Critical Review Form

Therapy

Hypotensive Resuscitation during Active Hemorrhage: Impact on In-Hospital Mortality, *J Trauma* 2002; 52: 1141-1146

Objective: **To test the hypothesis that "fluid administration directed to a systolic blood pressure (SBP) of 70 mm Hg would lead to an increased survival compared with conventional fluid administration directed to a SBP > 100 mg Hg." (p. 1142)**

Methods: **Randomized trial conducted from 1996 to 1999 at Maryland Shock Trauma (?) with the following eligibility criteria: presented directly from the scene of the injury, evidence of ongoing hemorrhage, SBP <90 mm Hg at least once within the first hour after injury. Exclusion criteria included pregnancy, central nervous system injury impairing consciousness of motor function, age >55, or history of DM or CAD.**

Randomization (when, how and by whom is not reported) was to one of two groups. In the "conventional" group fluid administration was titrated to SBP >100mm Hg, whereas in the "low" group the target SBP was 70 mm Hg. Fluid administration included "blood products" and crystalloid (target Hct 25%). Patients in both groups also received appropriate doses of anesthetic or analgesic medications.

The trauma surgeon and/or anesthesiologist using one or more of the following criteria determined "end of active bleeding": visible hemorrhage control, stable BP not requiring fluid administration, tolerance of analgesia and sedation, and CT/angio diagnostic studies showing no evidence of ongoing hemorrhage. After the end of active bleeding resuscitation was completed following ATLS guidelines: normal SBP, normal heart rate, Hct >25%, urine output > 0.5 mL/kg/h, arterial lactate < 2 mg/dL, normal arterial base deficit.

Medical records were used to ascertain patient outcomes and to abstract the injury severity score (ISS) and blood pressures. No modeling to adjust for unequal distributions of prognostic variables was reported. There are no details provided regarding length of follow-up, expected size for primary outcome(s) or *a priori* (or *post hoc*) power calculations/sample size.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Eligible patients were prospectively randomized to one of two groups…" (p. 1142) The authors do not provide any details about how, when, or by whom patients were randomized.
2.	Was randomization concealed (blinded)?	No. "The physicians caring for the patient did not know the group assignment until after the patient was randomized." Therefore, clinicians could not influence to which group patients were randomized (assuming the method was not one that could be guessed), but they could have altered subsequent management at a crucial time in patient course (co-intervention bias, Hawthorne effect).
3.	Were patients analyzed in the groups to which they were randomized?	Uncertain, No clear intention to treat statement or CONSORT figure by which to judge crossovers.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No, the low pressure group were sicker (ISS 23.9 vs. 19.5) with more blunt trauma (56% vs. 42%)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes, there was no blinding reported.
2.	Were clinicians aware of group allocation?	Yes, see I-A-2 response above.
3.	Were outcome assessors aware of group allocation?	Yes, there was no blinding reported. There is no reason why outcome assessors cannot be blinded to group allocation in such trials.
4.	Was follow-up complete?	There is no loss to follow-up (or follow-up interval) reported.

II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 110 patients were enrolled over 20-months but no CONSORT diagram is provided to quantify exclusions. At a busy Level I trauma center that probably evaluated >100 young non-pregnant hemorrhaging trauma patients every month, these enrollment numbers suggest a significant selection bias. • Patients had mean age 31 years, 79% were male, and 51% had suffered penetrating trauma. • Significant difference in mean SBP during the study period (114 mm Hg conventional care group vs. 100 mm Hg low group) but no differences were noted in the duration of active hemorrhage (2.97 vs. 2.57 hours) or mortality (4/55 = 7.3% in both groups). • There were "No significant differences in the number of patients in each group who underwent surgery, angiography or non-operative management" (p. 1143), although no quantitative details are provided.
2.	How precise was the estimate of the treatment effect?	No 95% CI are provided so precision cannot be estimated.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Probably. These were inner-city young male blunt and penetrating trauma patients with moderately severe injuries and documented hypotension with persistent hemorrhage – much like the Level I trauma patients we care for at Barnes Jewish Hospital.

2.	Were all clinically important outcomes considered?	No, there was no assessment of functional recovery or unintended consequences of low BP target (end-organ damage).
3.	Are the likely treatment benefits worth the potential harm and costs?	"Deliberate hypotensive management of the actively hemorrhaging trauma patient…has no greater impact on mortality than conventional therapy." (p. 1145) **Based upon the current trial one cannot advocate for or against hemorrhagic trauma lower versus normal BP targets for resuscitation.**

Limitations

1) **No details about method of randomization (when, how, by whom?) meaning that one cannot be certain that allocation equally distributed prognostic variables between the two groups.**

2) **No modeling to adjust for unequal distribution of prognostic variables between groups.**

3) **No description of blinding (patient, family, physicians, outcome assessors).**

4) **No description or definition of the primary outcome.**

5) **No power (sample size) was reported which is simultaneously unethical and leaves readers uncertain how to use the results when a Type II error is possible. Although the authors note no differences between these two therapies, this trial was not designed or powered as a non-inferiority trial or equivalence trial so neither can be confidently assumed.**

6) **No details about what fluid therapies were used (normal saline, lactated ringers, blood products).**

7) **No CONSORT diagram to describe patient flow.**

8) **Possible selection bias limiting external validity.**

9) **Failure to report details for hemorrhage-control interventions between groups.**

10) **Exclusion of pregnant, elderly and traumatic brain injury patients limits the external validity of these findings.**

Bottom Line

This is an inconclusive trial for several reasons: select patient population in a renowned trauma center with an undefined effect of hemorrhage control interventions and a high likelihood of Type II error. This research neither supports nor refutes permissive hypotension in hemorrhaging male blunt and penetrating trauma victims. Better trial designs are needed utilizing CONSORT methods and acceptable metrics for tissue hypoperfusion before we are to amend ATLS guidelines or alter current bedside practice.