DEM Journal Club

Article Appraisal

Article: Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage - ATACH-2

Date of Journal Club: March 2, 2017

Resident Reviewer Name(s) and Residency Affiliation: Ben Millar (PGY-2) and Trisha Mackle (PGY-2), UBC FRCP Program

Faculty Methodology/Bio-statistics Resource Person: Dr. Devin Harris

---

Background and Study Objective(s):

Acute hypertensive response in patients with intracerebral hemorrhage (ICH) is common and may be associated with hematoma expansion and increased mortality. The INTERACT2 trial was the last major study on this topic and it included patients with spontaneous ICH who had a sBP of 150 - 220 mmHg within 6 hours after symptom onset. The rate of death and disability among patients randomly assigned to intensive BP reduction (target sBP < 140 mmHg within 1 hour) was non-significantly lower than guideline-recommended treatment of sBP < 180 mmHg. However, there is evidence that hematoma expansion and rate of death and disability might be reduced with very early and more aggressive sBP reduction among patients who are hypertensive. The objective of this trial was to determine whether aggressively lowering sBP to < 140 mmHg at an earlier time window would lead to decreased death or disability at 90 days.

Study Design:

The ATACH-2 trial was a randomized multicentre (110), multinational (6), open label trial. Patients with acute spontaneous intracerebral hemorrhages were enrolled as per inclusion and exclusion criteria. Of note, patients were required to have a GCS greater or equal to 5 at time of arrival, intraparenchymal hematoma size less than 60cc, a systolic BP greater than 180mmhg, and the ability to be randomized and treated with IV Nicardipine within 4.5 hours of symptom onset. Initially they had determined 3 hours however new data was published during the trial period and their protocol was altered mid-trial.

The goal of treatment was to reduce and maintain hourly minimum systolic blood pressure between 140-179 mmhg in the standard arm and 110-139 mmhg in the intensive arm, for 24 hours. They used a standardized titration of nicardipine. Labetalol was used as a second agent. Primary treatment failure was defined by not meeting BP targets within two hours of randomization. Secondary treatment failure was defined as being outside the target for more than 2 hours during the period of 2-24 hours after randomization.

The primary outcome was the proportion of patients scoring between 4-6 on the modified Rankin Score at 3 months. Secondary outcomes included a quality of life score (EQ-5D) at 3 months, proportion of patients with a hematoma expansion of 33% or more at 24 hours, as well as multiple safety outcomes.

Analysis was conducted as intention to treat, results were adjusted for effects of age, GCS, and the presence or absence of intraventricular hemorrhage.

Results:

A total of 8532 patients were screened and 1000 were recruited with 500 assigned to each treatment group. The mean sBP on presentation was 200 +/- 27 mmHg and baseline characteristics were similar between the two groups. Primary treatment failure (not achieving target BP within 2 hours after randomization) was observed in 12.2% of patients in the intensive treatment arm and 0.8% in the control arm ($p<0.001$). Secondary treatment failure (hourly minimum sBP above target range for 2 consecutive hours) was observed in 15.6% of patients in intensive treatment arm and 1.4% in the control arm ($p<0.001$). The study was stopped early due to futility for the primary outcome at a pre-specified interim analysis. The primary outcome of death or disability (mRS 4-6) occurred in 38.7% of the intensive treatment arm and 37.7% of the control arm (RR 1.02; 95% CI 0.83 – 1.25). There were no statistically significant differences between groups on any subgroup analysis including baseline GCS score, baseline hematoma volume, race or patients who successfully met the BP targets. Secondary outcomes were also non-significant with the exception of renal adverse events, which was found on post-hoc analysis to have occurred in 9% of the intensive treatment arm and 4% of the control arm ($p = 0.002$).

Validity of Results:

The ATACH-2 trial asked a clear question in a specific population. They appropriately randomized the patients, matching groups using the biased coin method, and attempted to account for all patients with a 96.1% follow up rate and imputation of missing data. The used intention to treat analysis, however the trial was stopped early due to futility. While patients and treating physicians were not blinded, radiologists and subsequent clinical examiners were blinded. Compared to compared to previous literature the event rate was lower (rationale for such was debated in the papers discussion). This meant the trial was underpowered to see an effect of treatment. Finally, there was a higher failure rate, both primary and secondary, in the intensive group, however subgroup analysis of patients who met the targets in both groups demonstrated no significant difference in outcomes.

Generalizability of Results:

The multicenter, multinational nature of this study increases the overall generalizability to different populations. However, more than 50% of patients were Asian which may limit the applicability to other races. Subgroup analysis by race was performed to help mitigate this concern, and no significant difference was found. The authors also state that the results of this trial cannot be generalized to patients with large ICH, increased intracerebral pressure, or compromised cerebral perfusion pressure. Furthermore, additional exclusion criteria that limit the generalizability of results include patients with traumatic ICH, infratentorial ICH, pregnancy, any bleeding diathesis, unreliable time of onset and consecutive sBP readings > 240 mmHg on admission.

The Bottom Line:

Overall this was a well designed trial regarding spontaneous intracerebral hemorrhage which failed to demonstrate a benefit to intensive blood pressure lowering. That being said the event rate was lower in this trial than previously demonstrated. At this point it is difficult to know if that is due to the patient characteristics or an effect of more rapid blood pressure lowering. Taking this into consideration there is likely a benefit to lowering blood pressure below sBP of 180mmhg however there is no evidence to point to a specific target number and therefore should be titrated on a case by case basis.