Hypotensive Resuscitation Strategy Reduces Transfusion Requirements and Severe Postoperative Coagulopathy in Trauma Patients With Hemorrhagic Shock: Preliminary Results of a Randomized Controlled Trial

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Background: Trauma is a leading cause of death worldwide and is thus a major public health concern. Previous studies have shown that limiting the amount of fluids given by following a strategy of permissive hypotension during the initial resuscitation period may improve trauma outcomes. This study examines the clinical outcomes from the first 90 patients enrolled in a prospective, randomized controlled trial of hypotensive resuscitation, with the primary aim of assessing the effects of a limited transfusion and intravenous (IV) fluid strategy on 30-day morbidity and mortality.

Methods: Patients in hemorrhagic shock who required emergent surgery were randomized to one of the two arms of the study for intraoperative resuscitation. Those in the experimental (low mean arterial pressure [LMAP]) arm were managed with a hypotensive resuscitation strategy in which the target mean arterial pressure (MAP) was 50 mm Hg. Those in the control (high MAP [HMAP]) arm were managed with standard fluid resuscitation to a target MAP of 65 mm Hg. Patients were followed up for 30 days. Intraoperative fluid requirements, mortality, postoperative complications, and other clinical data were prospectively gathered and analyzed.

Results: Patients in the LMAP group received a significantly less blood products and total IV fluids during intraoperative resuscitation than those in the HMAP group. They had significantly lower mortality in the early postoperative period and a nonsignificant trend for lower mortality at 30 days. Patients in the LMAP group were significantly less likely to develop immediate postoperative coagulopathy and less likely to die from postoperatively bleeding associated with coagulopathy. Among those who developed coagulopathy in both groups, patients in the LMAP group had significantly lower international normalized ratio than those in the HMAP group, indicating a less severe coagulopathy.

Conclusions: Hypotensive resuscitation is a safe strategy for use in the trauma population and results in a significant reduction in blood product transfusions and overall IV fluid administration. Specifically, resuscitating patients with the intent of maintaining a target minimum MAP of 50 mm Hg, rather than 65 mm Hg, significantly decreases postoperative coagulopathy and lowers the risk of early postoperative death and coagulopathy. These preliminary results provide convincing evidence that support the continued investigation and use of hypotensive resuscitation in the trauma setting.

Key Words: Trauma, Hypotensive resuscitation, Coagulopathy.

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Trauma has long been a major cause of preventable deaths in the United States and worldwide. Approximately one-third of trauma deaths occur because the victims bleed to death within the first several hours after their injury.[1] For the past 50 years, high-volume fluid resuscitation strategies have typically been used by surgeons and emergency medical personnel in an attempt to reverse hemorrhagic shock by replacing lost blood with intravenous (IV) fluids or transfusions.[2] Although these strategies are currently considered to be the gold standard of care for trauma patients, they have considerable limitations[3–5] and, unlike many other treatment modalities, have not been extensively tested in prospective, randomized clinical trials.

Hypotensive resuscitation has recently been advocated as an alternative to the current standard of care. In contrast to standard fluid resuscitation, this strategy uses less fluids and blood products during the early stages of treatment for hemorrhagic shock. Although intraoperative hypotensive resuscitation has not been prospectively tested in a surgical trauma setting, it has been successfully used in animal models[6] and has also been safely used in patients undergoing elective operations.[7–11] To our knowledge, this study is the first randomized, prospective study of intraoperative hypotensive resuscitation for trauma in human subjects. The aim of this study is 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 complications, and mortality within the trauma population. Our hypothesis is that patients randomized to a hypotensive resuscitation strategy will have decreased transfusion and intraoperative fluid utilization, decreased transfusions, decreased operative blood loss, decreased postoperative coagulopathy, comparable postoperative morbidity, and decreased mortality compared with patients randomized to a standard fluid resuscitation strategy.

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PATIENTS AND METHODS

Overview of Study Design

This study is a single institution, prospective, two-arm, intent-to-treat, randomized, controlled clinical trial conducted at Ben Taub General Hospital, a Level I trauma center in Houston, TX. Approval for the study was obtained from the Baylor College of Medicine Institutional Review Board (IRB) before patient enrolment, and the trial was also registered with the U.S. National Institute of Health at clinicaltrials.gov. This study was performed under an exception from informed consent required for emergency research as described in Federal regulation 21CFR50.24.[12]

According to the federal law, emergency researchers seeking waiver of consent from participants must first consult with "representatives of the communities in which the research will be conducted" who must approve of moving forward with the trial. The community consent is designed to take the place of individual consent, such that each patient enrolled is not required to consent for himself or to have a personal advocate to consent on his behalf. The federal law expressly prohibits the enrollment of prisoners, fetuses, and pregnant women in studies conducted under a waiver of consent, and these patients were excluded from our study. In compliance with 21CFR50.24, we obtained community consent before conducting this trial. We defined our target community as the patients and family members of patients who seek care in our institution's emergency room. This allowed us to assess the acceptability of the study to a group of people in the community who we felt best represented the population of patients who would ultimately be enrolled in the trial. With the approval from our local IRB and in cooperation with the Center for Medical Ethics and Health Policy at Baylor College of Medicine, we developed a tool for ascertaining community consent that was modeled on a similar method previously published in the literature.[13]

In accordance with federal regulations, the community from which these patients were drawn was informed of the study through public disclosure via public announcements at community centers and by public service announcements through the radio, television, and newspapers distributed throughout the greater Houston area. Detailed information about the trial is also available to the general public via the Baylor College of Medicine website and clinicaltrials.gov. The federal regulations also require that the researchers must "apprise the community" of the study's results on completion of the trial. In compliance with this requirement, our final results will be made available online at clinicaltrials.gov. In compliance with local IRB regulation, "Opt-Out" bracelets were also made available to the public free of charge. These bracelets (which were modeled after the popular "LIVESTRONG" rubber bracelets) can be worn by individuals who do not wish to be included in the study and can express the patient's wishes even if he or she is unconscious or unable to communicate on arrival to the hospital. Information on how to obtain "Opt-Out" bracelets was provided in all community notifications of the trial.

Patients undergoing laparotomy or thoracotomy for blunt and penetrating trauma who had at least one in-hospital documented systolic blood pressure (SBP) ≤90 mm Hg were randomized to one of the two treatment groups. Randomization occurred on arrival to the operating room (OR), 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). Methods by which the target blood pressure goals were met were left to the discretion of the treating anesthesiologist. It should be noted that these target MAPs represent the minimum blood pressures at which further specific resuscitative interventions (e.g., fluids, transfusions, or vasopressors) were administered. It was not our intent to ensure that patients remained at their minimum target MAP for the duration of the case; if patients were able to spontaneously maintain a MAP above their assigned target, the blood pressure was never intentionally lowered to reach this minimum target MAP. Before the OR and in all other aspects of their care, the patients were treated as per standard of care. Figure 1 illustrates the sequence of events immediately preceding and following patient randomization. All patients were followed up for 30 days postoperatively, and laboratory and clinical data were recorded prospectively on a daily basis.

Determination of Randomization Groups

Although no explicit cutoff point exists as a guideline for intraoperative MAP, it is routine for trauma patients to be kept at a MAP of around 65 mm Hg during surgery. For a young, otherwise healthy individual, a MAP of 65 mm Hg essentially amounts to about 80% of a normal MAP. Most trauma patients are young (average, 29 ± 2 years)[2] and usually have normal blood pressures and MAPs if not otherwise injured. To confirm that maintaining an intraoperative MAP of 65 mm Hg would be acceptable to other surgeons throughout the United States, an online survey was devel-

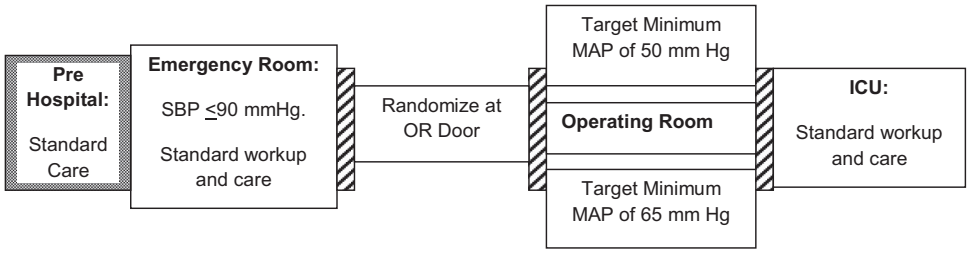

Figure 1. Diagram of the patient flow from left to right.

oped. After seeking permission from the directors of the Eastern Association of Surgical Trauma and American Association of Surgical Trauma, an online survey was e-mailed to each of these organizations' members. Surveys were completed on a voluntary basis and were confidential. The overwhelming majority (80.4%) of surgeons indicated that a MAP within 5 mm Hg of a minimum MAP of 65 mm Hg was an appropriate standard of care for young trauma patients in whom head injury has been ruled out. Therefore, the group of patients whose assigned target goal for intraoperative MAP is 65 mm Hg was labeled the control arm.

With regard to the hypotensive resuscitation group, very little previously published data existed to guide the choice for the target MAP in the experimental arm of this study. However, there has been some research in the delivery of anesthetic agents that drop the MAP to 50 mm Hg in elective hip surgery. These studies have demonstrated a decreased amount of blood loss in these patients with no significant increase in adverse events. These studies differ from this study in that they are elective cases where the patient is not in a state of ongoing blood loss before the procedure even begins. However, they served as a guideline for the choice of a safe target MAP that was sufficiently lower than the control arm to be thought to have clinical impact on outcomes. Therefore, the group of patients whose assigned target goal for intraoperative MAP was 50 mm Hg was labeled the experimental arm.

Inclusion and Exclusion Criteria

Previous studies indicate that the patients who are likely to benefit from hypotensive resuscitation are those in hemorrhagic shock due to uncontrolled sources of bleeding.[14,15] In these patients, increase in blood pressure above the minimum pressure required to maintain organ perfusion may result in dislodging any tenuous clot that has been formed at the site of injury or simply increase the rate of blood loss in those patients who are not able to achieve spontaneous hemostasis. Therefore, we targeted trauma patients with an uncontrolled source of bleeding for inclusion in this study.

Hemorrhagic shock was defined as an SBP $\leq$90 mm Hg in any severely injured patient. Need for emergent laparotomy or thoracotomy (e.g., direct disposition from the trauma bay to the OR) was presumed to be a reasonable marker for the presence of ongoing blood loss requiring operative control. Therefore, inclusion criteria for this study included all trauma patients seen in the Ben Taub emergency center (EC) with a documented SBP $\leq$90 mm Hg who were brought emergently to the OR from the trauma bay for a laparotomy or thoracotomy for surgical control of ongoing bleeding. A concise list of inclusion and exclusion criteria is shown in Figure 2. Patients older than 45 years were excluded, because these patients could potentially have underlying cardiovascular disease that would make them more susceptible to organ hypoperfusion in the face of prolonged hypotension. Exception from informed consent extends to minors younger than18 years, as described by the official Office of Human Resource Protections guidelines, so minors were included in the study.[16] It does not extend to pregnant women, fetuses, or prisoners, so these populations were excluded from the study. Trauma victims younger than 14 years are not treated at our institution and were thus excluded because they are not part of our hospital patient population. Great care was also taken to exclude patients with potential traumatic brain injury, because a set of evidence-based resuscitation guidelines already exists for this particular group of patients and requires maintaining a sufficiently high MAP to provide an adequate cerebral perfusion pressure.

Inclusion Criteria:

- Traumatic injury to the chest or abdomen requiring emergent laparotomy or thoracotomy
- At least one documented SPB ≤90mm Hg
- Patient thought to be in hemorrhagic shock as per attending surgeon's judgment

Exclusion Criteria:

- Age >45 years or <14 years
- Pregnant women
- Incarcerated individuals
- Known history of previous myocardial infarction, coronary artery disease, renal disease, or cerebrovascular disease
- Unable to definitively rule out traumatic brain injury based on mechanism of injury, clinical exam and/or negative CT scan of the head
- Patient is wearing an "Opt-Out" bracelet
- Patient's legal representative is readily available and does not consent to participation in the trial.

Figure 2. Inclusion and exclusion criteria.

Data Collection

Baseline Characteristics

Groups were compared with regard to demographic and presenting clinical characteristics to assess for any statistically significant differences at baseline. All data were obtained from the ER records or hospital trauma registry or both. Continuous variables (age, Injury Severity Score [ISS], trauma ISS, Glasgow coma score, abbreviated injury score, time to intervention, baseline vital signs, hemoglobin level, and base deficit value) were compared using Student's *t* tests. Categorical variables (gender, race, mechanism of injury, location of injury, type of injury) were compared using χ^2 analysis (or Fisher's exact test, if indicated for values of $n < 5$).

Intraoperative Variables

Differences between the two groups with regard to intraoperative parameters were assessed in a similar manner, using Student's *t* tests for the following continuous variables: mean intraoperative blood pressures, body temperature, heart rate, dosage of anesthetic agents, dosage of the amount of IV 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), and total resuscitation fluids (all colloids, crystalloids, carriers, and transfusions administered during the resuscitation process). Duration of surgery (from "skin to skin") was measured as well. All data except for continuously measured vital signs were obtained from the anesthesia record.

Intraoperative vital signs were measured every 15 seconds using an automated system that records a variety of vital signs

including heart rate, respiratory rate, systolic, diastolic, and mean arterial pressures (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 General Hospital. The software automatically highlights any values that do not seem to be legitimate measurements (such as that might occur when devices are being calibrated, the arterial line is being flushed/aspirated, or if the noninvasive blood pressure cuff is not properly applied). These data points were deleted from analysis. Each data point was also reviewed by hand and cross-checked with anesthesiologist's intraoperative notes as a secondary measure to ensure that extreme outliers or physiologically impossible values or both were omitted from the data set.

Primary Outcome, 30-Day Mortality

Kaplan–Meier curves and Cox proportional hazards model were used to compare 30-day survival between the two groups.

Secondary Postoperative Outcomes

Groups were compared with regard to markers of postoperative morbidity. All data were prospectively collected on a daily basis. Continuous variables (length of intensive care unit [ICU] stay, length of hospitalization, length of mechanical ventilation, postoperative hemoglobin levels, platelet levels, international normalized ratio [INR] values, and base deficit values) were compared using Student's *t* tests. Categorical variables (24-hour mortality, development of postoperative complications, etc.) were compared using a χ^2 analysis (or Fisher's exact test if indicated for values of $n < 5$).

Logistic Regression Models

As it is only a preliminary interim analysis, this study is not adequately powered to determine a statistically significant difference in our primary outcome between the two randomization arms. With a sample size of only 90 patients, it is not expected that logistic regression will be able to identify significant predictors of mortality at this interim point. Nevertheless, multiple logistic regression analysis was performed to assess for risk factors, with 30-day mortality being the binary dependent variable. The analysis was also repeated for several of the secondary outcomes of the study.

Data Analysis

All statistical analyses were performed using a commercially available software package (STATA, version 10.0, StataCorp LD, College Station, TX). All continuous variables were compared using Student's *t* tests. Categorical variables were compared using χ^2 analysis or Fisher's exact test, as indicated. Linear, logistic, or multiple regression analysis was performed as indicated.

RESULTS

Patient Enrollment and Follow-Up

Between July 1, 2007, and February 14, 2009, a total of 90 patients were enrolled in the study: 44 to the experimental group (LMAP) and 46 to the control group (HMAP). All subjects were followed up for the entire 30-day postoperative period except for five patients who were lost to follow-up after hospital discharge. Two of these patients were in the LMAP group and three were in the HMAP group.

Baseline Characteristics

Baseline demographic characteristics and mechanism of injury are shown in Table 1. There were no statistically significant differences between the two groups with regard to age, gender, or race. Blunt mechanism of injury (e.g., fall, motor vehicle crash, or crush injury) was more common in the HMAP group than the LMAP group (n = 6 vs. 0, $p = 0.01$). Both groups presented to the EC with similar vital signs—including SBP, diastolic blood pressure, and heart rate—indicating similar degree of shock (Table 2). Similarly, there were no significant differences between the two groups with regard to baseline laboratory results including blood glucose, hematocrit, or base deficit on arterial blood gas (Table 3).

Multiple widely accepted clinical scoring systems were used to compare severity of injury between the two groups at baseline, including Glasgow coma scale (GCS), revised trauma score (RTS), abbreviated injury scale, ISS, and trauma-related injury severity score (TRISS). These data are given in Table 4. There were no statistically significant differences between the two groups with regard to any of these scores except for ISS, which was higher in the HMAP group than that in the LMAP group (25.1 vs. 17.9, $p = 0.02$), suggesting greater severity of injury or greater number of anatomic regions involved. This significant difference persisted even when controlled for penetrating trauma alone (24.6 vs. 17.9, $p = 0.04$).

Prerandomization Resuscitation Fluids

As is routine practice for the emergency rescue personnel in our district, no IV boluses of fluid was given in the field

TABLE 1. Baseline Demographics and Mechanism of Injury

	MAP = 50 mm Hg (n = 44)	MAP = 65 mm Hg (n = 46)	*p*
Sex			0.97
Male	41	40	
Female	3	6	
Age (yr), mean (SD)	30.8 (9.3)	33.8 (9.0)	0.12
Race			0.88
White	3	3	
Black	21	18	
Hispanic	19	24	
Asian	1	1	
Mechanism			0.01
Penetrating	44	40	
GSW	37	28	
Stab	7	12	
Blunt	0	6	

GSW, gunshot wound.

TABLE 2. Baseline Vital Signs

	MAP = 50 mm Hg (n = 44)				MAP = 65 mm Hg (n = 46)				
Baseline Vitals	**n**	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
Systolic blood pressure	39	78.4	20.0	72.0–84.9	42	73.3	23.7	65.9–80.7	0.29
Diastolic blood pressure	38	45.1	18.0	39.2–51.0	41	38.8	17.1	33.3–44.2	0.11
Heart rate	40	105	28.2	96.0–114.1	42	101	36.1	89.5–112.0	0.55

CI, confidence interval.

TABLE 3. Baseline Laboratory Results

	MAP = 50 mm Hg (n = 44)				MAP = 65 mm Hg (n = 46)				
Baseline Laboratory	**n**	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
Base excess	41	−10.7	7.6	− 13.1 to − 8.3	45	−11.1	1.4	− 13.9 to − 8.3	0.81
Hematocrit	41	32.7	6.3	30.7 to 34.7	45	30.5	6.9	28.4 to 32.5	0.13
Glucose	42	214	80	189 to 239	45	214	79.9	190 to 238	0.99

CI, confidence interval.

TABLE 4. Baseline Clinical Scores

	MAP = 50 mm Hg				MAP = 65 mm Hg				
Clinical Scores	**n**	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
RTS	28	7.0	1.9	6.2–7.7	28	6.8	1.3	6.3–7.3	0.66
ISS	38	17.9	10.8	14.3–21.4	41	25.1	20.3	20.3–29.8	0.02
TRISS	28	0.909	0.26	0.808–1.00	30	0.844	0.311	0.728–0.960	0.39
GCS	41	12.1	4.5	10.7–13.5	39	12.2	4.1	10.8–13.5	0.93
AIS abdomen									
Total scores	38	4.6	4.8	3.1–6.2	41	6	5.3	4.4–7.7	0.22
Highest score	38	2.2	1.6	1.7–2.7	41	2.7	1.7	2.2–3.3	0.14
AIS chest									
Total scores	38	3.4	3.8	2.2–4.7	41	4.5	5.1	2.8–6.1	0.31
Highest score	38	2.0	1.8	1.4–2.6	41	2.3	1.6	1.8–2.9	0.42
AIS spine									
Total scores	38	0.5	4.7	0.1–1.0	41	1.6	4	0.3–2.9	0.11
Highest score	38	0.3	1	0.1–0.6	41	0.8	1.7	0.3–1.4	0.11
AIS extremity									
Total scores	38	1.4	2.2	0.7–2.1	41	3.2	3.8	2.0–4.4	0.01
Highest score	38	0.9	1.2	0.5–1.3	41	1.4	1.3	1.0–1.9	0.07

AIS, abbreviated injury scale; CI, confidence interval.

or during transport to the hospital. Although an IV line is typically placed in the field, only the minimal amount of fluid necessary to keep the line open is given and is considered to have negligible contribution to the overall fluid resuscitation of the patient. Although it is not a common practice for our emergency responders to administer fluids in the prehospital setting, one patient in the LMAP group received 750 mL of normal saline (NS) and two patients in the HMAP group received 600 mL of NS before hospital arrival. Similarly, some of the patients included in the study received resuscitation fluids in the EC before their actual enrollment in the trial at the time of arrival in the OR. In the LMAP group, 16 patients received an average of 1,081 mL of NS while still in the EC; in the HMAP group, 17 patients received an average of 1,104 mL of NS. None of these differences in prerandomization fluids were statistically significant.

Timing of Intervention

There were no significant differences between the two groups with regard to timing intervention. The time from arrival in the EC until arrival in the OR and start of the surgical case was similar for both groups, as was the duration of surgery. In approximately one-fourth of the cases (23 of 90), the surgeon was able to record the exact time during surgery at which the source of ongoing bleeding was definitively controlled. The time from arrival in the EC until control of surgical bleeding was also similar between the two groups. These data are summarized in Table 5.

TABLE 5. Timing of Intervention, Starting From Time of Arrival to the EC

	MAP = 50 mm Hg				MAP = 65 mm Hg				
Surgery Times	**n**	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
Time to OR (min)	43	14.4	12.3	11.7–19.2	43	19	19.3	13.2–25.2	0.31
Time to surgery start (min)	42	25.6	11.8	21.9–29.3	44	27.7	12.2	20.6–34.8	0.56
Time to control of bleeding (min)	10	45.9	35.4	20.6–71.2	13	40.3	27.7	23.5–57.1	0.67
Duration of case (min)	43	107.6	57	90.1–125.1	46	105.7	61.1	87.6–123.9	0.88

CI, confidence interval.

Intraoperative Resuscitation Fluids

The HMAP group received significantly larger amounts of total blood product transfusions than the LMAP group (2,898 mL vs. 1,594 mL, $p = 0.03$). Specifically, they received significantly more PRBCs and FFP than those who were randomized to the LMAP group. There was no standardized "massive transfusion protocol" in place at our institution at the time this study was initiated or was there a protocol in place for one-to-one replacement of PRBCs to FFP. The PRBC:FFP ratio was significantly higher in the LMAP group than the HMAP group (6.7:1 vs. 4.2:1, $p < 0.001$). There were no statistically significant differences with regard to the amount of crystalloid, colloid, total IV fluids, or estimated blood loss (EBL) between the two groups. All inputs and outputs of the intraoperative fluid are summarized in Table 6.

There were no statistically significant differences in the amount of vasopressors administered to the two groups (Table 7). There were also no statistically significant differences with regard to the type or amount of anesthetic agents administered intraoperatively.

Intraoperative Vital Signs

Despite having different targets for resuscitation, there were no statistically significant differences between the actual MAP between the two groups for the duration of the case (64.4 mm Hg vs. 68.5 mm Hg, $p = 0.15$). There were also no statistically significant differences in mean intraoperative

TABLE 6. Intraoperative Fluids

	MAP = 50 mm Hg				MAP = 65 mm Hg				
	n	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
IVF									
Crystalloid (mL)	44	2,883	1,921	2,299–3,467	46	3,282	2,010	2,667–3,866	0.34
Colloid (mL)	44	512	469	367–656	46	609	470	469–748	0.33
Blood products									
PRBC (mL)	44	1,335	1,812	784–1,886	46	2,244	2,466	1,512–2,977	0.05
FFP (mL)	44	198	471	54–341	46	528	860	272–783	0.02
Platelets (mL)	44	61	214	3–137	46	114	242	42–186	0.27
Total inputs									
Non-blood products (mL)	44	3,438	2,103	2,791–4,086	46	3,875	2,098	3,252–4,498	0.33
Blood products (mL)	44	1,594	2,292	897–2,291	46	2,898	3,299	1,918–3,877	0.03
Total fluids	44	5,070	3,631	3,952–6,187	46	6,762	4,559	5,408–8,116	0.06
Total outputs									
Estimated blood loss (mL)	44	1,964	2,215	1,290–2,637	46	3,008	2,948	2,132–3,883	0.06
Urine output (mL)	40	272	284	181–363	40	347	353	234–460	0.29
Total fluid balance	40	3,026	2,470	2,225–3,826	40	3,089	2,383	2,327–3,851	0.90

CI, confidence interval.

TABLE 7. Dosage of Vasopressors Administered Intraoperatively

	MAP = 50 mm Hg				MAP = 65 mm Hg				
	n	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
Phenylephrine (μg)	43	359	524	178–866	46	847	458	201–1,617	0.31
Norepinephrine (μg)	43	28	90	0–55	46	259	1,223	104–623	0.22
Epinephrine (μg)	43	344	1,696	198–521	46	909	2,384	76–1,770	0.20

CI, confidence interval.

TABLE 8. Intraoperative Vital Signs

	MAP = 50 mm Hg				MAP = 65 mm Hg				
	n	Mean	SD	CI	n	Mean	SD	CI	*p*
Temperature (°C)	29	35.1	1.5	34.6–35.7	36	34.7	1.5	34.2–35.3	0.32
SBP (mm Hg)	42	96.7	18.4	91.0–102.4	46	100.6	19.5	94.8–106.3	0.34
DBP (mm Hg)	41	50.6	8.7	47.8–53.3	45	54.3	1.6	51.2–57.4	0.08
MAP (mm Hg)	42	64.7	11.7	61.0–68.3	46	68.5	12.9	64.7–72.3	0.15
MAP, first 30 min (mm Hg)	42	64.6	11.7	61.0–68.3	46	67.7	12.6	64.3–71.5	0.23
Duration at MAP <65 (min)	42	42.9	35	32.0–53.8	46	31.5	29.5	22.8–40.3	0.10

DBP, diastolic blood pressure; CI, confidence interval.

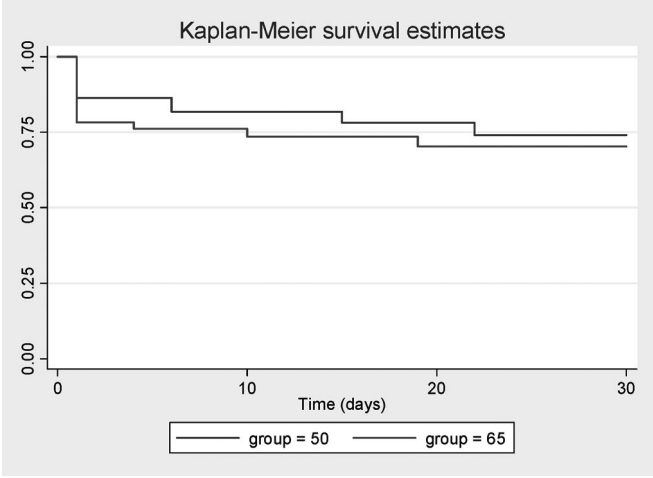

Figure 3. Kaplan–Meier survival curves.

temperature and systolic or diastolic blood pressures. These data are summarized in Table 8.

Survival

Kaplan–Meier survival curves are shown in Figure 3. Using a Cox regression model, a hazard ratio of 1.10 was calculated ($p = 0.58$, confidence interval = 0.96–1.07). Overall, there were 10 deaths in the LMAP group and 13 in the HMAP group during the first 30 days after surgery. This difference was not statistically significant. Within the LMAP group, 6 of the 10 deaths occurred within 24 hours of hospital admission secondary to exsanguination. Of the 13 deaths in the HMAP group, 10 occurred within 24 hours of hospital admission secondary to exsanguination, often associated with coagulopathy. The number of early postoperative deaths was significantly lower in the LMAP group compared with the HMAP group ($p = 0.03$). A summary of the timing of deaths is shown in Table 9 and cause of death is shown in Table 10.

Multiple regression analysis was performed to assess for risk factors for mortality. In a model containing age, ISS, mechanism of injury (blunt vs. penetrating), amount of intraoperative blood transfusions, and randomization group as variables, only ISS ($p = 0.01$) and amount of intraoperative blood transfusions ($p < 0.001$) were statistically significant predictors of 30-day mortality. Only amount of intraoperative blood transfusions ($p < 0.001$) was associated with 24-hour mortality.

TABLE 9. Timing of Deaths

	MAP = 50 mm Hg (n = 44)	MAP = 65 mm Hg (n = 46)	*p*
Died in OR	5	2	0.26
Died within 24 h of ICU admission	1	8	0.03
Total deaths <24 h	6	10	0.32
Died 1-10 d after ICU admission	2	2	1.00
Died >10 d after ICU admission	2	1	1.00
Total deaths >24 h	4	3	1.00
Overall deaths at 30 d	10	13	0.55

Hematologic Complications

Significantly more patients in the HMAP group died as a direct result of coagulopathic bleeding in the immediate postoperative period (<24 hours) compared with the LMAP group (n = 7 of 10 vs. n = 0 of 6, Fisher's exact $p = 0.01$). Excluding patients who died within the first 24 hours, both groups had similar rates of coagulopathy, as defined by an INR >1.3 at any point in the 30-day postoperative period. Patients in both groups also had similar rates of postoperative anemia, as defined as hemoglobin level <10.0 at any point in the 30-day postoperative period. There was no significant difference between the two groups with regard to the development of postoperative thrombocytopenia (Table 11).

In the immediate (24-hour) postoperative period, patients in both groups had similar total fluid requirements, as shown in Table 12. Creatinine levels and calculated base deficit on arterial blood gas were also similar between the two groups in the immediate postoperative period, as shown in Table 13. Mean postoperative transfusion of PRBCs, FFP, and platelets was nearly identical in both groups during the immediate postoperative period (Table 11). Postoperative hematocrit and platelet levels were also similar between the groups; however, PT, partial thromboplastin time, and INR were significantly higher in the HMAP group compared with the LMAP group. Although we attempted to collect thromboelastogram data postoperatively, these laboratory data were not consistently drawn in a timely manner (mean time to

TABLE 10. Causes of Death

MAP = 50 mm Hg		MAP = 65 mm Hg	
Timing	**Cause of Death**	**Timing**	**Cause of Death**
In OR	Exsanguination (patient expired before start of case)	In OR	Exsanguination
In OR	Exsanguination (patient expired before start of case)	In OR	Exsanguination
In OR	Exsanguination	<24 h	Exsanguination (unable to control surgical bleeding)
In OR	Exsanguination	<24 h	Coagulopathy/exsanguination
In OR	Exsanguination	<24 h	Coagulopathy/exsanguination
<24 h	Exsanguination (missed aortic injury)	<24 h	Coagulopathy/exsanguination
HD 4	Anoxic brain injury/care withdrawn	<24 h	Coagulopathy/exsanguination
HD 6	Respiratory failure	<24 h	Coagulopathy/exsanguination
HD 15	Respiratory failure/pneumonia	<24 h	Coagulopathy/exsanguination
HD 22	Abdominal sepsis, pneumonia	<24 h	Coagulopathy/exsanguination
		HD 3	MOFS
		HD 10	MOFS/pneumonia
		HD 19	Abdominal sepsis, pneumonia

TABLE 11. Postoperative Complications

	MAP = 50 mm Hg (n = 38)	MAP = 65 mm Hg (n = 36)	*p*
Coagulopathy	23 (60.5%)	22 (61.1%)	0.93
Thrombocytopenia	15 (39.5%)	8 (22.2%)	0.09
Anemia	16 (42.1%)	17 (47.2%)	0.97

thromboelastogram = 7 hours; range, 1–36 hours) and often occurred after additional transfusion of blood products in the surgical intensive care unit, limiting their usefulness for evaluating postoperative coagulopathy.

DISCUSSION

Theoretical concerns regarding the safety of hypotensive resuscitation are based on the possible harmful effects of decreased oxygen delivery to the various tissues of the body. Maintaining a blood pressure that is too low could potentially result in inadequate perfusion and subsequent organ failure, with potentially catastrophic outcomes. On the other hand, critics of aggressive fluid resuscitation argue that maintaining a high or "normal" blood pressure in the face of uncontrolled hemorrhagic shock can result in equally catastrophic outcomes secondary to exsanguination and the "lethal triad" of hypothermia, acidemia, and coagulopathy.[17,18] Several potential risks and benefits to both strategies certainly exist, yet the issue has never been subjected to a randomized prospective clinical trial humans. This is the first such study to examine an intraoperative hypotensive resuscitation strategy for human trauma patients in hemorrhagic shock. By evaluating the effects of a hypotensive resuscitation strategy aimed at reducing the amount of fluids and blood products administered, the trial provides concrete data to support an evidence-based answer to the longstanding debate on hypotensive versus standard high-volume fluid resuscitation. It should be emphasized that this article reflects the results of an interim analysis of an ongoing clinical trial (n = 90) and that enrollment has not yet reached its final accrual (n = 271).

Mortality and Morbidity

With regard to the primary endpoint of the study (30-day mortality), hypotensive resuscitation seems to be a safe management strategy in this patient population. There were no statistically significant differences with regard to 30-day mortality, and in fact, there was a trend toward fewer deaths in the LMAP group. Although there seems to be a slightly higher number of intraoperative deaths in the LMAP group than the HMAP group, two of these deaths occurred before either the operation or the intraoperative resuscitation

TABLE 12. Fluid Balance and Transfusion Requirements for the First 24 h Postoperatively

	MAP = 50 mm Hg				MAP = 65 mm Hg				
	n	**Mean**	**SD**	**CI**	**n**	**Mean**	**SD**	**CI**	***p***
PRBC (units)	38	2.2	3.1	1.2–3.3	36	2.1	4.1	0.8–3.5	0.47
FFP (units)	38	1.0	1.7	0.4–1.5	36	1.1	1.9	0.4–1.7	0.55
Platelets (units)	38	0.7	1.7	0.2–1.3	36	0.5	1.1	0.1–0.8	0.24
Total inputs	38	6,406	4,662	4,873–7,938	36	5,990	4,803	4,364–7,615	0.71
Total outputs	38	3,965	3,813	2,711–5,218	36	3,943	2,973	2,937–4,949	0.98
Net fluid balance	38	2,326	2,895	1,374–3,278	36	2,141	2,965	1,137–3,144	0.79

CI, confidence interval.

TABLE 13. Immediate Postoperative Laboratory Results

	MAP = 50 mm Hg				MAP = 65 mm Hg				
	n	Mean	SD	CI	n	Mean	SD	CI	*p*
Creatinine	38	1.1	0.2	1.0 to 1.1	39	1.0	0.2	0.9 to 1.1	0.20
Base excess on ABG	34	−5.4	1.0	− 7.3 to − 3.4	36	−6.0	0.7	− 7.5 to − 4.5	0.58
Net change (pre-op)	33	5.2	1.1	2.9 to 7.4	36	3.4	1.4	0.5 to 6.2	0.33
Hematocrit	38	28.3	4.1	27.0 to 29.7	41	29.6	7.6	27.2 to 32.0	0.36
Net change (pre-op)	38	−2.4	7.7	−4.9 to 0.2	41	−1.0	10.3	−4.4 to 2.3	0.53
Platelet count	38	162	72	138 to 185	42	158	79	134 to 183	0.87
PTT	42	39.1	23.2	31.8 to 46.3	42	56.0	44.8	41.1 to 70.9	0.03*
PT	42	14.0	2.2	13.3 to 14.6	37	21.7	23.8	13.7 to 29.6	0.04*
INR	42	1.4	0.7	1.2 to 1.5	37	2.2	2.5	1.4 to 3.1	0.02*

CI, confidence interval; ABG, arterial blood gas; PTT, partial thromboplastin time.

strategy were even initiated, so they could not have possibly been a result of the resuscitation strategy assigned; however, these patients were included in the analysis on an intent-to-treat basis.

Hypotensive resuscitation also seems to be safe with regard to early postoperative mortality. Of those patients who survived the operation after control of surgical bleeding, significantly fewer deaths occurred in the LMAP group than in the HMAP group during the first 24 hours postoperatively. Interestingly, the majority of early postoperative deaths in the HMAP group (7 of 8) occurred as a result of ongoing bleeding after successful control of surgical bleeding in the OR, as determined by examination of each patient's intraoperative and postoperative records. INR was increased in each of these patients and exceeded the maximum value measurable in the laboratory (>10.0) in three of the patients. The single early postoperative death that occurred in the LMAP group was not attributed to coagulopathic bleeding, based on hospital records and autopsy findings. Taken together, these results suggest that hypotensive resuscitation is not only safe but may also reduce risk of early mortality from coagulopathy: an explanation that is consistent with the known pathophysiology of the lethal triad associated with high-volume resuscitation.

There were no statistically significant differences between the two groups with regard to late mortality (>24 hours). Similarly, there were no statistically significant differences between with two groups with regard to postoperative organ failure, infection, length of hospital or ICU stay, or duration of mechanical ventilation.

With regard to hematologic complications, it was expected that patients in the HMAP group would be more coagulopathic postoperatively, as it is known that standard high-volume resuscitation can exacerbate the lethal triad of acidemia, hypothermia, and coagulopathy. Although the number of patients with INR >1.5 was similar between the groups, the measured INR was drastically higher among coagulopathic patients in the HMAP group compared with those in the LMAP group. Furthermore, significantly more patients in the HMAP group died of exsanguination in association with coagulopathy during the early postoperative period. This occurred despite the fact that patients in the HMAP group received significantly larger amount and proportion of FFP as a part of their intraoperative resuscitation. Furthermore, despite having received less FFP than the HMAP group intraoperatively, the LMAP group did not have an increased requirement for FFP during the 24 hours after surgery, and the total number of patients who went on to develop coagulopathy for the remaining 30-day period was similar between the two groups. These data strongly support the idea that a hypotensive resuscitation strategy reduces the amount of FFP transfusions with no adverse effect on the incidence or severity of coagulopathy. In addition, hypotensive resuscitation seems to significantly reduce early mortality from coagulopathy compared with standard fluid resuscitation in this patient population.

It was expected that the HMAP group would have greater incidence and severity of anemia than the LMAP group as a result of excessive blood loss associated with both increased intraoperative blood pressure and increased dilution via the administration of high-volume crystalloids. Indeed, the HMAP group on average lost over a liter more blood than the LMAP group intraoperatively and required almost 1 L more of intraoperative PRBC transfusions. Both groups had nearly identical postoperative hemoglobin levels and 24-hour postoperative requirements for additional units of PRBCs. The total number of patients in each group who developed anemia at any point during their 30-day follow-up was also similar.

All these data suggest that hypotensive resuscitation is safe with regard to hematologic end points, because patients in the LMAP group require significantly fewer blood product transfusions and yet experience no significant differences in the incidence or severity of coagulopathy, thrombocytopenia, or anemia. In fact, there is significantly decreased mortality from coagulopathy in this group as well. This finding alone has profound implications from a resource-utilization standpoint. If targeting a minimum MAP of 50 mm Hg rather than 65 mm Hg in the OR can significantly reduce the amount of blood products that are expended during the resuscitation process without any adverse effect on morbidity or mortality, this could mean not only significant cost savings to the hospital but also increased availability of blood products for other patients as well.

Limitations

The intention of this study was to test the effectiveness of an intraoperative hypotensive resuscitation strategy that used a minimum target MAP of 50 mm Hg, the actual average intraoperative MAP for patients randomized to the LMAP arm was much higher than 50 mm Hg. In fact, although the average MAP for the LMAP group was slightly lower than that of the HMAP group, this difference was not statistically significant, and the actual MAPs for the two groups were much more similar than might be expected based on the target goals for resuscitation.

The study protocol prohibited the anesthesiology team from artificially lowering blood pressure to the minimum target MAP if the patient was already spontaneously maintaining a higher blood pressure on his or her own. The reason for this was primarily one of the safety efforts: to pharmacologically reduce blood pressure (such as by administering vasodilators or increasing the level of sedation) may accidentally overshoot the minimum target, resulting in a dangerously low MAP $<$50 mm Hg. Furthermore, the body's ability to automatically maintain a MAP between 50 and 65 mm Hg may reflect a beneficial physiologic response to low-volume resuscitation—such as effective clotting and natural hemostasis—which would be important to identify and could possibly account for any potential differences in outcomes.

There are several possible explanations for failure to achieve the desired intervention of maintaining a MAP closer to 50 mm Hg in the LMAP group. One possible explanation is that the anesthesiology team, who could not be blinded to the randomization assignment, failed to perform the intervention as intended. To determine whether this was the case, the intraoperative management of each group was evaluated for evidence of whether the two arms were indeed treated in a similar manner. This was accomplished by comparing the amount of fluids administered and other pharmacological agents at the anesthesiologists' disposal, which could be used to affect blood pressure.

An alternative, and more likely, explanation for the unexpected similarities in actual MAP between the two groups is that patients in the LMAP group were able to automatically maintain a blood pressure above the minimum target of 50 mm Hg without requiring further intervention from the anesthesiologist apart from a modest initial fluid administration. It is possible that by autoregulation, these patients were able to naturally maintain a MAP that was higher than the investigators expected when they initially decided on the target MAP for hypotensive resuscitation. In fact, Dutton et al., previously reported this precise phenomenon during their clinical trial of hypotensive resuscitation in the emergency room setting.[15]

The amount and types of anesthetic agents administered to achieve sedation (which can also reduce blood pressure) were not statistically different, indicating that the anesthesiologists did not attempt to artificially lower the blood pressure in one group rather than another, which was in keeping with the study protocol. One would expect to see some difference between the two groups with regard to interventions that raise blood pressure, such as administration of fluids or vasopressors, because the intended intervention was to raise the MAP whenever it fell below the minimum target. The LMAP group did indeed receive significantly less blood product transfusions. But although they also received less crystalloids and colloids, these differences were less dramatic and were not statistically significant. These findings do suggest that the two groups are being treated in a different manner—even though their intraoperative MAPs are similar—with a notable difference in transfusion of blood products.

Another limitation of this study is the presence of several potentially confounding variables. As a prospective randomized trial, this study was not designed to specifically control for certain patient characteristics, but rather it was presumed that any variability with regard to baseline characteristics would be evenly distributed between the two groups given the random, blinded process of group allocation at the time of enrollment. Patient demographics, mechanism/severity of injury, and prerandomization vital signs/laboratory results were compared between the two groups in this analysis to ensure that there were no significant differences between the two groups at baseline. With regard to most characteristics, the two groups were indeed similar. However, two notable differences were discovered at baseline, which could potentially serve as significant confounders: distribution of blunt injuries and ISS.

A disproportionate number of patients randomized to the HMAP group suffered blunt mechanism of trauma as opposed to the LMAP group. Given that randomization envelopes are prepared and sealed by a third party and that the process of patient allocation is blinded, there is no way for the surgeon to know to which group the patient will be randomized when they decide to enroll the patient in the study. Thus, it is extremely unlikely that this difference is due to systematic selection bias on the part of the enrolling physician. Given the lack of plausible explanations for this statistically significant difference at baseline, it is presumed that this discrepancy has occurred due to chance. Nevertheless, this significant difference at baseline may have had some influence on patient outcomes. Since presenting this interim data to our data safety monitoring board, the decision has been made to stop enrolling blunt trauma patients for the remainder of the study to eliminate this confounding effect.

It was decided a priori that results of this study would be analyzed on an intent-to-treat basis and that patients inadvertently enrolled as a result of a protocol deviation would remain in the analysis. In keeping with the original design and intent of the study, blunt trauma patients will be presented in this and subsequent analyses—even though blunt trauma is now considered to be an exclusion criterion for ongoing enrollment—as will all other patients who were enrolled due to protocol deviation (e.g., age $>$45, concomitant head injury, etc.) However, to try and account for this important baseline difference, the entire analysis was repeated to exclude blunt trauma patients. Repeating the analysis had no effect on our overall results. There were no statistically significant differences between blunt and penetrating trauma groups at baseline with regard to demographics, ISSs (RTS, ISS, TRISS, and GCS), and baseline physiologic status. There was also no

new effect on the repeated analysis with regard to intraoperative fluids, pressors, vital signs, or timing of intervention. Nor was there any difference in any of the intraoperative or postoperative results, except as described below.

The only difference in statistical significance occurred with regard to EBL which actually further supported our hypothesis; whereas the difference in EBL for the original analysis barely failed to reach statistical significance (1,964 mL [LMAP] vs. 3,008 mL [HMAP], $p = 0.06$), the difference in EBL was statistically significant in the penetrating-only group (1,964 mL [LMAP] vs. 3,252 mL [HMAP], $p = 0.03$). Repeating the analysis to exclude blunt trauma did not affect results with regard to postoperative incidence of hematologic complications (including coagulopathy and anemia). As with our original analysis, patients in the HMAP group who were coagulopathic still had a significantly higher INR than their coagulopathic counterparts in the LMAP group (2.4 vs. 6.3, $p = 0.015$). None of the patients in the blunt-trauma group died within our 30-day study period; thus, excluding these patients had no appreciable effect on our analysis of either 24-hour or 30-day mortality.

Multivariate analysis including both randomization group and blunt trauma status as independent variables was also performed for several of the major outcomes variables: 30-day mortality, 24-hour mortality, EBL, intraoperative PRBCs, postoperative coagulopathy, and postoperative anemia. Randomization group remained a significant predictor of EBL in this analysis (with MAP = 50 associated with lower blood loss, $p = 0.03$) but not of any of the other dependent variables listed above. Blunt trauma was not a significant predictor of any of the measured variables.

To assess differences in severity of injury, a variety of standardized clinical scales were used to quantify injury severity, including GCS, RTS, abbreviated injury scale, ISS, and TRISS, as well as presenting vital signs, hemoglobin, and base deficit. Again, it is difficult to explain the statistically significant difference in ISS at baseline, because there is no way for surgeons to know which group the patients will be assigned to when the decision to enroll is made; thus, it is hard to imagine a mechanism by which more severely injured patients could be systematically included in the HMAP group. The calculation of all clinical scores is performed by a third party with no connection to the clinical trial and with no knowledge of the patients' randomization assignments. Thus, a plausible mechanism by which biased clinical scoring could have occurred is likewise difficult to conjure.

Despite the fact that differences in all other markers of injury severity were not statistically significant between the groups, this significant difference in ISS should not be ignored. If the HMAP group did indeed contain more severely injured patients than the LMAP group then it is possible that this discrepancy alone, rather than the intended intervention, may account for poorer outcomes among this group. In this respect, the difference in ISS at baseline is truly a confounding factor, as one cannot be absolutely certain that the standard fluid resuscitation strategy alone accounts for findings such as increased transfusion and fluid requirements and worse postoperative clinical status.

The fact that method of reaching the target intraoperative MAP is left up to the discretion of the anesthesiologist also introduces numerous potentially confounding variables. Although the goal for all patients in a given arm is the same, the actual manner in which they are treated can vary significantly—any amount or combination of fluids and vasopressors is permitted, which introduces considerable heterogeneity among patients in the same arm of the trial. Thus, if any significant differences in administration of one of these agents exist between the groups, one cannot be entirely certain that it is the entire resuscitation strategy as a whole—and not just this single aspect of the intervention—that accounts for any differences in outcome. This type of bias is often referred as "co-intervention bias," and should be taken into consideration when interpreting the results of a study such as this.

Another type of potential bias inherent in this study design is "intervention bias," or "motivation bias," related to the fact that neither the operating surgeon nor the treating anesthesiologist is blinded to the intervention after patient allocation has occurred. This type of bias is inherent in any randomized trial involving an intervention in which a caregiver who is aware of randomization assignment is also in a position to, either consciously or unconsciously, affect study outcomes. 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. It is conceivable that, once aware of the randomization assignment, either the surgeon or anesthesiologist changed his or her behavior (intentionally or unintentionally) in such a way that outcomes were systematically affected.

Finally, the small sample size used in this analysis is another limitation when interpreting the results. Because this interim analysis occurred after the enrollment of only 90 patients, it is possible that a type II error may occur as a result of the relatively small sample size. In other words, it is possible that outcomes or interventions that seem to be statistically similar in this analysis may later become statistically significant on accrual of additional patients into the study. Similarly, it is possible that apparent differences at baseline, such as the proportion of blunt versus penetrating trauma or ISS, may eventually even out once the randomization process continues. Thus, it deserves repeating that this analysis is merely an early examination of the overall safety of the trial. By demonstrating that patients randomized to the experimental LMAP arm are not more likely to die or develop serious complications than those randomized to the control HMAP arm, this analysis supports continuation of the trial and provides reassurance that neither group is being subjected to an undue safety risk as a result of participation in the study.

CONCLUSIONS

In summary, based on the data presented in this study, it seems that a hypotensive resuscitation is a safe strategy for use in the trauma population, although its safety in any of the patient groups specifically excluded in the study design cannot be inferred. Specifically, a hypotensive resuscitation strategy to a minimum intraoperative target MAP of 50 mm Hg

does not increase the risk of 30-day mortality compared with a standard fluid resuscitation strategy to a minimum intraoperative MAP of 65 mm Hg. Furthermore, hypotensive resuscitation does not significantly increase the risk of intraoperative mortality and may even reduce the risk of early postoperative mortality from coagulopathic bleeding. A hypotensive resuscitation strategy does not seem to adversely affect risk of ischemic, hematologic, respiratory, or infectious complications, nor does it seem to negatively affect secondary measures of morbidity including length of hospitalization or length of ICU stay. Although there are several limitations of this study, which must be taken into consideration, we think that our preliminary data support continued investigation of hypotensive resuscitation for the management of trauma patients in hemorrhagic shock.

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