBP reduction to <180 mmHg. On March 11th, 2012, the National Institute of Neurological Disorders and Stroke approved recruitment of subjects with ICH within 4.5 h of symptom onset in ATACH II. According to this modification, randomization and initiation of treatment (IV nicardipine) to reduce SBP must occur within 4.5 h of symptom onset. Here, we present the data that formed the basis for the modification in protocol. The expansion of the recruitment window was based on data from the recent ATACH-I study analysis that suggests reduction of hematoma expansion and death, and disability in those subjects who were treated within 4.5 h after symptom onset. The reduction was comparable to those who were treated within 3.1 h. Another recent single center study further provided additional support to the recent ATACH-I analysis. This study, as described below, also suggested that initiating SBP reduction within the 3.1–4.5-h window has the potential to improve subject outcomes because hematoma expansion, the primary target for SBP reduction, appears to be equally prevalent in the extended time window as compared within 3 h.

Analysis from ATACH I

An open-labeled prospective study funded by National Institute of Neurological Disorders and Stroke (R01 NS044976) was conducted to obtain an estimate of the proportion of subjects who can achieve the targeted SBP goal and to ascertain acute (i.e., within 72 h) safety of

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*Correspondence to: AI Qureshi, Email: qureshi@umn.edu, Tel: +1-612-6251969, Fax: +1-612-6269464

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Table 1.

Relationship between systolic blood pressure (SBP) treatment target and hematoma expansion at 24 h and 90 days modified Rankin Scale (mRS) in ATACH I trial.

	SBP reduction of ≥60 mmHg	SBP reduction of <60 mmHg	Relative Risk (95% Confidence Interval)
Subjects treated within 3.1 h of symptom onset	*N* = 11	*N* = 9	
Hematoma expansion (increase of >33%)	18.2%	37.5% (missing *N* = 1)	0.48 (0.10–2.26)
Relative edema expansion (increase of >40%)	30.0% (missing *N* = 1)	37.5% (missing *N* = 1)	0.8 (0.22–2.94)
Death or disability (mRS 4–6) [4]	12.5% (missing *N* = 3)	42.9% (missing *N* = 2)	0.29 (0.04–2.21)
Subjects treated within 4.5 h of symptom onset	*N* = 17	*N* = 21	
Hematoma expansion (increase of >33%)	12.5% (missing *N* = 1)	35.0% (missing *N* = 1)	0.36 (0.09–1.49)
Relative edema expansion (increase of >40%)	33.3% (missing *N* = 2)	57.9% (missing *N* = 2)	0.58 (0.26–1.29)
Death or disability (mRS 4–6) [4]	21.4% (missing *N* = 3)	57.9% (missing *N* = 2)	0.37 (0.13–1.08)
Subjects treated within 6 h of symptom onset	*N* = 27	*N* = 25	
Hematoma expansion (increase of >33%)	18.5% (missing *N* = 1)	32.0% (missing *N* = 1)	0.58 (0.22–1.54)
Relative edema expansion (increase of >40%)	45.8% (missing *N* = 4)	58.3% (missing *N* = 2)	0.79 (0.45–1.36)
Death or disability (mRS 4–6) [4]	37.5% (missing *N* = 4)	52.2% (missing *N* = 3)	0.72 (0.38–1.38)
All subjects	*N* = 32	*N* = 28	
Hematoma expansion (increase of >33%) [2]	19.4% (missing *N* = 1)	33.3% (missing *N* = 1)	0.58 (0.24–1.42)
Relative edema expansion (increase of >40%) [3]	42.9% (missing *N* = 4)	57.7% (missing *N* = 2)	0.74 (0.43–1.27)
Death or disability (mRS 4–6) [4]	32.1% (missing *N* = 4)	52.0% (missing *N* = 3)	0.62 (0.32–1.19)

three levels of antihypertensive treatment goals using IV nicardipine initiated within 6 h (expanded to 12 h in the last part of the study) and continued for 18–24 h after onset for acute hypertensive response associated with ICH. The methodology and main results of the study have been described in the previous publications [2,3].

SBP measures were analyzed using two methods. Baseline SBP was calculated using the average of maximum and minimum SBP recorded prior to initiation of treatment. Average SBP, derived from maximum and minimum hourly recording, at 6 h, was used to determine SBP reduction compared from baseline value. The derived variable (baseline SBP–post-treatment SBP) was dichotomized to reduction by <60 and ≥60 mmHg approximately based on the median value. A subgroup analysis was performed including only subjects treated within 3.1, 4.5, and 6 h after symptom onset. Hematoma expansion was defined as an increase in the volume of intraparenchymal hematoma of >33% as measured by image analysis on the 24-h CT scan compared with the baseline CT scan. Relative edema volume was defined as absolute edema volume divided by hematoma volume, yielding a unitless ratio variable. The difference in the ratio of relative edema volume between baseline and 24 h CT scans was converted to %change by dividing the difference by the baseline ratio and multiplying by 100. The %change was dichotomized at the median value of 40% because there was no previous cutoff with prognostic validation. Primary clinical outcome was death or disability, defined by mRS of 4–6 (moderate or severe disability or death) at 3 months following treatment.

The results are summarized in Table 1. A total of 60 subjects were enrolled, 53% had the SBP reduction of ≥60 mmHg at 6 h, whereas 47% had <60 mmHg reduction. There was an absolute reduction by 14% in hematoma expansion (with relative risk (RR) = 0.58, 95% confidence interval (CI) = 0.24–1.42) in subjects with SBP reduction ≥60 mmHg compared with those with <60 mmHg SBP reduction at 6 h following initiation of treatment. Limiting the analysis to only subjects treated within 3.1 h of symptom onset increased the absolute reduction in rates of hematoma expansion, relative edema expansion, and death and disability associated with SBP reduction of ≥60 mmHg with corresponding reduction in RR values for all three parameters. These findings suggest a protective effect of SBP reduction of ≥60 mmHg that is amplified among subjects treated within 3.1 h of symptom onset. A similar magnitude of protective effect was seen with SBP reduction of ≥60 mmHg among subjects treated within 4.5 h of symptom onset. However, such amplification was not observed in subjects treated within the 6-h time window. The reduction in the RR of hematoma expansion, relative edema expansion, and proportion of death and disability was similar, if not better, between subjects treated within 3.1 h and those treated within 4.5 h. These results need to be interpreted with caution and an understanding of the

Table 2.
The rates of hematoma expansion in subject groups defined by time interval between symptom onset and first computed tomographic (CT) scan acquisition.

Variables	Subjects presented within 3 h of symptom onset	Subjects presented within 4.5 h of symptom onset
	N = 43	*N* = 61
Hematoma expansion (increase of >33%)	16 (37.2%)	23 (37.7%)
Modified Rankin Scale at discharge	*N* = 32	*N* = 47
Death or disability (mRS 4–6)	17 (53.1%)	24 (51.0%)

limitations associated with the use of small sample sizes, substituting the treatment group distinction in ATACH II (<140 vs. 141–180 mmHg), and the dichotomization of subjects using arbitrarily chosen cutoff based on the median value of the SBP reduction in ATACH I.

Single center analysis

Another descriptive analysis of data derived from patients admitted with the primary diagnosis of ICH at University of Minnesota Medical Center-Fairview system within 6 h of symptom onset based on initial CT scan acquisition is summarized in Table 2. A total of 61 patients (43 presenting within 3 h of symptom onset) were evaluated. The method of measuring hematoma volume at baseline and at 24 h was very similar to that used in ATACH I. Hematoma expansion was defined as an increase in the volume of intraparenchymal hemorrhage of >33% as measured by image analysis on the 24-h CT scan compared with the baseline CT scan. Primary clinical outcome was death or disability, defined by mRS of 4–6 (moderate or severe disability or death) at discharge [mean (SD) of hospital days = 10.5 (10)]. The risk of any hematoma enlargement (58.1 and 60.6%) and enlargement of >33% was similar (37.2 and 37.7%) between those presenting within 3 h and those presenting within 4.5 h of symptom onset. Therefore, hematoma expansion, the primary target for SBP reduction, appeared to be equally prevalent in patients who are presenting between 3 and 4.5 h. Furthermore, the proportion resulting in death and disability between the two patient populations was comparable. Note that these data do not account for the SBP reduction in either time group.

Analysis of screening logs of ATACH II

The ATACH II screening log, which records pertinent data for all patients with ICH who present at the participating clinical sites within 6 h of symptom onset, was reviewed. As of January 26, 2012, 317 screening failures had been recorded. We used exclusion criteria 2 (onset of new neurological deficits beyond 2.5 h at the time of randomization), 3 (IV nicardipine cannot be initiated within 3 h of symptom onset), and 9 (consent was not obtained) to determine how many patients were excluded that might have been eligible with a longer randomization window. Also, we considered the onset to presentation times of 3 h (3.0–3.9) and 4 h (4.0–4.9) to be relevant to the question at issue. Of 88 screen failures, 44 (who arrived between 3 and 5 h) had time-sensitive primary exclusion criteria. While such estimates can be misleading, a more conservative estimate would suggest that an additional 5–10% of otherwise eligible patients can be recruited in a 4.5-h recruitment window.

Experience of the European Cooperative Acute Stroke Study (ECASS) III

The ECASS III [4] was a double-blind, parallel-group trial based on the combined analysis of data from six previous randomized trials [5]. In a total of 2,775 subjects, a higher proportion of favorable outcome was observed even if alteplase was given between 3 and 4.5 h, as compared with placebo [5]. ECASS III enrolled subjects who were able to receive alteplase within 3–4 h after the onset of symptoms. After 228 subjects had been recruited, the time window of 3–4 h was extended by 0.5 h (3–4.5 h). The extension of the time window was secondary to the benefit observed with thrombolytic treatment administered up to 4.5 h after the onset of symptoms and inadequate rate of subject recruitment. The rate of favorable outcome in the alteplase group (52%) was significantly higher than that in the placebo group (45%). The proportions of subjects recruited in the 3.0–3.5, 3.5–4.0, and 4.0–4.5 h interval after symptom onset were similar between the two groups: alteplase group (*N* = 418): 9.6, 45.7, and 41.6%, respectively; and placebo group (*N* = 403): 10.4, 47.9, and 36.7%, respectively. The ECASS III represents a trial with successful implementation of extension of recruitment window without compromising the scientific validity of the study hypothesis.

Conclusions

Although the data from ATACH I and a single center observational data provided above required cautious interpretation due to a variety of limitations, they suggest a reasonable scientific justification to expand the recruitment time window for the ATACH II from 3 to 4.5 h from symptom onset. The ATACH II Steering Committee, Data Safety and Monitoring Board, and the Independent Oversight Committee will carefully monitor recruitment in the expanded time window. The expansion has the potential to evaluate the efficacy of the treatment intervention in a larger group of patients with ICH. Careful scrutiny will be exerted throughout the conduct of the trial to ensure that there is no heterogeneity in trial intervention, safety endpoints, and response among the subjects recruited in the expanded time window.

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