Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma: Early termination of a randomized prospective clinical trial

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BACKGROUND: Hemorrhagic shock is responsible for one third of trauma related deaths. We hypothesized that intraoperative hypotensive resuscitation would improve survival for patients undergoing operative control of hemorrhage following penetrating trauma.

METHODS: Between July 1, 2007, and March 28, 2013, penetrating trauma patients aged 14 years to 45 years with a systolic blood pressure of 90 mm Hg or lower requiring laparotomy or thoracotomy for control of hemorrhage were randomized 1:1 based on a target minimum mean arterial pressure (MAP) of 50 mm Hg (experimental arm, LMAP) or 65 mm Hg (control arm, HMAP). Patients were followed up 30 days postoperatively. The primary outcome of mortality; secondary outcomes including stroke, myocardial infarction, renal failure, coagulopathy, and infection; and other clinical data were analyzed between study arms using univariate and Kaplan-Meier analyses.

RESULTS: The trial enrolled 168 patients (86 LMAP, 82 HMAP patients) before early termination, in part because of clinical equipoise and futility. Injuries resulted from gunshot wounds (76%) and stab wounds (24%); 90% of the patients were male, and the median age was 31 years. Baseline vitals, laboratory results, and injury severity were similar between groups. Intraoperative MAP was 65.5 ± 11.6 mm Hg in the LMAP group and 69.1 ± 13.8 mm Hg in the HMAP group ($p = 0.07$). No significant survival advantage existed for the LMAP group at 30 days ($p = 0.48$) or 24 hours ($p = 0.27$). Secondary outcomes were similar for the LMAP and HMAP groups: acute myocardial infarction (1% vs. 2%), stroke (0% vs. 3%), any renal failure (15% vs. 12%), coagulopathy (28% vs. 29%), and infection (59% vs. 58%) ($p > 0.05$ for all). Acute renal injury occurred less often in the LMAP than in HMAP group (13% vs. 30%, $p = 0.01$).

CONCLUSION: This study was unable to demonstrate that hypotensive resuscitation at a target MAP of 50 mm Hg could significantly improve 30-day mortality. Further study is necessary to fully realize the benefits of hypotensive resuscitation. (*J Trauma Acute Care Surg.* 2016;80: 886–896. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic study, level II.

KEY WORDS: Trauma; hypotensive resuscitation; hemorrhage control; mortality.

In the United States, trauma is the leading cause of death for persons 1 year through 44 years of age.[1] Approximately one third of trauma deaths occur because of exsanguination within the first several hours after injury.[2] Traditionally, surgeons and emergency medical personnel use high-volume fluid resuscitation strategies to replace lost blood, along with expedient hemorrhage control in an attempt to reverse hemorrhagic shock.[3] These strategies have considerable limitations[4–6] and are beginning to be tested in prospective, randomized clinical trials.[4,7] Still, high-volume fluid resuscitation strategies are commonly used.

Hypotensive resuscitation is increasingly being accepted as an alternative to the current standard fluid resuscitation. This strategy uses less fluids and blood products during the early stages of treatment for hemorrhagic shock compared with the standard of care.[7] Intraoperative hypotensive resuscitation has been successfully used in animal models[8] and safely used in patients undergoing elective operations.[9–13] Hypotensive resuscitation has also been shown to be feasible and safe during early resuscitation of patients in the out-of-hospital and hospital settings.[14] Our previously published findings from a preliminary interim analysis of the first 90 patients enrolled in our randomized controlled trial demonstrated that hypotensive resuscitation significantly decreased postoperative coagulopathy and lowered the risk of early postoperative death and coagulopathy.[7] The interim analysis provided convincing evidence to continue investigation and the use of hypotensive resuscitation in the trauma setting. This report expands on our interim results with penetrating trauma patients to assess additional patient outcomes after an intraoperative hypotensive resuscitation strategy. We hypothesized that an intraoperative hypotensive resuscitation strategy would improve survival for patients undergoing operative control of hemorrhage following penetrating trauma. A priori secondary outcome measures were also examined.

PATIENTS AND METHODS

This study was a single-institution, prospective, two-arm, intent-to-treat, randomized, controlled clinical trial conducted at Ben Taub Hospital, a Level I trauma center in Houston, Texas. This trial is registered (ClinicalTrials.gov Identifier: NCT00459160). Approval for the study was obtained from the Baylor College of Medicine and Ben Taub Hospital institutional review boards before patient enrollment and was performed under an exception from informed consent for emergency research (federal regulation 21CFR50.24.12),[15] as previously described by Morrison et al.[7]

Previous studies indicate that the patients most likely to benefit from hypotensive resuscitation are those in hemorrhagic shock caused by uncontrolled sources of bleeding.[16,17] Consequently, we targeted trauma patients with an uncontrolled source of bleeding requiring operative control defined as the need for emergent laparotomy or thoracotomy (e.g., direct disposition from the trauma bay to the operating room [OR]). Hemorrhagic shock was defined as a systolic blood pressure (SBP) of 90 mm Hg or lower in the emergency department.

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This study was presented at the 74th annual meeting of the American Association for the Surgery of Trauma, September 9–12, 2015, in Las Vegas, Nevada.

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Initially, patients undergoing laparotomy or thoracotomy for blunt or penetrating trauma with at least one in-hospital documented SBP of 90 mm Hg or lower were randomized into one of two treatment groups as follows: the experimental group whose target minimum mean arterial pressure (MAP) for resuscitation was 50 mm Hg (LMAP) or the control group with a target minimum MAP of 65 mm Hg (HMAP). An interim analysis found that a disproportionate number of blunt trauma patients were randomized to the HMAP group as opposed to the LMAP group. Given the use of a third party for randomization and that the process of patient allocation was blinded, there was no way for the surgeon to know to which group the patient would be randomized when they decided to enroll the patient in the study. As such, it was presumed that the discrepancy occurred because of chance. To eliminate this confounding effect, the data safety monitory board made the decision to stop enrolling blunt trauma patients.

Therefore, inclusion criteria for this study included all penetrating trauma patients seen in the Ben Taub Hospital Emergency Center (EC) with a documented SBP of 90 mm Hg or lower who were brought emergently to the OR from the trauma bay for a laparotomy or thoracotomy to control bleeding.

Exclusion criteria included blunt mechanism; age of less than 14 years or greater than 45 years (older patients could potentially have underlying cerebrovascular or cardiac disease, making them more susceptible to organ hypoperfusion with prolonged hypotension); known or suspected head injury; pregnant women and incarcerated individuals (who were excluded based on their protection from enrollment in waiver of consent trials);[18] and patients with "opt-out" bracelets that signify their refusal of participation in the project, as previously described by Morrison et al.[7]

Randomization occurred on arrival to the OR using envelopes prepared and sealed by a third party; all patients were assigned to either the experimental arm (LMAP) or control arm (HMAP). A target minimum intraoperative MAP of 50 mm Hg was chosen as the experimental arm based on research in the delivery of anesthetic agents that drop the MAP to 50 mm Hg in elective hip surgery.[19,20] Although these studies are elective cases where the patient is not in a state of ongoing blood loss before the procedure begins, they served as a guideline in choosing a safe target MAP thought to be sufficiently lower than the control arm and to have clinical impact on outcomes. In choosing the control arm intraoperative MAP, while no

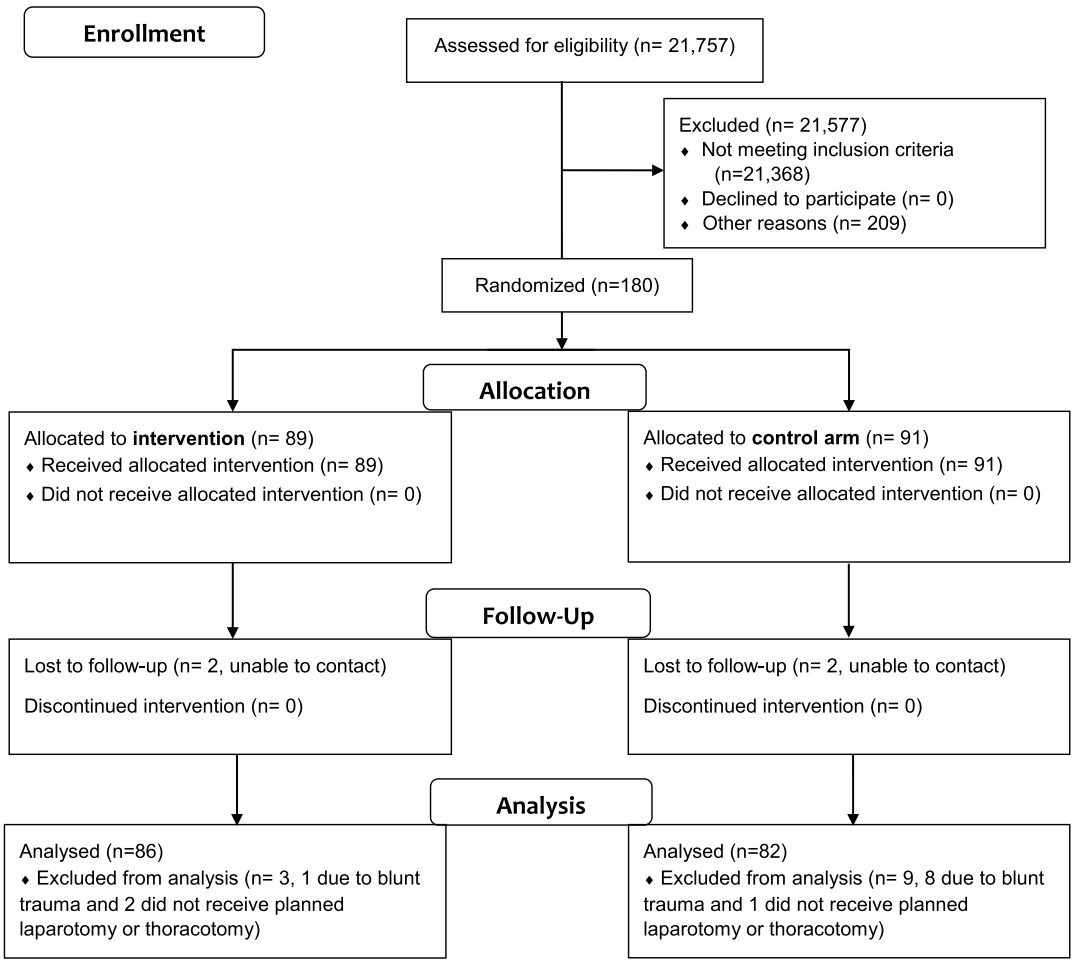

Figure 1. CONSORT diagram.

TABLE 1. Baseline Demographics and Clinical Characteristics

	Experimental Arm MAP ≥ 50 mm Hg		Control Arm MAP ≥ 65 mm Hg		*p*
	N	n (%) or Median (Range)	N	n (%) or Median (Range)	
Male sex	86	79 (91.9)	82	73 (89.0)	0.53
Age, y	84	28 (16 to 54)	80	32 (15 to 54)	0.24
Race	86		82		0.97
White		7 (8.1)		6 (7.3)	
Black		39 (45.4)		40 (48.8)	
Hispanic		38 (44.2)		34 (41.5)	
Asian		2 (2.3)		2 (2.4)	
Mechanism	86		82		0.37
Gunshot wound		68 (79.1)		60 (73.2)	
Stab		18 (20.9)		22 (26.8)	
SBP, mm Hg	62	85 (11 to 161)	52	79 (40 to 144)	0.16
Diastolic blood pressure, mm Hg	56	53 (20 to 142)	47	48 (10 to 102)	0.26
Heart rate, mean (SD), beats/min	68	108 (27)	66	112 (34)	0.52
Base excess, mmol/L	82	−8.0 (−29.0 to 5.4)	80	−10.0 (−30.0 to 27.3)	0.25
Hematocrit, %	82	34.1 (20.9 to 47.4)	80	33.1 (14 to 90.2)	0.51
Glucose, mg/dL	83	205 (105 to 591)	80	192 (75 to 717)	0.61
AIS score	83	4.0 (1 to 5)	79	4.0 (2 to 6)	0.53
ISS	83	17 (1 to 43)	79	18 (4 to 75)	0.43
GCS score	82	15 (3 to 15)	74	14 (3 to 15)	0.35
Minutes to OR*	86	10 (1 to 59)	82	10 (1 to 84)	0.88
Minutes to surgery start*	86	20 (6 to 146)	82	20 (7 to 105)	0.71
Minutes to control of bleeding*	37	49 (12 to 190)	37	43 (16 to 130)	0.92
Duration of case, min*	86	97 (12 to 515)	82	96 (22 to 324)	0.77

*Starting from time of arrival in the Emergency Center.
Percentage calculated as n/N.

cutoff point exists as a guideline, it is routine for trauma patients to be kept at a MAP of approximately 65 mm Hg during surgery, which represents approximately 80% of a normal MAP for a young, otherwise healthy individual. Most trauma patients are young (mean [SD], 29 [2] years)[3] and have normal blood pressures and MAPs if not otherwise injured. An intraoperative target MAP of 65 mm Hg was deemed the control arm based on routine standard of care and was confirmed acceptable to surgeons throughout the United States via an online survey.[7] The assigned minimal MAP of 50 mm Hg or 65 mm Hg was to be maintained from surgery start to surgery finish (control of hemorrhage).

Methods for achieving the target blood pressure goals were left to the discretion of the treating anesthesiologist. These target MAPs represent the minimum blood pressures at which further specific resuscitative interventions (e.g., fluids, transfusions or vasopressors) were administered. Ensuring that patients remained at their minimum target MAP for the duration of the case was not our intent; if patients were able to spontaneously maintain a MAP greater than their assigned target, the blood pressure was not intentionally lowered.

Before the OR and in all other aspects of care, the patients were treated as per standard of care. All patients were followed up for 30 days postoperatively; laboratory and clinical data were recorded prospectively on a daily basis, from the emergency department records and/or hospital trauma registry.

Demographic and presenting clinical characteristics were compared between groups to assess for any statistically significant differences at baseline. Variables collected included age, sex, race, mechanism of injury, Injury Severity Score (ISS), trauma ISS, Glasgow Coma Scale (GCS) score, Abbreviated Injury Scale (AIS) score, baseline vital signs, base deficit value, hematocrit, glucose, and time to intervention.

Differences between the two groups with regard to intraoperative parameters were assessed for the following continuous variables: mean intraoperative blood pressures, percentage of operative time spent under the assigned target MAP, body temperature, heart rate, dosage of anesthetic agents, dosage of the amount of intravenous fluids (crystalloids/colloids), amount of blood transfusions (packed red blood cells [PRBCs], fresh frozen plasma [FFP], platelets, and all transfusions combined), estimated blood loss (as determined by anesthesiologist estimation at the end of the case), total resuscitation fluids (all colloids, crystalloids, carriers, and transfusions administered during the resuscitation process), and operative time. All data were obtained from the anesthesia record.

Intraoperative vital signs were measured every 15 seconds to 30 seconds using an automated system that records a variety of vital signs including heart rate, respiratory rate, as well as systolic, diastolic, and MAPs (directly from the arterial line and a noninvasive blood pressure cuff). These values were stored electronically by the CompuRecord software (Philips Electronics, Eindhoven, the Netherlands) routinely used by the anesthesiology staff at Ben Taub Hospital. The software automatically highlights any values that do not seem to be legitimate measurements (such as when devices are calibrated,

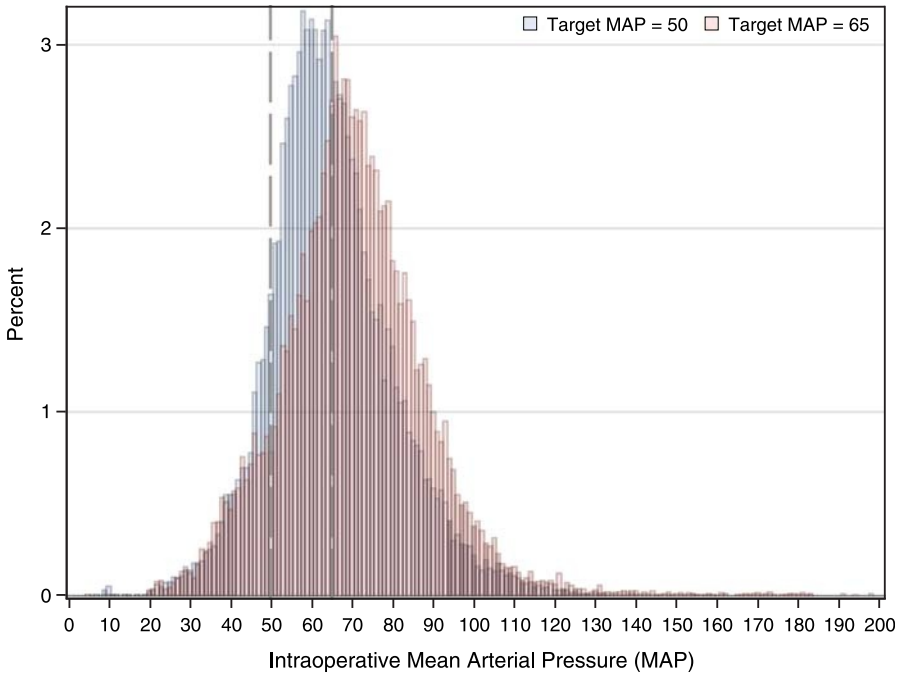

Figure 2. Distribution of all intraoperative MAPs by study group, $p < 0.001$.

the arterial line is flushed/aspirated, or if the noninvasive blood pressure cuff is not properly applied). These data points were deleted from the analysis.

The primary outcome of the study was 30-day mortality. In addition, 24-hour mortality was examined as well as the following postoperative complications among patients who survived the first 24 hours after admission: myocardial infarction (two of the following three: elevated cardiac enzymes + electrocardiogram changes + pathologic findings of myocardial infarction), stroke (focal neurologic deficit + pathologic findings of cerebrovascular accident or neurosurgery/neurology call stroke), any renal failure (creatinine > 2.0 or need for hemodialysis), acute renal injury (ARI, >50% rise in creatinine within the first 48 hours after admission), hypotension (any episode requiring vasopressor support), coagulopathy (international normalized ratio > 1.3 at any time), thrombocytopenia (platelets < 100,000 at any time), anemia (postoperative hemoglobin < 10.0), and infection.

The estimated sample size (n = 271) was centered on the primary outcome of 30-day mortality. The estimate was based on achieving power of at least 80%, $\alpha < 0.05$, and detecting a treatment difference of 10% (60% and 70% survival in the HMAP and LMAP group, respectively), with a 10% loss to follow-up. The treatment difference was a conservative estimate reflecting the only human trial at the time, which evaluated the effect of delaying fluid resuscitation until surgical intervention in hypotensive victims of penetrating truncal injury.[21]

Statistical analyses were performed using commercially available software packages (STATA, version 10.0, StataCorp LD, College Station, TX, and SAS, version 9.3, Cary, NC). All analyses were defined a priori and performed in accordance with the study Protocol and the Statistical Analysis Plan. The Harrington Modification to the O'Brien Fleming stopping points were used for the interim analyses, with a final $p < 0.0458$. Continuous variables were compared using Student's *t* test or Mann-Whitney U-test. Categorical variables were compared using χ^2 or Fisher exact test. Kaplan-Meier curves and Cox proportional hazards models were used to compare 30-day and 24-hour survival between the two groups. Secondary outcomes were analyzed with χ^2 tests.

RESULTS

Patient Enrollment and Follow-up

Between July 1, 2007, and March 28, 2013, a total of 180 patients were enrolled in the study. Nine patients with blunt rather than penetrating trauma and three patients who did not receive the planned laparotomy or thoracotomy were excluded; thus, there were a total of 168 patients in the analysis. Six patients included in the analysis were older than 45 years, and two had unknown head injuries at the time of enrollment but are included in this intention-to-treat analysis. Eighty-six patients (51.2%) were randomized to the experimental LMAP group and 82 (48.8%) to the control HMAP group. All subjects were followed up for 30 days postoperatively, except for four patients who were lost to follow-up after hospital discharge. Two of these patients were in the LMAP group, and two were in the HMAP group (Fig. 1). The Data Safety Monitoring Board recommended early termination of the study, which originally intended to recruit 271 subjects, in part because of the unlikelihood of reaching a statistically significant difference in 30-day mortality by the end of enrollment.

Baseline Characteristics

Baseline demographic and clinical characteristics are shown in Table 1. There were no statistically significant differences

TABLE 2. Intraoperative Vitals, Fluid Administration, and Dosage of Vasopressors

	Experimental Arm MAP ≥ 50 mm Hg		Control Arm MAP ≥ 65 mm Hg		*p*
	N	n (%) or Median (Range)	N	n (%) or Median (Range)	
Vital signs					
Temperature, °C	68	34.9 (31.2–39.3)	69	35.1 (18.8–38.7)	0.98
SBP, mm Hg	84	97.8 (45.7–132.6)	82	102.5 (20.6–160.3)	0.19
DBP, mm Hg	84	50.2 (29.1–74.6)	82	55.5 (25.7–83.3)	0.03
MAP, mean (SD), mm Hg	84	65.5 (11.6)	82	69.1 (13.8)	0.07
MAP, first 60 min, mean (SD), mm Hg	84	64.9 (11.8)	82	68.7 (13.0)	0.052
Percentage of time with a MAP*	23,076		21,224		<0.001
<50 mm Hg		2,906 (12.6)		2,291 (10.8)	
50–65, mm Hg		9,389 (40.7)		5,179 (24.4)	
≥65 mm Hg		10,781 (46.7)		13,754 (64.8)	
Intravenous fluids					
Crystalloid, mL	86	2,200 (0–11,200)	82	2,000 (0–11,000)	0.41
Colloid, mL	86	500 (0–2,000)	82	500 (0–5,000)	0.90
Blood products					
PRBCs, mL	86	1,125 (0–11,250)	82	1,500 (0–9,250)	0.14
FFP, mL	86	0 (0–13,000)	82	0 (0–4,000)	0.01
Platelets, mL	86	0 (0–6,500)	82	0 (0–1,500)	0.10
Ratio of PRBCs to FFP	27	2.3 (0.4–12.0)	40	2.2 (0–9.9)	0.79
Total inputs					
Nonblood products, mL	86	2,650 (0–12,200)	82	3,000 (0–11,500)	0.30
Blood products, mL	86	1,250 (0–30,750)	82	1,700 (0–13,762)	0.08
Total fluids, mL	86	4,125 (0–34,250)	65	5,200 (500–21,613)	0.07
Total outputs					
Estimated blood loss, mL	84	1,150 (20–12,000)	78	1,500 (10–10,000)	0.23
Urine output, mL	69	250 (0–1,935)	61	250 (50–2,460)	0.98
Vasopressor dosages					
Received vasopressor in the first hour	84	50 (59.5)	81	68 (84.0)	<0.001
Phenylephrine, μg	85	0 (0–2,400)	81	100 (0–8,210)	0.37
Norepinephrine, μg	85	0 (0–1,945)	81	5 (0–8,130)	0.04
Epinephrine, μg	85	0 (0–11,930)	81	0 (0–21,000)	0.02

*Counts represent the number of 20-second intraoperative intervals at which the MAP was recorded.
Pecentage calculated as n/N.
DBP, diastolic blood pressure.

between the two groups with regard to age, sex, race, or mechanism of injury. Both groups presented to the EC with similar vital signs, laboratory results, and injury severity, indicating similar degrees of shock between the two groups.

The timing of intervention was similar between the two groups. There were no differences observed in the time from arrival in the EC to arrival in the OR, to the start of surgery, or the duration of the case. In addition, when it was possible to record the exact time during surgery that the hemorrhage was controlled, there were no differences among groups from arrival in the EC until control of the surgical bleeding (Table 1).

Intraoperative Characteristics

Intraoperative vitals, fluid administration, and the dosage of vasopressors received are summarized in Table 2. Although the LMAP and HMAP study groups had different target intraoperative MAPs for resuscitation, no difference was observed in the mean MAPs recorded intraoperatively (65.5 ± 11.6 mm Hg vs. 69.1 ± 13.8 mm Hg, $p = 0.07$; Table 2). When analyzing each intraoperative MAP recorded approximately every 20 seconds, the percentage of time under the target MAP was significantly less for the LMAP group compared with the HMAP group (12.6% vs. 35.2%, $p < 0.001$; Fig. 2).

The HMAP group received significantly more norepinephrine and epinephrine intraoperatively compared with the LMAP group. The HMAP group received more, although not statistically significant, total fluids intraoperatively (median, 5,200 vs. 4,125, $p = 0.07$), driven largely by the significantly increased volume of FFP given to the HMAP group (Table 2). Forty patients (49%) in the HMAP group received FFP in comparison with 26 patients (30%) in the LMAP group. Among those patients who received FFP in the HMAP and LMAP groups, there was no difference in the median volume of FFP given (998 mL vs. 958 mL, $p = 0.46$). Otherwise, the two study groups received similar amounts of intraoperative crystalloid, colloid, PRBCs, and platelets. There were no differences observed in estimated blood loss or urine output between the two groups. The total blood product requirements in the first 24 hours after admission, including emergency department, OR, and postoperatively, did not differ between groups.

Primary Outcome

Overall, a significant difference was not observed in our primary outcome (Table 3); there were 18 deaths in the LMAP group and 21 deaths in the HMAP group during the first 30 days after surgery (p = 0.47). Kaplan-Meier survival curves are shown in Figure 3*A* (Cox proportional hazard, p = 0.48). Within the first 24 hours after admission, 11 deaths (13%) occurred in the LMAP group and 16 (20%) in the HMAP group. As shown in Figure 3*B*, no difference in 24-hour mortality was detected between the HMAP and LMAP groups (Cox proportional hazard, p = 0.27). In the LMAP group, 10% (9 of 86) of patients died in the OR, 3% (2 of 77) within the first 24 hours upon arrival to the intensive care unit (ICU), and 10% (7 of 73) died more than 24 hours after their ICU admission. In the HMAP group, 7% (6 of 82) of patients died in the OR, 13% (10 of 76) within the first 24 hours upon arrival to the ICU, and 9% (6 of 64) died more than 24 hours after their ICU admission, of which one death occurred beyond 30 days.

Ten (56%) of the 18 deaths in the LMAP group and 15 (71%) of the 21 deaths in the HMAP group were caused by exsanguination. The remaining deaths in the LMAP group were due to a dead bowel (n = 1), multiple organ failure (n = 1), respiratory failure (n = 3), abdominal sepsis and pneumonia (n = 1), and care was withdrawn in two patients with anoxic brain injuries. In the HMAP group, four of the remaining deaths were caused by combinations of multiple-organ failure, dead bowel, pneumonia, and sepsis, and the fifth was caused by a coronary artery air embolism.

TABLE 3. Postoperative Complications

	Experimental Arm MAP ≥ 50 mm Hg		Control Arm MAP ≥ 65 mm Hg		p
	N*	n (%)	N*	n (%)	
Overall deaths at 30 d**	84	18 (21.4)	80	21 (26.3)	0.47
Acute myocardial infarction	75	1 (1.3)	66	1 (1.5)	1.0
Stroke	75	0 (0)	66	2 (3.0)	0.22
Any renal failure	75	11 (14.7)	66	8 (12.1)	0.66
ARI	75	10 (13.3)	66	20 (30.3)	0.01
Hypotension	75	10 (13.3)	66	11 (16.7)	0.58
Coagulopathy	75	21 (28.0)	66	19 (28.8)	0.92
Thrombocytopenia	75	23 (30.7)	66	22 (33.3)	0.73
Anemia	75	68 (90.7)	66	53 (80.3)	0.08
Infection	75	44 (58.7)	66	38 (57.6)	0.90

*The 30-day mortality denominators exclude the four patients who were lost to follow-up. The denominators for the remaining postoperative complications exclude the 27 patients who died within the first 24 hours after admission.

**One death in HMAP group at 42 days, not included in 30-day mortality count.

Percentage calculated as n/N.

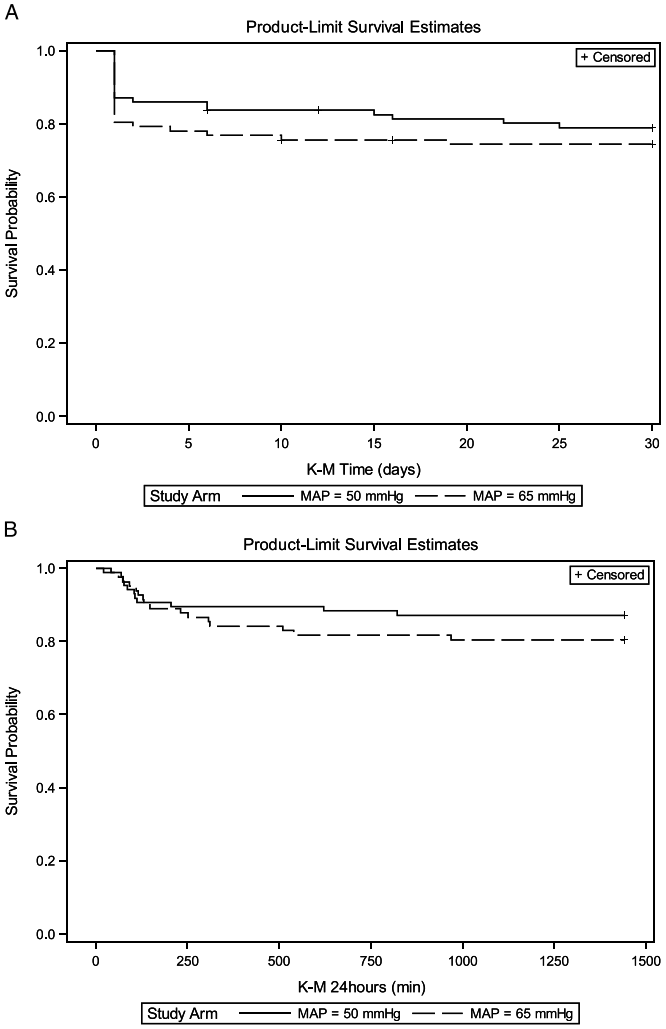

Figure 3. *A,* Kaplan-Meier 30-day survival curves, p = 0.48; *B,* Kaplan-Meier 24-hour survival curves, p = 0.27.

Secondary Outcomes

Between the two study groups, no significant differences existed in the following postoperative complications: acute myocardial infarction (1% vs. 2%), stroke (0% vs. 3%), any renal failure (15% vs. 12%), hypotension (13% vs. 17%), coagulopathy (28% vs. 29%), thrombocytopenia (31% vs. 33%), anemia (91% vs. 80%), and infection (59% vs. 58%) ($p > 0.05$ for all, Table 3). While the rate of renal failure was similar between the groups, ARI was significantly higher in the HMAP group (13% vs. 30% p = 0.01) (Table 3).

DISCUSSION

The concern regarding the safety of hypotensive resuscitation stems from the potential harmful effects of decreased oxygen delivery to the various tissues of the body, resulting in inadequate perfusion and subsequent organ failure.[7] Aggressive fluid resuscitation to maintain a high or "normal" blood pressure in the setting of uncontrolled hemorrhagic shock acts to increase bleeding and "pop the clot."[22] Thus, undesirable outcomes are again possible, this time secondary to exsanguination and the "lethal triad" of hypothermia, acidemia, and coagulopathy.[22,23]

This study was unable to demonstrate an effect on the primary outcome measure, that hypotensive resuscitation at a target MAP of 50 mm Hg could significantly improve 30-day mortality. Despite the lack of statistical significance there was a 5% difference in mortality favoring the hypotensive group. Further investigation into this primary outcome measure could be powered to detect a difference in this range.

While the mean MAP for each patient is not statistically different between groups, the amount of time spent below the target MAP (Fig. 2) suggests that it is not as difficult to maintain an intraoperative MAP of greater than 50 mm Hg as it is to maintain one that is greater than 65 mm Hg. It seems more patients in the LMAP group are able to independently maintain this minimum level of MAP. If the two treatment arms are ignored, additional variables that were found to be significantly associated with 30-day mortality in univariate analysis included OR and 24-hour levels of PRBCs, FFP, and platelets, along with OR blood loss and injury severity (data not shown).

Despite what was felt to be successful control of surgical bleeding in the OR, all of the early postoperative deaths (<24 hours) in the HMAP group occurred as a result of ongoing nonsurgical bleeding (n = 10). International normalized ratio was also increased in each of these patients. Two early postoperative deaths occurred in the LMAP group; one was a result of coagulopathic bleeding, and the other was caused by a nonviable small bowel. These results suggest that hypotensive resuscitation may reduce the risk of early mortality from coagulopathy.

Despite receiving 1,000 mL less of intraoperative fluids, there were no significant differences between the two groups with regard to postoperative acute myocardial infarction, stroke, renal failure, or hypotension. While it was expected that the patients in the HMAP group would have a higher incidence of coagulopathy and anemia postoperatively,[7] these differences were not observed. The similarities between groups for postoperative complications caused by coagulopathy and anemia could be due to the fact that more patients in the HMAP group died of exsanguination associated with coagulopathy in the early postoperative period. Alternatively, the volumes of fluid received by the LMAP and HMAP groups (4,125 mL and 5,200 mL, respectively) are less than reported in other studies.[24,25] The low amounts of fluid used in both the LMAP and HMAP groups may contribute to the inability to detect differences in outcomes.

Although the rate of renal failure was similar between the groups, ARI was significantly higher in the HMAP group. While it might have been predicted that randomization to the LMAP group would have resulted in increased rates of ARI due to a proposed lack of renal perfusion, it seems that the opposite occurred, and the HMAP group had higher rates of ARI. This is perhaps caused by organ injury secondary to the damaging effects of increased amounts of fluid, blood, and plasma.[26]

While our study was unable to demonstrate that hypotensive resuscitation at a target MAP of 50 mm Hg could significantly improve 30-day mortality, others have shown benefits of hypotensive resuscitation. An out-of-hospital, prospective, randomized pilot trial conducted by Schreiber et al.[14] assessed the feasibility and safety of hypotensive resuscitation for the early resuscitation of patients with traumatic shock caused by blunt or penetrating trauma. They found that hypotensive resuscitation is feasible and safe for the initial resuscitation of trauma patients and that there was no statistically significant difference in mortality at 24 hours between hypotensive and standard resuscitation, where SBPs were maintained at 70 mm Hg and 110 mm Hg, respectively. Similarly, Dutton et al.[17] found no difference in in-hospital mortality when trauma patients with hemorrhage were resuscitated with conventional (target SBP > 100 mm Hg) and low strategies (target SBP = 70 mm Hg). In a retrospective analysis, Duke et al.[27] demonstrated that patients with penetrating torso injuries who were managed with damage-control resuscitation principles and restricted fluid resuscitation, defined as less than 150 mL of crystalloid preoperatively, have an improved OR mortality and overall survival compared with those managed with standard fluid resuscitation (>150-mL crystalloid).

Several limitations exist in this study. Although the intent was to examine the ability to improve 30-day mortality with an intraoperative hypotensive resuscitation strategy (minimum target MAP, 50 mm Hg), the actual average intraoperative MAP for the experimental arm was greater than anticipated. While the LMAP group's actual MAP was lower than that of the HMAP group, it was not statistically lower. There are two reasons postulated that could contribute to the higher-than-expected MAP in the LMAP group. First, the anesthesiology team could not be blinded to the randomization assignment. It is theoretically possible that the anesthesiology team did not perform the intervention as intended. This however seems unlikely. In comparing fluids and pharmacologic agents administered, the HMAP group received more fluids and statistically more vasopressors than the LMAP group, suggesting that the two groups were being treated differently, despite their similar intraoperative MAPs. Another argument in favor of the two groups being treated differently is that when analyzed not as an average blood pressure but as a distribution of all intraoperative MAPs by study group (Fig. 2), the groups were significantly different. One factor that likely caused the average MAPs to not be statistically different is autoregulation. This phenomenon, described by Dutton in his 2002 hypotensive study, is one that anesthesiologists are familiar with and may explain why patients in the LMAP group were able to maintain a higher MAP than initially expected on their own.[17] For safety reasons, the study protocol prohibited the anesthesiology team from artificially lowering the blood pressure to the minimum target MAP.

A second limitation of the study is temporal confounders. Multiple process changes, both in the prehospital and emergency department settings, and personnel changes occurred during the trial period. While randomization could allow for the impact of these changes to be balanced between the two treatment arms, given the slow enrollment during the past several years, patients could be imbalanced based on chance alone. However, the number of patients enrolled per year to each treatment arm was examined and was not statistically different.

Finally, it was not possible for the operating surgeon or the anesthesiologist to be blinded to the intervention after the patient allocation occurred. This could result in an intervention or motivation bias in which the treating physician either consciously or unconsciously changed their behavior in a way that could affect study outcomes. However, the vasopressor differences observed between the LMAP and HMAP group support the anesthesiologists adhering to and treating each group per the allocation.

In conclusion, this trial was terminated early because of temporal changes in processes of care, lack of equipoise, slow accrual, and futility and therefore was underpowered and unable to demonstrate an improvement in 30-day mortality within a penetrating trauma population when using a hypotensive resuscitation strategy. Further study is necessary to statistically

demonstrate if there are benefits of hypotensive resuscitation. Future efforts could be based on hypotheses generated from this study, such as those aimed at conducting a study powered to detect a 5% difference in groups, or directed at exploring the 24-hour survival between groups.

AUTHORSHIP

M.M.C. supervised and contributed to all aspects of the study from design through manuscript writing and critical revisions. C.A.M. contributed to the study design, literature search, data collection, data analysis, data interpretation, and critical revisions. N.M.T. contributed to the data collection and data analysis J.L. contributed to the literature search, data analysis, data interpretation, and writing. J.W.S. contributed to the data collection, data interpretation, and critical revisions. M.A.N. contributed to the study design, data collection, and critical revisions. F.J.W., B.G.S., K.R.L., S.R.R., M.J.W., and K.L.M. contributed to the data collection and study design.

DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

Dr. Raul Coimbra (San Diego, California): The authors are to be congratulated for another important study addressing new paradigms in resuscitation of the injured patient. They hypothesized that intraoperative hypotensive resuscitation would improve survival for patients undergoing operative control of hemorrhage following penetrating trauma. The study was a single institution, prospective, two-arm, intent-to-treat, randomized, controlled clinical trial. As you heard, the study failed to demonstrate that hypotensive resuscitation at a target mean arterial pressure of 50 could significantly improve 30-day mortality. The authors concluded that hypotensive resuscitation is safe in the penetrating trauma population and it does not increase end organ damage, infectious complications or coagulopathy.

I have several questions for the authors.

Was this study designed to be a safety study or an effectiveness study? The authors used both terms indistinctively but they are not the same. Based on the hypothesis and aims, the study seems to be an effectiveness study, therefore the conclusions related to safety may not be warranted. Please comment.

Why was age limited to 45 years? Shouldn't we consider this resuscitation strategy in patients older than 45 years of age?

The target blood pressure was only achieved in 40% of the patients in the study group and 65% in the controlled group.

Does this invalidate the trial results? Is a trial using such a narrow difference in mean arterial pressure doable and able to reach valid conclusions?

The authors stated that their results suggest that hypotensive resuscitation is not only safe but may reduce the risk of early mortality from coagulopathy.

It seems that they are not considering that in the controlled group a much smaller percentage of patients died in the operating room compared to the study group, an effect expected to be the opposite if hypotensive resuscitation is superior to the control strategy.

Is this a real benefit or advantage of conventional resuscitation in having a higher blood pressure or just a shift in the time to death?

Therefore, the question that begs an answer is whether or not there is an early survival bias in the data. More intraoperative deaths in the experimental group, consequently more patients who survived initial operation observed in the controlled group, go on to die of coagulopathy in the ICU.

Again, I congratulate the authors for taking on such a controversial topic to study in a prospective, randomized fashion, and performed under an exception from informed consent for emergency research.

I thank the Program Committee of the AAST for the opportunity of the floor.

Dr. Eileen M. Bulger (Seattle, Washington): Important study. A couple of questions. You mentioned in your title this was an early termination. Can you indicate why it was terminated? Did you meet your futility boundaries? Was it terminated for feasibility? Why did you terminate early?

My second question is what were your power calculations? What was your initial proposed sample size? And how close were you to that at the time the study was terminated?

My third question is, from a safety standpoint, are you powered to look at renal failure with a sample this size? Thank you.

Dr. John Owings (Shreveport, Louisiana): I applaud the authors for doing an intent-to-treat which the original study out of Baylor was not. I have two questions.

It appeared, if my calculations were correct, only .08% of the eligible patients were included. What was the primary barrier to inclusion? And was there a significant bias initiated by that?

The second question that I had for the authors is based on working with rural trauma centers. Based on doing trauma development courses, many people talk about how hypotensive is better; however, most rural trauma centers see over 90% blunt trauma. Is your study applicable to trauma patients with blunt trauma?

Or is this another article about penetrating trauma? And if so, could you please put cautionary words to those surgeons who see blunt trauma with transit times of one to two-hour or more transit times? And what would your recommendations regarding hypotensive resuscitation be for them?

Dr. Weidun Alan Guo (Buffalo, New York): This is a nice study. Your conclusion is that hypotensive resuscitation is safe for penetrating patients requiring laparotomy or thoracotomy. I noticed that you only included patients who were younger than 45 years old in your study. Can you explain why you excluded patients who were older than 45 years old? It is worthwhile to look at the latter group since they may not tolerate hypotensive resuscitation due to preexisting medical conditions.

Dr. Juan Asensio (Omaha, Nebraska): Congratulations and a great study. I noticed that both of your groups had relatively low estimated blood losses so my questions are:

How many of your patients were admitted with cardiac, thoracic and vascular injuries? Did you measure the time to get these patients to the operating room? We know that less than 15 minutes is good.

And why did you choose stroke (CVA) and MI as your complications to be tracked? These complications are relatively uncommon in trauma patients unless you have a large number of carotid artery injuries.

Thank you. I enjoyed your study.

Dr. Matthew W. Carrick (Southlake, Texas): I thank you very much for the thoughtful commentary, in particular by Dr. Coimbra who sent it to me ahead of time.

To address the question of early survival bias—in Dr. Schreiber's talk last year at the AAST, Dr. Rhee asked him, "Well, what about the first 24 hours? What happened then?" And that's a good question.

If you look at a survival plot in the first 24 hours, both LMAP and HMAP groups are taking a big turn down to the right (dying early). If you look at the times at which they died a few more died in the OR in the LMAP group than in the HMAP group, but you can see that both of them pretty consistently die early of exsanguination.

Hopefully that helps answer the question of whether or not there is survival bias. That is certainly a concern with the study.

For the question on whether this is an effectiveness or a safety study, we consider it an effectiveness study. But, when you have a prospective, randomized, clinical trial you establish a primary outcome. The primary outcome we established was 30-day mortality. Moving forward, we will refer to our primary and secondary outcomes as defined in the initial protocol and eliminate using the terms safety and effectiveness.

Both Dr. Coimbra and Dr. Guo asked about our age cut-off of 45 years old. The IRB was concerned that because of undiagnosed cerebrovascular disease you would end up causing MIs and strokes in people if you included more than 45 years old.

In the research we had from the elective field, patients received pre-op cardiac workups to exclude coronary artery disease. Pre-op workups were not something we could do in the 10 minutes you have to get to the OR.

A question was asked about the ability to achieve the target MAP. The target is a mean minimum arterial pressure, so to say we didn't achieve the target is inaccurate. The anesthesiologists were supposed to resuscitate above that level.

For example, if your target is 50, having all your blood pressures come in just slightly above 50 is actually the result you would expect.

Dr. Bulger asked why was the study terminated? The sample size is based upon a 10% difference in the Kaplan Meier survival. The study was terminated because we were unlikely to achieve our primary outcome with the proposed sample size of 270 patients. Also, too much had changed in terms of processes and personnel over time.

When examining renal failure, we used definitions from an NIH funded trial at our hospital. We will try to comment more on renal failure in the manuscript.

Dr. Owings asked about the barriers to eligibility. Patients that made it to the ER and were randomized, had to actively be randomized. You can imagine these people are pretty sick. As the attending or resident with someone dying in front of you, it is hard to remember to grab a packet and enroll the patient in the study as you roll by.

Addressing blunt traumas, I certainly wanted to include blunt traumas because the study would be more generalizable. But, during the interim analysis, it was noted that a disproportionate number of blunt trauma patients were randomized to the HMAP group than the LMAP group, and they were therefore eliminated from the study by the DSMB.

Dr. Asensio, the time to the operating room is 10 minutes for both groups and the time to surgery start is 20 minutes for both groups. Thank you.