UAMS Journal Club
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Joe Brown MD and Brad Florence DO
Faculty Advisor: Carly Eastin MD

Early vs late systolic blood pressure control in emergency room patients diagnosed with intracranial hemorrhage

Clinical Bottom Line

To date, the two most well-known trials that address this topic are the INTERACT2 and the ATACH2 trials. The INTERACT2 trial shows no difference in death or major disability, and secondary outcomes were not consistent. The post-hoc analysis of the ATACH2 trial favors early (< 2hrs) blood pressure control but has limitations. Further investigation is needed to show better evidence for lower blood pressure goals. For now, we would recommend considering early blood pressure management on a case-by-case basis.

PICO Question

Does early intensive systolic blood pressure management improve outcomes in patients with acute intracranial hemorrhage?

P – Patients presenting to the ED with ICH
I – Intensive/early systolic blood pressure control
C – Guideline blood pressure control/delayed blood pressure control
O – Decreases in rates of death or severe disability

Background

Acute intracranial hemorrhage is almost universally included at some point in the differential diagnosis of those that present to the emergency department with a headache. Unfortunately, for a relatively small number of these patients, this pathology is confirmed. A number of these patients will be hypertensive at time of diagnosis, leading to the provider to start antihypertensive treatment in an effort to reduce bleeding and have better functional outcome. The timing and overall goal of BP lowering has remained controversial.

Trial 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 Jun 20;368(25):2355-65. doi: 10.1056/NEJMoa1214609. Epub 2013 May 29. PMID: 23713578.

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/23713578/

Validity Rating: A large sample size with randomization was reassuring but the nature of an open-treatment trial allows for some introduction of bias. The blinded-endpoint aspect of the trial was an interesting way to attenuate some of this potential bias.

The Basics: The INTERACT2 trial was an international, multi center, prospective, randomized, open-treatment, blinded endpoint trial. Goals of the trial were to compare the effect of a management strategy targeting a lower systolic blood pressure within 1

hour with the current guideline-recommended strategy, which targets a higher systolic blood pressure, in patients who has a systolic blood pressure between 150 and 220 mm Hg and who did not have a definite contraindication to such treatment. A systolic goal of <140 mm Hg was used for the intensive group, compared to a goal of <180 for the guideline group. For this trial 2839 patients were enrolled.

Inclusion Criteria:
1. Spontaneous intracerebral hemorrhage within the previous 6 hours
2. Diagnosis of the above confirmed by CT or MRI
3. Systolic blood pressure between 150 and 220 mm Hg

Exclusion Criteria:
1. Contraindication to blood pressure lowering treatment
2. Structural cerebral cause for the ICH
3. Score of a 5 or below on Glasgow Coma Scale
4. Massive hematoma with a poor prognosis
5. Early surgery to evacuate the hematoma was planned

Primary Outcomes:
1. Proportion of participants with death or major disability, defined as a score of 3 to 5 on the modified Rankin scale, at 90 days

Secondary Outcomes:
1. All-cause mortality
2. 5 dimensions of health-related quality of life
3. Duration of initial hospitalization
4. Residence in a residential care facility
5. Poor outcomes at 7 days and at 28 days
6. Serious adverse events

Results:
In terms of the primary outcome, 52% participants in the intensive group were found to have major disability or death, compared to 55.6% participants receiving guideline therapy. This results in an OR of 0.87 (CI of 0.75-1.01), p = 0.06. All but three secondary outcomes were found to have odds ratios with confidence intervals including 1. They found that 46.8% of the patients in the intensive group were found to have problems with self-care compared to 51.6% in the other group, (OR 0.83 [CI 0.70-0.97]). In the intensive group, 60.8% of participants had problems with usual activities compared to 66.1% in the guideline group, (OR 0.79 [0.67-0.94]). In the intensive group, 39.8% of participants had problems with pain or discomfort compared to 45.0% in the guideline group, (OR 0.81 [0.69-0.95]). Of note, a decision to withdraw active treatment and care was made in the case of more participants in the intensive-treatment group, 5.4%, than in the guideline group, 3.3%, p=0.005.

Limitations/Bias:
While the groups are similar and this study has a large number of participants, there are numerous limitations and areas in which bias can be introduced. The fact that this study is of open-treatment design introduces bias. This study began with an estimation of the rate of non-adherence to treatment of 10%, which seemed high. While the modified Rankin score is a much better tool of measure than, for instance, mortality, in terms of patient-centered outcomes, it does have a level of subjectivity that can lead to bias. When looking at the safety outcome results, caution must be used given that this study is for benefit and not a non- inferiority trial.

Trial 2

Li Q, Warren AD, Qureshi AI, Morotti A, Falcone GJ, Sheth KN, Shoamanesh A, Dowlatshahi D, Viswanathan A, Goldstein JN. Ultra-Early Blood Pressure Reduction Attenuates Hematoma Growth and Improves Outcome in Intracerebral Hemorrhage. Ann Neurol. 2020 Aug;88(2):388-395. doi: 10.1002/ana.25793. Epub 2020 Jul 1. PMID: 32453453; PMCID: PMC8697414.

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/32453453/

The Basics: The atach-2 trial was a large, multi center, RCT which included ~1,000 patients randomized to intensive vs standard, guideline treatment. This study found no statistically significant difference in outcomes between the groups. This paper is a post hoc analysis in which they attempted to determine a “therapeutic window” of time using the existing attach-2 data. The data was reviewed and patient’s in the intensive arm were subdivided into >2 hr from symptom onset to blood pressure management and < 2 hrs.
Inclusion:
ICH <4.5 hrs from symptom
onset. 18 yr and older
GCS >/= 5
ICH volumes <60ml

Primary Outcome: Hematoma growth >33% between baseline and follow up head CT.
Secondary outcomes: Good outcome (mRS 0-3) and functionally independent (mRS 0-2).

Results:
Those who received intensive BP control within 2 hours were more likely to be functionally independent (27.8% vs 41.7%). No difference in rate of death at 3 months. Relative risk of hematoma growth was 0.56 in those who received treatment within 2 hrs even when adjusting for confounding variables.

Limitations/Bias:
This is a post hoc analysis using existing data that was not designed to be analyzed for these outcomes. Open label trial creates an opportunity for bias. Primary outcome is size of hematoma, which may correlate to clinically meaningful outcomes, but is not particularly patient-centered.. mRS is an excellent patient centered outcome, but does allow for some subjectivity and bias. This post hoc analysis, though hypothesis generating and thought provoking does not provide robust enough data to make broad based recommendation.