

Halil İbrahim Akçay, Murat Kürtüncü  
Istanbul University Faculty of Medicine, Department of Neurology, Istanbul, Turkey

### The Effect of Rapid Treatment of Hypertension in Patients with Spontaneous Intracerebral Hemorrhage

The treatment approach for the acute stage of hypertension, often seen in hemorrhagic cerebrovascular diseases has been a subject of debate. In the manual published by American Heart Association (AHA) in 1999, it was recommended that the mean arterial blood pressure (MABP) should be reduced to 130 mmHg and below when systolic blood pressure (SBP)  $\geq 180$  mmHg, diastolic blood pressure (DBP)  $\geq 105$  mmHg or when MABP  $\geq 130$  mmHg. The association also revised its recommendation in 2007 in collaboration with American Stroke Association (AHA/ASA) and recommended that blood pressure should be reduced to 160/90 mmHg and MABP to 110 mmHg when (SBP)  $\geq 180$  mmHg or MABP  $\geq 130$  mmHg. The actual effect of these recommendations on the enlargement of hematoma or long-term survival or debilitation is still unknown.

There is a concern about the possibility that an aggressive intervention to hypertension during spontaneous intracranial hemorrhage may cause negative effects on the cerebral hemodynamics and further impair the perfusion. For this reason, excessive antihypertensive treatment should be avoided in many cases. In accordance with these concerns, Anderson et al. compared aggressive antihypertensive treatment to conservative treatment in an article published in New England Journal of Medicine (1).

In the study titled "Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2" (INTERACT2), 2839 patients with hypertension were randomized into two groups: a group that received intense antihypertensive treatment within 6 hours of the event and another group that received an antihypertensive treatment according to the guidelines. The mean age of the patients were 64 and 62.9% were male. The goal for the intense antihypertensive group was to reduce SBP to  $<140$  mmHg within an hour, and to maintain the SP  $<180$  mmHg in the other group. The aims of the study were to measure and compare the mortality or severe debilitation (the patients who score between 3 to 5 in modified Rankin scale) ratios between the two groups firstly after 90 days,

and secondly after the first 4 hours. Another outcome measure was determined as the investigation of all causes of mortality and their specificity.

This international, multicenter, prospective and randomized study excluded patients who had hemorrhage due to structural causes, who scored between 3 to 5 in Glasgow Coma Scale, who had massive hematomas, and whose hematoma could be drained with early surgical treatment.

Intense antihypertensive treatment group received iv and oral antihypertensive treatment in combination when it was necessary and their SBP was reduced to  $<140$  mmHg level within an hour. In the guideline treatment group, the patients who had SBP  $>180$  mmHg received oral antihypertensive treatment. The patients were re-evaluated in 28<sup>th</sup> and 90<sup>th</sup> days either over the phone or in individual examinations.

Intense antihypertensive treatment group's average SBP was measured as 150 mmHg at the end of one hour and only 34% of the patients were able to reach the designated levels ( $<140$  mmHg). Guideline treatment group's mean SBP level was 164 mmHg and the difference between the two groups were 14 mmHg.

At the end of the study, 52% of the intense antihypertensive treatment group and 56% of the guideline treatment group showed mortality or major debilitation ( $p = 0.06$ ). Not only the difference between the groups were not found to be statistically significant, the modified Rankin scores of the intense antihypertensive group were found to be lower ( $p=0.04$ ). In addition, the indices of quality of life were higher for the intense antihypertensive group.

In conclusion, it was seen that the mortality and severe debilitation following an intense antihypertensive treatment with an early onset was not different than the treatment following standard guidelines, although the intense antihypertensive group had lower debilitation and higher scores in quality of life indices. While failing to demonstrate a large difference between the two groups, the study is importance in the sense that it clinically demonstrated that early and aggressive treatment of tension in spontaneous intracerebral hemorrhage does not pose a negative effect on brain perfusion. The ongoing "Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH)" trials are expected to provide

insight on the effects of aggressive antihypertensive treatment within the first 4.5 hours of intracerebral hemorrhage.

## References

1. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J; INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013;368(25):2355-2365.

## Can High Doses of Glatiramer Acetate Reduce the Frequency of Its Administration in Multiple Sclerosis?

Glatiramer acetate (GA) is a synthetic mixed polypeptide composed of 4 aminoacids. It is hypothesized that the drug's immunomodulator effect in multiple sclerosis (MS) is a product of modifying the functions of antigen presenting cells, T and B lymphocytes. It was shown that subcutaneous administration of 20mg/day GA reduces the annual relapse rate and radiological disease activity in numerous placebo-controlled studies. In the phase 3 study conducted by Comi et al. 2 years ago where they compared 40 mg/day and 20 mg/day doses, they found similar effects and safety profiles for both doses (1). In addition, when the daily administration of 20 mg was compared to administration made every other day or twice every week, there were no significant differences were found between the dosage groups (2, 3). In addition to observing the lack of a meaningful effect of dose, it was seen that infrequent applications reduce the injection site reactions like lipoatrophy and motivated further research.

Khan et al. investigated the security and efficacy profile of 40 mg GA administration 3 times a week in their trial titled "Glatiramer Acetate Low Frequency Administration" (GALA), published in *Annals of Neurology* (4). This was a placebo-controlled, phase 3 study. In the study, 1404 patients received 2:1 higher doses with less frequent injections of either GA or placebo treatment for a year.

At the end of the study, the relapse rate of the GA group was seen to be 34% lower than the placebo group (0.331 in GA

group, 0.505 in placebo group,  $p < 0.0001$ ). Additionally, time elapsed until the first relapse is longer in the GA group (393 days versus 377 days,  $p < 0.0001$ ). Despite the reduction in the relapse frequency, the statistical power and the duration of the study were insufficient to reflect any changes on the EDSS progression.

It is seen that the clinically favorable state parallels the status of the radiological parameters. It is noteworthy that there was a 45% decrease in the active T1 lesions and 35% decrease in the new T2 lesions of patients in the GA group. However, there was no difference between the two groups in terms of parameters of atrophy.

The efficacy profile seen in this study, which tested a high dosage of GA, is seemingly the same as the studies that use lower doses. The most common adverse effect seen in the study was the injection site reaction with 21% frequency. The most common systemic symptom was dyspnea with 3.1%.

In conclusion, administration of 40mg GA 3 times a week, similar to 20 mg/day, reduced the relapse rate and improved radiological signs compared to placebo. The infrequent administration saved patients from 4 additional injections per week and prevented adverse reactions.

## References

1. Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M, FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. *Ann Neurol* 2011;69:75-82.
2. Khan O, Caon C, Zak I, et al. Randomized, prospective, raterblinded, four-year, pilot study to compare the effect of daily versus every-other-day glatiramer acetate 20 mg subcutaneous injections in relapsing-remitting multiple sclerosis. *Mult Scler* 2008;14:296.
3. Khan O, Perumal J, Caon C, et al. Glatiramer acetate 20mg subcutaneous twice-weekly versus daily injections: results of a pilot, prospective, randomised, and rater-blinded clinical and MRI 2-year study in relapsing-remitting multiple sclerosis. *Mult Scler* 2009;15:249-250.
4. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol*. 2013;73:705-713