Adjunctive treatment of abdominal catastrophes and sepsis with direct peritoneal resuscitation: Indications for use in acute care surgery

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BACKGROUND: The success of damage-control surgery (DCS) for the treatment of trauma has led to its use in other surgical problems such as abdominal sepsis. Previous studies using direct peritoneal resuscitation (DPR) for the treatment of trauma have yielded promising results. We present the results of the application of this technique to patients experiencing abdominal sepsis.

METHODS: We enrolled 88 DCS patients during a 5 year-period (January 2008 to December 2012) into a propensity-matched study to evaluate the utility of using DPR in addition to standard resuscitation. DPR consisted of peritoneal lavage with 2.5% DELFLEX, and abdominal closure was standardized across both groups. Patients were matched using Acute Physiology and Chronic Health Evaluation II (APACHE II) variables. Univariate and multivariate analyses were performed.

RESULTS: There were no differences between the control and experimental groups with regard to age, sex, ethnicity, or APACHE II at 24 hours. Indications for damage control included pancreatitis, perforated hollow viscous, bowel obstruction, and ischemic enterocolitis. Patients undergoing DPR had both a higher rate of (68% vs. 43%, $p < 0.03$) and a shorter time to definitive fascial closure (5.9 [3.2] days vs. 7.7 [4.1] days, $p < 0.02$). DPR patients had a decreased APACHE II and Sequential Organ Failure Assessment (SOFA) score compared with the controls at 48 hours. In addition, DPR patients had fewer abdominal complications compared with the controls (RR, 0.57; 95% confidence interval, 0.32–1.01; $p = 0.038$). Ventilator days and intensive care unit length of stay were both significantly reduced in the DPR group. The DPR group showed a lower overall mortality at 30 days (16% vs. 27%, $p = 0.15$).

CONCLUSION: DPR reduces time to definitive abdominal closure, increases primary fascial closure, and reduces intra-abdominal complications following DCS. DPR may also attenuate progressive physiologic injury as demonstrated by a reduction in 48-hour intensive care unit severity scores. As a result, DPR following DCS may afford better outcomes to patients experiencing shock. (*J Trauma Acute Care Surg*. 2014;77: 393–399. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level III.

KEY WORDS: Damage-control surgery; abdominal emergency; DPR; peritoneal resuscitation.

Since the seminal paper by Rotondo et al.[1] in 1993, damage-control surgery (DCS) has become increasingly common in the management of traumatic abdominal injuries. When faced with coagulopathy, acidosis, and hypothermia, regardless of the initiating event, controlling hemorrhage and gastrointestinal contamination, correcting coagulopathy, and delayed definitive surgery leads to better patient outcome.[2–4] The resuscitation after DCS is clinically assessed by the normalization of central hemodynamic parameters such as mean arterial pressure (MAP), heart rate (HR), and central venous pressure. However, clinical and laboratory evidence demonstrates that improvement in the standard end points of resuscitation may not restore blood flow to the visceral organs and suggests that a progressive vasoconstriction following shock or ischemia caused by endothelial cell dysfunction can occur.[5–7] This persistent hypoperfusion can lead to derangements in fluid exchange and electrolyte handling, tissue ischemia, and worsening inflammation.[8] These abnormalities in microcirculatory perfusion and cellular function are hypothesized to contribute to prolonged tissue hypoxia, irreversible cellular injury, multiorgan failure, and death.

We have previously demonstrated that the application of a hypertonic glucose-based peritoneal dialysis fluid to the peritoneal cavity (direct peritoneal resuscitation [DPR]) can improve microvascular perfusion and reduce tissue injury following hemorrhagic shock in a rodent laboratory model.[9–11] We have also demonstrated in preliminary clinical studies that the use of DPR as an adjunct to hemorrhagic shock resuscitation was associated with less tissue edema, decreased abdominal complications, as well as decreased time to definitive abdominal closure.[12] We hypothesized that the beneficial effects of DPR would exist in patients undergoing DCS for nontraumatic, emergency general surgery indications and therefore have undertaken this sequential cohort study to determine the effects of DPR on general surgery patients undergoing DCS for an abdominal emergency.

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PATIENTS AND METHODS

From January 2008 to December 2012, an institutional review board–approved sequential prospective study was conducted at the University of Louisville Hospital, enrolling all patients age 18 years to 80 years who underwent damage-control abdominal surgery to treat their acute surgical emergency. From January 2008 to September 2010, patients underwent DCS using a standardized closure and resuscitation protocol as outlined later. In the second arm of the study, from October 2010 until December 2012, all patients undergoing DCS were given DPR in addition to the standardized resuscitation and closure technique.

The temporary abdominal closure technique was standardized in the all patients. A 19 Fr silicone elastomer round Blake drain (Ethicon) was placed in the left upper lateral quadrant and directed around the root of the mesentery along the left pericolic gutter and down into the pelvis. A sterile x-ray cassette cover was fenestrated and placed over the abdominal contents but under the fascia. A sterile operating room towel was placed over the plastic cover, and another drain was placed within the towel. The abdomen was covered with an occlusive dressing, and the towel drain was placed to low-pressure suction. In the patients receiving DPR, dialysate was instilled using the left upper quadrant drain, allowing a continuous lavage within the abdomen until suctioned out the top of the wound through the towel drain. DPR was initiated using commercially available 2.5% glucose-based peritoneal dialysis solution (Delflex, Fresenius) within 1 hour of completion of damage-control operation. A bolus of 800-mL Delflex fluid was instilled during the first hour and followed at a rate of 400 mL/h until a repeat laparotomy was performed. Intravenous blood and crystalloid resuscitation were administered at the discretion of the treating physicians, with an aim toward rapid restoration of hemodynamics and resuscitative parameters (goal-directed therapy). However, total intravenous resuscitation volumes and primarily timing of repeat staged laparotomy were determined by the treating physician as dictated by clinical needs and were not protocolized.

Two propensity-matched groups were then created for comparison in this study. Group 1 represents patients who did not receive DPR (controls), while Group 2 represents patients who did receive DPR (DPR group). The propensity score was estimated with a logistic regression model with DPR use as the dependent variable and a group of patient characteristics identified at admission as the predictor variables. Age, sex, temperature (°F), systolic blood pressure (SBP), MAP, pH, HR, respiratory rate, sodium (Na), potassium (K), creatinine (Cr), blood urea nitrogen (BUN), hematocrit, hemoglobin concentrations, white blood cell (WBC) count, Glasgow Coma Scale (GCS) score, Pa_{O_2}, P_{CO_2}, and fraction inspired oxygen (FIO_2) were included in the propensity score to create groups matched for the severity of their initial illness. Additional clinical parameters were evaluated including the presence of peritoneal soiling, whether a malignancy was identified, and total blood loss at the initial operation. Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score (SAPS II) were also calculated for comparison.[13–18] The scores when applied within 24 hours of admission of a patient to an intensive care unit (ICU) allow "grading" of physiologic illness, with higher scores corresponding to more severe disease and a higher risk of death. Outcome variables included length of stay (LOS); ICU LOS, mortality, time to and type of definitive abdominal closure, volume of blood transfused in the first 24 hours and 48 hours, and volume of crystalloid transfused in the first 24 hours and 48 hours. Abdominal complications were evaluated and included organ space infection (abscess), bleeding, enteric fistula formation, evisceration or dehiscence after primary closure, and need for repeat unplanned laparotomy. Matching between the DPR and control patients was then based on the logit of the propensity score (p), which is defined as $\log(p / (1 - p))$.[19,20] The matching itself was performed using the GMATCH algorithm developed by the Mayo Clinic.[21,22] All statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC), with p values less than 0.05 considered significant. Matching proceeds by randomly sorting the patients in the DPR and control sets. For each patient in the DPR cohort, the patient with the closest logit of the propensity score from the controls was assigned as a match. Matching was without replacement and "greedy" in nature, in that once a match is made, it is not broken. To prevent poor matches from being made, a caliper width equal to 0.2 times the SD of the logit propensity score for the entire cohort was imposed. Matched pairs with a difference in logit propensity scores outside the caliper were discarded.

Analysis of differences in the patient who underwent DPR versus controls in the overall cohort were initially performed using unpaired Student's t test for continuous variables and the χ^2 test for categorical variables.[23] After propensity matching, residual differences in the covariates included in the model to estimate propensity scores were evaluated using the formulas for standardized differences proposed by Austin.[19] Standardized differences less than 0.1 in absolute value are generally considered to be insignificant in terms of introducing residual confounding.[24] Continuous covariates were summarized as mean (SD) and categorical covariates as count (percentage). Data were tested for normality using kurtosis and skewness z scores as well as Q-Q plot evaluation and Shapiro-Wilk p value analysis. Power analysis was performed to ensure greater than 80% confidence in $p < 0.05$ for clinically significant variables shown in Table 5. An n = 44 in each group allowed the study to achieve adequate power by a small margin; however, there still exists a 20% chance of a Type II error within these correlations.

RESULTS

One hundred eighteen patients were enrolled in the study between 2008 and 2012. Table 1 shows the values for the variables used in the propensity scoring for the two study groups. In the nonmatched controls, patients who underwent DPR were younger, less tachycardic, and more tachypneic and had a higher platelet count compared with the control patients. Differences in electrolytes were statistically significant but not clinically significant (Table 1). Indications for operation included necrotizing pancreatitis, perforated viscous, small bowel obstruction, anastomotic leak, and bowel ischemia and were not significantly different between the two groups. After propensity scoring, 44 patients were matched in each of the groups. There were no missing data within these propensity-matched groups. Table 2

TABLE 1. Study Population and Variables Collected During the 24-Hour Period of Initial Operation (Mean [SD])

	Open Abdomen Control (n = 67)	Open Abdomen DPR (n = 51)	*p*
Age	61 (21)	54 (16)	0.01*
Sex, male, n	41	29	—
HR	125 (29)	112 (40)	0.04*
SBP, mm Hg	98 (22)	89 (33)	0.07
MAP	57 (18)	63 (23)	0.11
Respiratory rate	16 (6)	22 (9)	0.001*
Temperature (°F)	101 (4)	100 (3)	0.14
GCS score	10 (5)	12 (6)	0.07
pH	7.19 (0.34)	7.11 (0.40)	0.24
P_{CO_2}, mm Hg	59 (15)	53 (12)	0.02*
Pa_{O_2}, mm Hg	64 (19	59 (17)	0.14
Base deficit	7 (4)	8 (4)	0.18
FIO_2 (fractional %)	100	100	—
Na^+, mEg/L	133 (15)	141 (20)	0.01*
K^+, mEg/L	3.4 (1.1)	4.1 (1.5)	0.04*
CO_2, mEg/L	14 (8)	16 (9)	0.20
BUN, mg/dL	30 (14)	33 (22)	0.36
Serum Cr, mg/dL	1.6 (1.1)	1.8 (0.9)	0.29
WBC, $\times 10^9$/L	12 (11)	15 (9)	0.11
Hct, %	37 (24)	33 (21)	0.34
Platelet, $\times 10^3/\mu L$	109 (55)	143 (89)	0.01*
Urine output, mL/h	38 (22)	29 (35)	0.09
Total bilirubin, mg/dL	1.3 (1.1)	1.1 (0.8)	0.28
Vasopressor use, n	41	40	—
Severe organ dysfunction prior to operation, n	5	2	—
Mechanical ventilation, n	67	51	—

depicts the baseline characteristics between the propensity-matched cohorts for general surgery controls and DPR patients, demonstrating that the groups were well matched by clinical variables at admission. Again, after matching, indication for operative intervention was not significantly different between the control and DPR groups. Perforated viscous (n = 17 and 18, respectively); small bowel obstruction (n = 8 and 8, respectively), intestinal ischemia (n = 11 and 10, respectively) represented the majority of cases. Necrotizing pancreatitis, anastomotic leak, dehiscence/evisceration, and abdominal compartment syndrome were also represented within the study population. Surgeon indications for performing DCS with an open abdomen at the initial operation were also not significantly different between the groups, with the majority of surgeons citing a planned second look because of bowel viability or contamination (58% overall) being the most common reason. Hemodynamic instability in the patient (21%) was also a prevalent indication for open abdominal management, as was abdominal hypertension at closing (8%) and significant bowel edema/distension at closure (4%) (Table 3).

Blood product administration within the first 24 hours and 48 hours was not different between the groups, with no patient requiring greater than 10 U of blood products with in the first 24 hours. Total intravenous crystalloid infusion (resuscitation and medication administration) during the first 24 hours and 48 hours demonstrated a higher rate of crystalloid infusion in the control patients (IVF at 24 hours: controls, 10,840 [1,740] vs. DPR 9,870 [1,600], $p = 0.01$; IVF at 48 hours: controls, 18,300 [2,650] vs. DPR, 15,900 [3,100], $p < 0.001$).

APACHE II, SOFA score, and SAPS II were calculated at time of surgery and 48 hours after surgery (Table 4). As would be expected, neither initial score was significantly different because of the standardization across the propensity-matched groups; however, at 48 hours the general surgery DPR group had significantly lower scores compared with the control patients who did not receive DPR. Moreover, several individual components of the SOFA, APACHE II and SAPS II were lower in the DPR group at 48 hours, with significant improvements in DPR patients seen in pH, P_{CO_2}, Pa_{O_2}, serum Cr, urine output, and total bilirubin. Table 5 compares selected physiologic parameters divided by organ systems between the DPR and control patients at 48 hours.

Outcome variables for general surgery groups are shown in Table 6. While not shown within the table, time to initial take back was similar between the control and DPR groups (26 [11] hours vs. 30 [13] hours, $p = 0.123$). DPR patients were closed earlier than their respective controls, required fewer trips to the operating room, and had a higher incidence of primary fascial closure when compared with the control patients. Overall, the total number of abdominal complications was lower in the DPR group. Complication types were not significantly different between the control and DPR groups, with intra-abdominal abscess (38% and 33%, respectively), enterocutaneous fistula

TABLE 2. Propensity-Matched Case Cohorts With Mean (SD) and *p* Value During the 24 Hours After DCS

	Open Abdomen Control (n = 44)	Open Abdomen DPR (n = 44)	*p*
Age	52 (12)	50 (8)	0.36
Sex (n male)	27	25	—
HR	121 (40)	111 (40)	0.20
SBP, mm Hg	91 (40)	87 (32)	0.60
MAP	55 (33)	59 (25)	0.50
Respiratory rate	22 (6)	20 (11)	0.29
Temperature (°F)	100.2 (3.3)	101 (3.1)	0.21
GCS score	11 (5)	10 (5)	0.35
pH	7.15 (0.39)	7.12 (0.44)	0.7
P_{CO_2}, mm Hg	57 (14)	55 (13)	0.49
Pa_{O_2}, mm Hg	60 (16)	57 (13)	0.33
Base deficit	7 (5)	7 (4)	—
FIO_2 (fractional %)	100	100	—
Na^+, mEg/L	138 (22)	141 (19)	0.49
K^+, mEg/L	4.0 (1.4)	4.1 (1.5)	0.73
CO_2, mEg/L	16 (8)	17 (10)	0.61
BUN, mg/dL	29 (11)	35 (22)	0.11
Serum Cr, mg/dL	1.6 (0.6)	1.8 (0.9)	0.22
WBC, $\times 10^9$/L	14 (12)	15 (9)	0.65
Hct, %	40 (19)	33 (22)	0.11
Platelet, $\times 10^3/\mu L$	140 (68)	123 (77)	0.27
Urine output, mL/h	30 (22)	23 (30)	0.21
Total bilirubin, mg/dL	1.3 (1)	1.2 (0.7)	0.59
Vasopressor use, n	27	26	—
Severe organ dysfunction prior to operation, n	0	0	—
Mechanical ventilation, n	44	44	—

TABLE 3. Propensity-Matched Cohorts With *p* Value 48 Hours After Initial Operation

	Open Abdomen Control (n = 44)	Open Abdomen DPR (n = 44)	*p*
Age	52 (12)	50 (8)	0.36
HR	127 (21)	111 (32)	0.09
SBP, mm Hg	91 (17)	94 (19)	0.43
MAP	68 (22)	73 (27)	0.34
Respiratory rate	16 (5)	15 (5)	0.35
Temperature (°F)	100.2 (2.3)	99.2 (3.1)	0.08
GCS score	11 (5)	10 (5)	0.35
pH	7.22 (0.23)	7.33 (0.18)	0.01*
P_{CO_2}, mm Hg	51 (16)	44 (14)	0.03*
Pa_{O_2}, mm Hg	79 (21)	92 (16)	0.002*
Base deficit	5 (5)	3 (4)	0.04*
Na^+, mEg/L	144 (12)	145 (16)	0.74
K^+, mEg/L	3.0 (1.9)	3.4 (2.2)	0.36
CO_2, mEg/L	19 (9)	21 (10)	0.32
BUN, mg/dL	22 (18)	27 (14)	0.15
Serum Cr, mg/dL	1.8 (0.9)	1.5 (0.5)	0.05*
WBC, $\times 10^9$/L	16 (6)	14 (6)	0.12
Hct, %	33 (9)	30 (16)	0.28
Platelet, $\times 10^3/\mu L$	100 (46)	123 (66)	0.06
Urine output, mL/h	57 (21)	69 (33)	0.04*
Total bilirubin, mg/dL	1.7 (1.2)	1.2 (0.8)	0.02*
Vasopressor use, n	19	12	0.09

(10% and 8%, respectively) and the need for abdominal reoperation after closure (5% and 8%, respectively) being the most common. ICU LOS and ventilator days were lower, and the number of ICU-free days was higher in patients receiving DPR; however, overall LOS was not different between matched cohorts within this study. Overall mortality was lower in the DPR patients compared with non-DPR patients in both groups but did not reach statistical significance. Moreover, power analysis demonstrated that a greater than 50% chance of Type II error exists for these mortality findings, and further analysis demonstrates that we would need twice the number of patients enrolled in this study to make that determination.

DISCUSSION

A number of resuscitation strategies have been studied during the past five decades that have focused on reversing or halting the pathophysiologic processes, which lead to late death in trauma patients. Changes in the type of resuscitation fluid provided, maintenance of normothermia, direct ATP delivery to organs, and supranormal oxygen delivery have all been tried with varying degrees of success.[25–28] The current resuscitative standard of care attempts to restore central hemodynamic parameters (HR, blood pressure, and cardiac output) by both blood transfusion and intravenous crystalloid solution infusion. Early goal-directed resuscitation has shown increased survival in septic shock.[27] However, increasing evidence suggests that despite restoration of adequate central hemodynamic parameters, cellular hypoxia, microcirculatory hypoperfusion, and inflammation occur. Continued cellular ischemia and dysfunction are thought to contribute significantly to multiple-organ failure. This study represents our initial efforts in applying a novel resuscitative strategy involving DPR to patients requiring DCS for general surgery conditions.

DPR patients demonstrated a significant reduction in ICU scores at 48 hours compared with the open abdomen controls patients. Multiple previous articles have discussed the utility of 24-hour and 48-hour ICU scores as well as the prognostic impact on mortality and outcome. Within our study, these scores generally demonstrated a positive reduction in physiologic derangement within the DPR group despite having

TABLE 4. Changes in Physiologic Scoring at 24 Hours and 48 Hours After Surgery

	Controls (n = 44)	DPR (n = 44)	*p*
APACHE II at 24 h	26 (12)	27 (13)	0.71
SOFA score at 24 h	13 (5)	13 (8)	1
SAPS II at 24 h	53 (21)	51 (22)	0.66
APACHE II at 48 h	23 (12)	16 (14)	0.01*
SOFA score at 48 h	11 (4)	9 (5)	0.04*
SAPS II at 48 h	45 (15)	39 (12)	0.04*

*Significance at $p < 0.05$.

TABLE 5. Physiologic Variables by Body Systems in Propensity-Matched Groups

	Controls (n = 44)	DPR (n = 44)	*p*
Pulmonary			
pH	7.22 (0.23)	7.33 (0.18)	0.01*
P_{CO_2}, mm Hg	51 (16)	44 (14)	0.03*
Pa_{O_2}, mm Hg	79 (21)	92 (16)	0.002*
Hepatic			
Total bilirubin, mg/dL	1.7	1.2 (0.8)	0.02*
ALT (U/L)	109 (60)	86 (47)	0.05*
Renal			
BUN, mg/dL	22 (18)	27 (14)	0.15
Serum Cr, mg/dL	1.8 (0.9)	1.5 (0.5)	0.05*
Urine output, mL/h	57 (21)	69 (33)	0.04*
Coagulation			
Platelet, $\times 10^3/\mu L$	100 (46)	123 (66)	0.06
International normalized ratio	1.8 (0.7)	1.4 (1.0)	0.04*

TABLE 6. Propensity-Matched Cohort Outcome Variables

	Controls (n = 44)	DPR (n = 44)	*p*
No. trips to the operating room	4 (2)	3 (2)	0.02
Time to definitive abdominal closure, d	7.7 (4.1)	5.9 (3.2)	0.02
Primary fascial closure, n (%)	19 (43)	29 (68)	0.03
No. abdominal complications	21 (47%)	12 (27%)	0.04
Ventilator days	14 (6)	10 (5)	0.01
ICU LOS, d	24 (11)	17 (9)	0.002
Total LOS, d	41 (13)	35 (16)	0.06
ICU-free days	26 (11)	31 (13)	0.05
Mortality, n (%)	12 (27)	7 (16)	0.15

similar central hemodynamic parameters. In addition, multiple visceral organ systems demonstrated a reduction in parameters traditionally associated with cellular injury caused by hypoperfusion. This supports our supposition that increased visceral blood flow as a result of the topical exposure to the hypertonic dialysate fluid leads to a reduction in end-organ injury and inflammation. The postulated reasons for this are myriad, and within this highly variable population, causative factors are difficult to ascertain; however, these findings suggest further that research into the mechanism for this clinical finding are warranted.

The changes in ICU scoring at 48 hours seemed to correlate with significant improvements in the pulmonary system including P_{O_2} and P_{CO_2} and with a reduction in ICU and ventilator days (which are often correlative). However, based on the physiologic principles and mechanism of action of DPR identified within the laboratory, it does not seem that the hypertonic fluid directly influences the pulmonary vasculature in the way that it affects the visceral microcirculation. Our studies indicate that the topically applied hypertonic solution inhibits obligate water transport into endothelial cells within the viscera, buffers cellular acidosis, and acts as vasodilator because of the glucose composition and acidic nature of the solution. This action leads to better blood flow both during and after initial physiologic insult but requires significant direct contact with the visceral tissue (i.e., continuous lavage) to assert this effect. We have postulated but not yet proven that this increase in visceral blood flow reduces damage associated with molecular profiles produced within the splanchnic organs leading to reduced systemic inflammatory activation. This effect could then lead to reduced cellular injury and improved organ function in distant organs. Further definition of this possible protective mechanism for DPR needs to be done. Regardless, the findings of remote organ effects of DPR are novel and unexpected.

Patients treated with DPR demonstrated a significant reduction in time to abdominal closure and number of operations as well as higher rate of primary fascial closure when compared with the controls. Bradley et al.[29] recently identified number of abdominal operations as a significant predictor of morbidity following DCS. This echoes previous literature, which also showed that time to abdominal closure beyond 7 days leads to significant increase in morbidity and mortality.[30] Hatch et al.[31] also noted that early fascial closure was an independent predictor of complication in DCS patients. We have previously shown a reduction in time to closure and increased primary fascial closure rates in a pilot group of trauma patients treated with our DPR protocol. While a causal relationship cannot be ascertained by this study, the finding of a decrease in ICU days and days on a ventilator as well as a lower overall rate of complications in the DPR group support the idea that early abdominal closure has significant benefits for patient managed with an open abdomen technique.

In addition, our rate of closure within this patient population is significantly lower than other published damage-control closure rates. The reason for this is unclear. Within our previous study of the use of DPR in trauma patient DCS, we showed a rate of abdominal closure of greater than 90% compared with 70% in this study. These data likely represent a difference in patient population and primary etiology of illness. In addition, difference in resuscitation practices between trauma patients and acute care surgery patients could be responsible. Regardless, further research into the differences between trauma patients and acute care surgery patients undergoing damage-control procedure is warranted.

There are several limitations to this study. First, the significant number of variables involved and the variance associated with these data make causal relationships difficult to ascertain. Study patients varied anywhere from stable urgent small bowel obstructions with too much edema to afford effective and safe closure at the first operation to patients who had frank peritonitis caused by hollow viscous perforation with a significant septic and inflammatory response. This variance makes individual comparisons and reliable multivariate regressions difficult. A propensity analysis was performed in our study since the number of evaluated covariates would not allow for meaningful multivariate regression to be accomplished. This statistical technique mitigated much of the variability and discrepancy in the original data at the cost of patient inclusion. Second, there exists the problem of surgeon and investigator bias. We attempted to control for this by separating the population temporally; however, since the practitioners were not blinded to the study, the question of investigator bias exists. Moreover, advances in resuscitation may have affected the outcomes identified. While there did not seem to be any significant difference in either the resuscitation volumes at 24 hours or the use of blood product during the first 48 hours, these variables were not controlled for in the study. Finally, the propensity score matching did not account for advances in the treatment of these patients and other temporal changes that may have occurred because of the nature of the prolonged and complicated clinical care delivered to these patients; there exists the possibility that variables not evaluated or considered may have some impact on the results shown and our analysis.

CONCLUSION

This study demonstrated compelling data to support the continued evaluation of peritoneal resuscitation as an adjunct for the management of open abdomens following emergency abdominal surgery. Patients receiving DPR demonstrated better physiologic parameters at 48 hours, had a decreased time to definitive abdominal closure, and spent less days on the ventilator and fewer days in the ICU overall. Our unique observations of restored central hemodynamics and reduction in end-organ injury that occurred with DPR seem to account for these improved clinical outcomes. Additional studies into the reasons for the differences in outcomes and the mechanisms involved for the beneficial effect to nonvisceral organs are warranted.

DISCLOSURE

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REFERENCES

1. Rotondo MF, Schwab CW, McGonigal MD, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*. 1993;35(3):375–382; discussion 382–383.
2. Shapiro MB, Jenkins DH, Schwab CW, Rotondo MF. Damage control: collective review. *J Trauma*. 2000;49(5):969–978.

3. Cirocchi R, Montedori A, Farinella E, Bonacini I, Tagliabue L, Abraha I. Damage control surgery for abdominal trauma. *Cochrane Database Syst Rev.* 2013;3.
4. Khan A, Hsee L, Mathur S, Civil I. Damage-control laparotomy in nontrauma patients: Review of indications and outcomes. *J Trauma Acute Care Surg*. 2013.
5. Boerma EC, Koopmans M, Konijn A, et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial. *Crit Care Med*. 2010;38(1):93–100.
6. A1buszies G, Radermacher P, Vogt J, et al. Effect of increased cardiac output on hepatic and intestinal microcirculatory blood flow, oxygenation, and metabolism in hyperdynamic murine septic shock. *Crit Care Med*. 2005;33(10):2332–2338.
7. Harrois A, Dupic L, Duranteau J. Targeting the microcirculation in resuscitation of acutely unwell patients. *Curr Opin Crit Care*. 2011;17(3): 303–307.
8. Fruchterman TM, et al. Selective microvascular endothelial cell dysfunction in the small intestine following resuscitated hemorrhagic shock. *Shock*. 1998;10(6):417–422.
9. Zakaria el R, et al. Generalized dilation of the visceral microvasculature by peritoneal dialysis solutions. *Perit Dial Int*. 2002;22(5):593–601.
10. Zakaria el R, et al. Intraperitoneal resuscitation improves intestinal blood flow following hemorrhagic shock. *Ann Surg*. 2003;237(5):704–711; discussion 711–713.
11. Hurt RT, Matheson PJ, Smith JW, et al. Preservation of hepatic blood flow by direct peritoneal resuscitation improves survival and prevents hepatic inflammation following hemorrhagic shock. *Am J Physiol Gastrointest Liver Physiol*. 2012;303(10):G1144–G1152.
12. Smith JW, Garrison RN, Matheson PJ, Franklin GA, Harbrecht BG, Richardson JD. Direct peritoneal resuscitation accelerates primary abdominal wall closure after damage control surgery. *J Am Coll Surg*. 2010;210(5):658–664, 664–667.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10): 818–829.
14. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100(6):1619–1636.
15. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med*. 1998;26(11): 1793–1800.
16. Moreno R, Morais P. Outcome prediction in intensive care: results of a prospective, multicentre, Portuguese study. *Intensive Care Med*. 1997;23(2): 177–186.
17. Livingston BM, MacKirdy FN, Howie JC, et al. Assessment of the performance of five intensive care scoring models within a large Scottish database. *Crit Care Med*. 2000;28(6):1820–1827.
18. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957–2963.
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424.
20. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265–2281.
21. Bergstralh E, Kosanke J. *GMATCH Mayo Clinic Division of Biomedical Statistics and Informatics*. 2003.
22. Austin P. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med*. 2008;27: 2037–2049.
23. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol*. 2001;54(4):387–398.
24. Schafer JL, Kang J. Average causal effects from nonrandomized studies: a practical guide and simulated example. *Psychol Methods*. 2008;13: 279–313.
25. Chang TM. From artificial red blood cells, oxygen carriers, and oxygen therapeutics to artificial cells, nanomedicine, and beyond. *Artif Cells Blood Substit Immobil Biotechnol*. 2012;40(3):197–199.
26. Mapstone J, Roberts I, Evans P. Fluid resuscitation strategies: a systematic review of animal trials. *J Trauma*. 2003;55(3):571–589.
27. Roberts I, et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2004;(4):CD000567. Update in Cochrane Database Syst Rev. 2007;(4):CD000567.
28. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858–873.
29. Bradley MJ, Dubose JJ, Scalea TM, et al. Independent Predictors of enteric fistula and abdominal sepsis after damage control laparotomy: results from the prospective AAST open abdomen registry. *JAMA Surg*. 2013.
30. Miller RS, Morris JA Jr, Diaz JJ Jr, Herring MB, May AK. Complications after 344 damage-control open celiotomies. *J Trauma*. 2005;59(6):1365–1371; discussion 1371–1374.
31. Hatch QM, Osterhout LM, Podbielski J, et al. Impact of closure at the first take back: complication burden and potential overutilization of damage control laparotomy. *J Trauma*. 2011;71(6):1503–1511.
32. Holcomb JB, Spinella PC. Optimal use of blood in trauma patients. *Biologicals*. 2010;38(1):72–77.

DISCUSSION

Dr. John B. Holcomb (Houston, Texas): Mr. Chairman, thank you for the opportunity to discuss this observational trial of over six years from Dr. Smith and the Louisville group.

They have continued their excellent work, focusing on managing edema after shock and improving their success rate of closing abdomens after damage control surgery. They now extend their peritoneal dialysis approach from trauma to emergency general surgery patients.

They have a large crystalloid resuscitation of greater than 10 liters in these patients, resulting in significant edema and persistent open abdomens. Addressing both of these problems is an outstanding goal.

In the introduction, the authors described how endothelial dysfunction after shock can lead to prolonged organ failure, hypoxia, multi-organ failure and death.

They suggest that improved resuscitation could improve outcomes which, of course, I completely agree with. In the trauma patient we are beginning to understand how this endotheliopathy, or damaged endothelium, is likely a common pathway that can be repaired or worsened after injury, depending on what fluid you decide to hang, and the volume of that fluid resuscitation.

In Houston and many other places we think crystalloids are really bad for patients that are in shock. And we and others have seen low, single digit multi-organ failure rates by limiting 24-hour totals to the 3 to 4 liter range.

By limiting crystalloid infusion we avoid, rather than treat, the iatrogenic resuscitation injury that we've started calling crystalloid-related acute lung injury, (CRALI), manifested as hypoxia, ARDS and bowel wall edema.

However, the Louisville group has taken a different approach. They've used large volumes of crystalloid resuscitation and then successfully treated the resulting bowel wall and lung edema with hypertonic peritoneal dialysis. A somewhat rhetorical question, why not just avoid the crystalloid?

With that I have a few specific questions:

The authors clearly describe the microvascular hypoperfusion resulting in cellular hypoxia and restoration of large

vessel blood pressure but do not report base excess or lactate or any measure of oxygen delivery or consumption in their paper. I anticipate the authors have these data. Since they used the post hoc propensity analysis to group retrospectively the patients over a six-year study can they provide these metabolic data, helping to assure us the groups have suffered a similar metabolic injury?

In Tables 1 and 2 of the paper the authors provide the extreme laboratory values, highs and lows, which are interesting but, again, to make sure the groups are balanced it might be more appropriate to use median values.

They describe ICU and hospital length of stay as outcome variables. It would likely be more useful to use hospital and ICU-free days instead to minimize but, of course, not remove the confounding issue of early deaths in these critically ill patients.

The primary endpoint of the paper was defined as a change in APACHE II scores of 33 percent. I do not believe they met this endpoint.

How long was it before these patients went back to the OR after their first operation? In our work in this area the variable of how long before you go back to that second operation has been extremely important to their final fascia closure rate.

What were the ARDS and MOF rates in these patients? You report many different scores but not the rates we discuss every day on rounds.

Last year Dr. Bryan Cotton from our group presented a 96 percent closure rate, minimizing crystalloid during the initial resuscitation and then followed by 24 hours of only 3 percent hypertonic saline. The authors think that by avoid the crystalloid they can increase their closure rate above 70%.

Finally, the last specific point: this was a six-year study. Did anything change in your care of the patient at all over this six-year period besides just your peritoneal dialysis?

In conclusion, I applaud the authors for their investigation. It is absolutely extremely important. They have obviously developed a mature and a very novel method of partially reversing the effects of large crystalloid resuscitation. And I look forward to future data from the Louisville group.

Dr. Weiden Alan Guo (Buffalo, New York): First let me congratulate you on your excellent study. Previous studies have shown that there is a high concentration of cytokines in peritoneal fluids in patients with open abdomen. I'm wondering if your beneficial effect is due to the decrease in proinflammatory cytokine levels, and therefore decreased systemic or local inflammatory response.

I have two questions for you: First, did you insert the catheter in your control groups? Perhaps draining of peritoneal fluid also improves the outcome. Also, did you measure the cytokine levels in the peritoneal fluid?

Dr. Basil A. Pruitt, Jr. (San Antonio, Texas): Dr. Smith, help us understand some of the mechanics here. Do I understand that you have a continuous infusion of hypertonic glucose into the peritoneal cavity? If so, have you measured the effluent so that we can appreciate that the hypertonic solution drew fluid from the interstitial space to account for its effect?

Dr. Jason W. Smith (Louisville, Tennessee): So, I'll start with Dr. Pruitt. We have. What we find is you get about 150% return, depending on the amount of fluid that they're given in their intraabdominal space.

We also previously looked at blood glucose levels and the glucose is not absorbed. There was no difference in blood glucose levels between those treated with DPR, the hypertonic saline, or hypertonic glucose solution and those who were not.

Dr. Holcomb, thank you very much for your comments. And I completely agree with you. I think the question becomes, as you go about this, how are we going to resuscitate our acute care surgery patients?

You know, we followed Dr. Holcomb's lead and many others when we were talking about resuscitating trauma patients. We give them plasma. We give them blood. We minimize the crystalloid. But for our acute care surgery patients, if their INR is okay and their hemoglobin is okay, when do you stop giving them blood and when do you stop giving them plasma? I agree that maybe that would be a better way of resuscitating these patients. I just don't think right now that I have the data to justify that.

While we do try to minimalize crystalloid, the simple fact is if you look at the amount of fluid that they got—the 10 liters, for example, in each group—that's IV resuscitation fluids, that's medication administration fluids, that's the resuscitation in the operating room and the first 24 hours. You can only minimize so much because there are many things that are going to be a bit out of your control if you are giving them pressors or what-have-you.

I agree maybe we should look. We do have the lactate and base deficit data. I'll be happy to place that into the paper to give a better idea of the overall perfusion of these vascular beds.

We did not look at ARDS or multi-organ system failure rates because what we were looking at typically was a change in physiologic parameters. We can probably get that from the data. We did look at the patients who came to us with significant organ dysfunction before they showed up to the operating room, and there was no significant difference in either one of those groups.

As far as changing over years, when you look at our overall resuscitation parameters it did not appear, that between the control patients versus the DPR patients there was a difference in the way they were resuscitated, the medications that were used to resuscitate the patients. We did standardize their abdominal closures. It was the same group of four to six surgeons operating on these patients during that period of time. So, as best we can control, over the six years there was not a significant difference in the treatment of these patients.

Finally, Dr. Guo, you are completely correct and I would be happy to tell you about what we have looked at with cytokine on the effluence in our laboratory models, and measuring the cytokines and the fluid in the change.

We have not looked at that in either the trauma patients or the acute care surgery patients as of yet. That is something we may look at in the future in one of our randomized prospective trials we are working on in trauma. But it is not something we have looked at just yet.

So, again, I thank you very much for the podium and I appreciate the questions and comments.