Critical Review Form
Therapy

Hypotensive Resuscitation Strategy Reduces Transfusion Requirements and Severe Postoperative Coagulaopathy in Trauma Patients with Hemorrhagic Shock: Preliminary Results of a Randomized Controlled Trial, *J Trauma* 2011; 70: 652-663

Objective: **"To assess patient outcomes after accrual of 90 patients to establish the safety of a hypotensive resuscitation strategy including its effects on intraoperative fluid administration, bleeding, postoperative complication, and mortality within the trauma population." (p. 652)**

Methods: **From July 2007 through February 2009 eligible adult trauma patients were recruited to this single-center prospective randomized trial at Ben Taub General Hospital, a Level I trauma center in Houston Texas. The research was performed under an exception from informed consent after informing the Houston community of the project via radio, television, and newspaper public service announcements. In addition, "Opt-out" bracelets were made and freely distributed in the community.**

Inclusion criteria included all trauma patients presenting to the Ben Taub ED with a documented SBP ≤ 90 mm Hg and brought emergently to the operating room (OR) for a laparotomy or thoracotomy in order to surgically control bleeding. Exclusion criteria included: 14 < age >45, pregnancy, prisoners, a past medical history of MI or CAD or CVA or renal disease, inability to rule out traumatic brain injury (TBI) based on the mechanism of injury or clinical exam or cranial CT, wearing "opt-out" bracelet, or if the patient's legally authorized representative was available and did not consent.

After identifying eligible patients, randomization occurred pre-OR to one of two groups: control group with target intra-operative mean arterial pressure 65 mm Hg (HMAP) or experimental group with target intra-op MAP 50 mm Hg (LMAP). The method of randomization is not detailed. The target MAP were selected based on an online survey of the membership of the Eastern Association of Surgical Trauma and American Association of Surgical Trauma in which 80.4% of responding surgeons indicated that a MAP within 5 mm Hg of 65 mmHg was an appropriate standard of care for young trauma patients (unpublished data). The level of 50 mm Hg was determined from experience with elective hip surgery which

demonstrated decreased blood loss (not referenced). Methods by which the target BP goals were met were left to the discretion of the treating anesthesiologist.

All data were abstracted from the ED records or hospital trauma registry including Injury Severity Score (ISS), Trauma ISS, GCS, revised trauma score, abbreviated injury scale, time to intervention, vital signs, hemoglobin levels, and base deficit, mechanism of injury, location of injury and type of injury. Anesthesia records were used to obtain intra-op blood pressures, body temperature, anesthetic agent dosing, crystalloid/colloid infusions, packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelet transfusions.

The primary outcome was 30-day survival and data were analyzed using a Cox proportional hazards model and logistic regression model.

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. "Randomization occurred on arrival to the operating room, and all patients were assigned to either an experimental group whose target minimum mean arterial pressure (MAP) for resuscitation was 50 mm Hg (LMAP) or to a control group whose target minimum MAP was 65 mm Hg (HMAP)." (p. 653)
2.	Was randomization concealed (blinded)?	Yes. "Randomization envelopes are prepared and sealed by a third party and that the process of patient allocation is blinded." (p. 661)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "This study is a single institution, prospective, two-arm, intent-to-treat, randomized, controlled clinical trial…" (p. 653)

4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Probably. "There were no significant differences between the two groups with regard to age, gender, or race" (p. 655), Table 1) however, blunt mechanism of injury was more common in the HMAP group (n=6 vs. 0, p=0.01) as was the ISS (25.1 vs. 17.9, p=0.02). There were no significant differences between LMAP and HMAP for GCS, RTS, abbreviated injury scale, TRISS, or in the receipt of pre-hospital or ED fluids. In Houston, it is the policy that EMS and ED not administer IVF as reflected by only 16 LMAP (mean 1.08 L) and 17 HMAP (mean 1.16) received IVF bolus.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes.
2.	Were clinicians aware of group allocation?	Yes. "As with any type of sentient intervention, it was neither feasible nor reasonable to blind the surgeon and anesthesiologist to randomization assignment once the envelope had been unsealed." (p. 662) Potential biases introduced by this lack of blinding include co-intervention bias (anesthesiologist altered fluid/pressor/blood product management in one group or another, surgeon operated faster in one group or another) or ascertainment bias (evaluating or documenting ISS or GCS more thoroughly in one group or another).
3.	Were outcome assessors aware of group allocation?	Yes. There is no clear statement of blinding outcome assessors and no good reason why they could not be blinded.
4.	Was follow-up complete?	Yes. "All subjects were followed up for the entire 30-day post-operative period except for five patients who were lost to follow-up after hospital discharge. Two of those patients were in the LMAP group and three were in the HMAP group." (p. 655) This is a 5.5% lost to follow-up rate without a sensitivity analysis.

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• 90 patients were enrolled (44 LMAP, 46 HMAP) but no CONSORT diagram was reported. • HMAP group received significantly more fluids (2898 mL vs. 1594 mL, p=0.03), including significantly more PRBC (1335 mL vs. 2244 mL, p=0.05) and FFP (198 mL vs. 528 mL, p=0.02) with the PRBC: FFP ratio significantly higher in the LMAP group (6.7:1 vs. 4.2:1, p<0.001) • No statistically significant differences in MAP (64.4 mm Hg vs. 68.5 mm Hg, p=0.15) • 10 deaths in LMAP group and 13 in HMAP group at 30-days with hazards ratio of 1.10 (95% CI 0.96-1.07, p=0.58). The number of early post operative deaths was significantly lower in the LMAP group (1/44 vs. 8/46 within 24 hours of ICU admission, p=0.03) • More patients in the HMAP group died because of coagulopathic bleeding (7/10 vs. 0/6, p=0.01) despite receiving significantly more blood products. • Multiple regression analysis controlling for age, ISS, injury mechanism (blunt vs. penetrating), volume of intra-operative blood transfusions, and randomization group yielded ISS and amount of blood products as statistically significant predictors of 30-day mortality.

2.	How precise was the estimate of the treatment effect?	See 95% CI above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Patient population (young urban male trauma patients with hemorrhagic hypotension necessitating immediate operative intervention) similar to a subset of our most critically ill Level I trauma patients. However, there are significant management differs between Houston and St. Louis regarding the "no bolus" policies in place for the Houston EMS and ED. The authors also do not evaluate trauma patients with VIR-interventions.
2.	Were all clinically important outcomes considered?	No patient-centric outcomes (morbidity, functional recovery) were reported, although it is difficult to enjoy any functional recovery if you die.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. Lower MAP targets intra-operatively can simultaneously reduce short term post-operative mortality while preserving blood products that are constantly in short supply. If these results are confirmed, expansion to VIR patients should be explored as well as EMS and ED protocols.

Limitations

1) **No CONSORT diagram.**

2) **No explanation of randomization methods or personnel.**

3) **No blinding of outcome assessor.**

4) **No description of multivariate analysis methods (inclusion criteria, step wise insertion, etc.)**
5) **No sensitivity analysis for 5.5% lost to flu.**

6) **No power calculation and not set up as a non-inferiority or equivalence trial.**

7) **OR setting with limited external validity to the ED.**

Bottom Line

Intra-operative hypotensive (target MAP 50) resuscitation strategies by anesthesiology in non-pregnant young adult trauma victims with SBP <90 may be a safe strategy that does not increase mortality and reduces the consumption of blood products. Future research efforts should follow CONSORT methods, evaluate patient-centric outcomes, and provide an assessment of similar lower target BP management in EMS and ED settings. These results cannot be extrapolated to pregnant or middle-aged/geriatric populations.