Damage control laparotomy in trauma: a pilot randomized controlled trial. The DCL trial

John A Harvin,1,2,3 Sasha D Adams,1,3 Shah-Jahan M Dodwad,1,3 Kayla D Isbell,1,3 Claudia Pedroza,2 Charles Green,2 Jon E Tyson,2 Ethan A Taub,1,3 David E Meyer,1,3 Laura J Moore,1,3 Rondel Albarado,1,3 Michelle K McNutt,1,3 Lillian S Kao,1,2,3 Charles E Wade,1,3 John B Holcomb4

ABSTRACT
Background Although widely used in treating severe abdominal trauma, damage control laparotomy (DCL) has not been assessed in any randomized controlled trial. We conducted a pilot trial among patients for whom our surgeons had equipoise and hypothesized that definitive laparotomy (DEF) would reduce major abdominal complications (MAC) or death within 30 days compared with DCL.

Methods Eligible patients undergoing emergency laparotomy were randomized during surgery to DCL or DEF from July 2016 to May 2019. The primary outcome was MAC or death within 30 days. Prespecified frequentist and Bayesian analyses were performed.

Results Of 489 eligible patients, 39 patients were randomized (DCL 18, DEF 21) and included. Groups were similar in demographics and mechanism of injury. The DEF group had a higher Injury Severity Score (DEF median 34 (IQR 20, 43) vs DCL 29 (IQR 22, 41)) and received more prerandomization blood products (DEF median 34 blood cells 8 units (IQR 6, 11) vs DCL 6 units (IQR 2, 11)). In unadjusted analyses, the DEF group had more MAC or death within 30 days (1.71, 95% CI 1.07 to 2.68, p=0.020) due to more deaths within 30 days (DEF 33% vs DCL 0%, p=0.010). Adjustment for Injury Severity Score and prerandomization blood products reduced the risk ratio for MAC or death within 30 days to 1.54 (95% CI 0.71 to 3.32, p=0.274). The Bayesian probability that DEF increased MAC or death within 30 days was 85% in unadjusted analyses and 66% in adjusted analyses.

Conclusion The findings of our single-center pilot trial were inconclusive. Outcomes were not worse with DCL and, in fact, may have been better. A randomized clinical trial of DCL is feasible and a larger multicenter trial is needed to compare DCL and DEF for patients with severe abdominal trauma.

Level of evidence Level II.

INTRODUCTION
Damage control laparotomy (DCL) is commonly performed and may be life-saving for patients with severe abdominal trauma. DCL was originally described for very narrow and limited indications.1,2 As comfort with the open abdomen has increased, indications for DCL have gradually broadened and its use has reached upward of 40% of all trauma laparotomies at some centers.3,4 However, when used liberally, DCL may result in more risks than benefits, as several studies from trauma centers across the country have reported increased complications associated with the open abdomen resulting from DCL.5–7

However, both the initial studies supporting the benefits of DCL and the subsequent studies suggesting harm have been limited by different inclusion and exclusion criteria and selection bias inherent to observational studies. Current indications for DCL are driven by expert opinion as opposed to high-quality evidence.8–10 Barriers to performing a randomized controlled trial (RCT) of DCL include a lack of equipoise about the indications and effectiveness of DCL, and the need for exception from informed consent (EFIC) to randomize patients during emergency surgery.4,11

The current pilot RCT had two aims: (1) to determine the feasibility of randomizing patients with severe abdominal trauma for whom surgeons had equipoise for DCL or definitive laparotomy (DEF) during emergency laparotomy and (2) to estimate the effect of DEF relative to DCL on the composite outcome of major abdominal complications (MAC) or death that might inform a larger definitive multicenter trial. We hypothesized that randomization during an emergency trauma laparotomy would be feasible and that DEF in our center would be associated with fewer MAC or death within 30 days.

METHODS
An EFIC was obtained from the Institutional Review Board to randomize patients into the trial during emergency trauma laparotomy.12 Patients were only included if they or their legally authorized representative consented to further participation. Patients were enrolled at the Red Duke Trauma Institute at Memorial Hermann Hospital-Texas Medical Center, which admits >6000 adult trauma patients per year and is one of two American College of Surgeons verified level I trauma centers in Houston, Texas, USA.

The study began on June 7, 2016 and ended on May 31, 2019. The trial was paused from July 9, 2018 through December 9, 2018 for safety evaluation by the Data Safety and Monitoring Board and Institutional Review Board. All trauma patients ≥16 years of age who underwent emergency laparotomy were screened. Emergency laparotomy was defined as: (1) time in emergency department (ED) ≤90 min and (2) admission directly to the operating room
from the ED or interventional radiology. Patients were included if they had an indication for DCL for which there was surgeon equipoise, including: (1) planned second look laparotomy, (2) planned second reoperation for abdominal contamination, (3) expedient of time to postoperative CT, (4) expedient of time to postoperative intensive care or (5) of isolated metabolic acidosis in the absence of ongoing transfusions or hypotension. Patients were excluded if a DCL was performed for the following indications: (1) need for gauze packing of the liver or retroperitoneum for hemorrhage control, (2) need for interventional radiology for hemorrhage control, (3) abdominal compartment syndrome prophylaxis (defined as inability to approximate fascia or >10 mm Hg increase in peak airway pressure during fascial closure) or (4) hemodynamic instability, when defined as persistent hypotension, ongoing transfusion requirement or continuous vasopressor use at the end of laparotomy. These inclusion and exclusion criteria were developed by consensus; surgeons agreed on absolute indications for both DCL and DEF as well as indications for DCL in which clinical equipoise was present.4 Patients were also excluded if they were known prisoners, pregnant, burned >20% total body surface area or wearing an opt-out bracelet.

Study design and intervention
Details of the study protocol were previously published.13 Briefly, this was a single-center, randomized trial to compare the effect of DCL with DEF on MAC or death within 30 days. MAC, as a composite outcome, included: (1) deep or organ/space surgical site infection, (2) enteric suture line failure, (3) enterocutaneous/enteroatmospheric fistula, (4) fascial dehiscence or (5) unplanned return to the operating room after fascial closure for an intra-abdominal complication. Death was included as it was a competing outcome with MAC.

Outcomes and sample size
The primary outcome of this study was MAC or death within 30 days. MAC, as a composite outcome, included: (1) deep or organ/space surgical site infection, (2) enteric suture line failure, (3) enterocutaneous/enteroatmospheric fistula, (4) fascial dehiscence or (5) unplanned return to the operating room after fascial closure for an intra-abdominal complication. Death was included as it was a competing outcome with MAC.

Secondary outcomes included non-abdominal morbidity (acute kidney injury, adult respiratory distress syndrome, deep vein thrombosis, pulmonary embolism, pneumonia and urinary tract infection) and hospital-free/intensive care unit-free/ventilator-free days.

Preliminary data from a matched analysis showed a MAC or death rate of 55% in patients undergoing DCL and 18% in patients undergoing DEF.6 Given these baseline rates of the primary outcome, an alpha of 0.05, a power of 0.80 and a dropout rate of 10%, the total sample size needed was 56 patients (28 in each arm).

Statistical analysis
Differences in the primary and secondary outcomes were compared on an intent-to-treat basis using frequentist statistics including Wilcoxon rank-sum test, Pearson’s $\chi^2$ test and Fisher’s exact test, for continuous, binary and sparse binary outcomes, respectively. Treatment effect was estimated using generalized

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Figure 1  Consolidated Standards of Reporting Trials diagram.
linear models and any imbalances in prerandomization variables were adjusted for evaluating the primary outcome. Because any prerandomization differences between treatment groups were necessarily due to chance, p-values for differences in baseline variables were not provided.

Partly because of the limited sample size of the trial and limitations of frequentist analyses, the frequentist analysis was augmented with a Bayesian analysis. A neutral prior probability (a prior risk ratio (RR) of 1.0 indicating an equal probability of benefit or harm from DCL and DEF) was used to estimate the posterior probability of benefit or harm from the DCL and DEF based on trial results. To indicate the uncertainty about the prior RR of 1.0, we used a 95% credible interval (CrI) of 0.5 to 2.0, which encompasses the treatment effect for most therapies on major clinical outcomes. Use of a neutral prior with this CrI has the effect of regularizing or shrinking the relative risk estimates back toward 1.0 (the null). As such, these analyses provide a more conservative relative risk of the treatment hazards or benefits than the frequentist analyses.17

RESULTS

Over the study period, 4595 patients were screened of whom 489 underwent emergency laparotomy (figure 1). Forty patients met inclusion criteria and were enrolled—21 to DEF and 19 to DCL. Three patients randomized to DEF did not receive the intervention (two underwent DCL due to changes in the patient condition after randomization and one died in the operating room before the intervention could be performed). One patient randomized to DCL did not consent to further participation in the trial, including inclusion of outcome data in the analysis.

Prerandomization

There were no clinically significant differences in patient demographics or specific injuries between the two groups. While both groups suffered severe trauma (median Injury Severity Score for entire group 33 (IQR 20, 43)), the DEF group had a higher median Injury Severity Score (table 1).

In the prehospital setting, the DEF group was more hypotensive (DEF systolic blood pressure 100 mm Hg (IQR 81, 130) vs DCL 116 (IQR 100, 142)) and tachycardic (DEF pulse 120 beats per minute (IQR 78, 130) vs DCL 101 beats per minute (IQR 90, 124)). The DEF group also received more prehospital transfusions (DEF prehospital red blood cells 1 unit (IQR 0, 2) vs 0 (IQR 0, 1); DEF prehospital fresh frozen plasma 0 units (IQR 0, 2) vs DCL 0 (IQR 0, 1)).

On arrival to the ED, the DEF group continued to be more hypotensive than the DCL group (table 2). There were no clinically significant differences in laboratory values or time in the ED. The DEF group received more transfusions in the ED than the DCL group.

The DEF patients arrived to the operating room with a higher pulse, but no other clinically significant differences in first vital signs or first laboratory values (table 3). The DEF group received more intra-operative transfusions of red blood cells, fresh frozen plasma, and platelets.

Overall, the DEF group received more red blood cell (DEF median 8 units (IQR 6, 11) vs DCL 6 units (IQR 2, 11)) and fresh frozen plasma (DEF median 8 units (IQR 6, 11) vs DCL 6 units (IQR 1, 11)) transfusions from the time of injury to the end of the primary laparotomy.

Compared with the DCL group, the DEF group had a higher rate of colectomy (DEF 43% vs DCL 22%), reorrhaphy or nephrectomy (DEF 25% vs DCL 6%) and splenectomy (DEF 52% vs DCL 28%) (table 4). The DEF group had a lower rate of hepatorrhaphy (DEF 24% vs DCL 39%). The most common indication for inclusion in the trial was isolated metabolic acidosis in the absence of ongoing transfusions or hypotension followed by planned second look laparotomy.

Postrandomization

There were no differences in initial postoperative vital signs. The DEF group had a higher initial postoperative lactic acid (DEF 3.9 mmol/L (IQR 3.1, 4.8) vs DCL 2.6 mmol/L (IQR 1.6, 3.6), p=0.010), but no difference in base excess, hematocrit, platelet level or any thrombelastography value. In the first 24 hours after surgery, the DEF group received more transfusions of red blood cells (DEF 1 unit (IQR 0, 2) vs DCL 0 unit (IQR 0, 0), p=0.036) and fresh frozen plasma (DEF 2 units (IQR 1, 4) vs DCL 0 unit (IQR 0, 2), p=0.013).

Outcomes

The DEF group had a clinically but not statistically significant higher rate of the primary outcome MAC or death within 30 days (RR 1.71, 95% CI 0.81 to 3.63, p=0.159; Bayesian RR...
Severity Score and prerandomization blood products indicate a 66% probability that DCL increased MAC or death within 30 days. There were also significantly more deaths in the DEF group. These worrisome findings were counter to our hypothesis—worse outcomes were not found with DCL and it may, in fact, have been beneficial. A larger, definitive randomized trial to delineate these findings is needed. Importantly, this trial demonstrated that 24/7 randomization during an emergency trauma laparotomy was feasible.

While the deaths were individually reviewed by the Data Safety and Monitoring Board and thought to be not directly due to the intervention, the finding was nonetheless concerning. Five of the seven deaths were associated with a transition to comfort care in light of concomitant injuries or complications. With our small sample size, the significant increase in deaths may be due to the intervention, baseline differences and/or chance. There was considerable imprecision around the effect of DCL on death. While we observed no statistically significant differences in organ/space surgical site infection (DEF 38% vs DCL 28%, p=0.496), reopening after fascial closure (DEF 29% vs DCL 11%, p=0.0429) and fascial dehiscence (DEF 20% vs DCL 0%, p=0.110), each outcome was more common in the DEF group.

This imprecision and uncertainty about the effect of DEF and the fragility of the trial results were reflected in the Bayesian analyses and their 95% CrIs. The RR point estimates of the unadjusted and adjusted primary outcome were 1.22 and 1.06, respectively. The 95% CrI in the adjusted analyses ranged from a 20% reduction to a 40% increase in MAC or death within 30 days. Both the unadjusted and adjusted Bayesian results are more consistent with an experienced clinician interpreting a lower margin of harm.

The trial was stopped on May 31, 2019 for futility of accruing the preplanned sample size due to reduced numbers of eligible patients within the prior 12-month period.

**DISCUSSION**

This first, pilot RCT of patients undergoing emergency laparotomy for trauma was inconclusive. While there was no significant difference in MAC or death within 30 days, conservative Bayesian analyses adjusted for baseline differences in Injury Severity Score and prerandomization blood products indicate a 66% probability that DCL increased MAC or death within 30 days. There were also significantly more deaths in the DEF group. These worrisome findings were counter to our hypothesis—worse outcomes were not found with DCL and it may, in fact, have been beneficial. A larger, definitive randomized trial to delineate these findings is needed. Importantly, this trial demonstrated that 24/7 randomization during an emergency trauma laparotomy was feasible.

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This trial was limited by its narrow scope, small size and a failure to accrue the targeted sample size. This trial focused on a very specific group of patients—those for whom surgeons had equipoise for DEF and DCL. Before planning this trial, there was significant variation in the use of DCL at our institution. The 3 years of work leading up to this study led to the stakeholder-driven creation of acceptable inclusion criteria and sample size estimation. This work also changed the practice around DCL at our institution, namely use of consensus-based acceptable and relative indications for DCL, which led to the decreased utilization of DCL from 39% to 17%. In addition to these internal changes, external events negatively affected enrollment. For unknown reasons, there was a temporary decrease in emergency laparotomies being performed at the trauma center, an occurrence that has now reversed. The trial was also limited by an imbalance of baseline characteristics in randomized groups and a lack of blinding. Inability to blind was addressed by having objective blinded, inpatient evaluations performed at the trauma center, an occurrence that was established prior to this trial in a quality improvement initiative. The results of this pilot trial were counter to the hypothesis, it provided important information to plan a larger, definitive trial. First, clinical equipoise among a group of surgeons was able to be achieved; the use of standardized indications for DCL was established prior to this trial in a quality improvement initiative. Results from a multicenter, prospective, observational study suggests that clinical equipoise for the same indications was also present outside our institution. These same indications may also present outside our institution, namely use of consensus-based acceptable and relative indications for important clinical outcomes. While a frequentist would conclude that there was no statistically significant difference between DEF and DCL, there was an 85% probability that DEF increased MAC or death compared with DCL in the unadjusted Bayesian analysis assuming no important baseline differences.

**Table 4 Operating room procedures**

| Procedures                      | DCL (n=18) | DEF (n=21) |
|---------------------------------|------------|------------|
| Hepatorrhaphy                   | 7 (39%)    | 5 (24%)    |
| Gastrorrhaphy                   | 3 (17%)    | 5 (24%)    |
| Enterorrhaphy                   | 3 (17%)    | 6 (29%)    |
| Entrectomy                      | 5 (28%)    | 4 (19%)    |
| Colorrhaphy                     | 1 (6%)     | 0 (0%)     |
| Colectomy                       | 4 (22%)    | 9 (43%)    |
| Renorrhaphy                     | 0 (0%)     | 3 (14%)    |
| Nephrectomy                     | 1 (6%)     | 2 (10%)    |
| Splenorrhaphy                   | 2 (11%)    | 0 (0%)     |
| Splenectomy                     | 5 (28%)    | 11 (52%)   |
| Major venous repair             | 0 (0%)     | 1 (5%)     |
| Major arterial repair           | 0 (0%)     | 0 (0%)     |
| Thoracotomy/Sternotomy          | 1 (6%)     | 2 (10%)    |

**Table 5 Outcomes**

| Primary outcome and components (<30 days) | DCL (n=18) | DEF (n=21) | P value |
|-------------------------------------------|------------|------------|--------|
| MAC or death <30 days                     | 6 (33%)    | 12 (57%)   | 0.137  |
| Organ/Space surgical site infection       | 5 (28%)    | 8 (38%)    | 0.496  |
| Enteric suture line failure               | 0 (0%)     | 0 (0%)     | –      |
| Enterocutaneous fistula                   | 0 (0%)     | 0 (0%)     | –      |
| Reopened                                   | 2 (11%)    | 6 (29%)    | 0.429  |
| Bleeding                                   | 0          | 2          | –      |
| Dehiscence                                 | 0          | 2          | –      |
| Sepsis                                     | 1          | 2          | –      |
| Ischemic bowel                             | 1          | 0          | –      |
| Fascial dehiscence                         | 0 (0%)     | 4 (20%)    | 0.110  |
| MAC                                         | 6 (33%)    | 8 (38%)    | 0.757  |
| Deaths                                     | 0 (0%)     | 7 (33%)    | 0.010  |
| Secondary outcomes (<30 days)              |            |            |        |
| Superficial surgical site infection        | 1 (6%)     | 4 (19%)    | 0.349  |
| Ileus                                       | 6 (33%)    | 7 (33%)    | 1.000  |
| Pulmonary embolus                          | 1 (6%)     | 1 (5%)     | 1.000  |
| Deep vein thrombosis                       | 0 (0%)     | 2 (10%)    | 0.490  |
| Sepsis                                     | 9 (50%)    | 11 (52%)   | 0.882  |
| Acute renal failure                        | 3 (17%)    | 7 (33%)    | 0.290  |
| Multiorgan failure                         | 4 (22%)    | 6 (29%)    | 0.726  |
| Lengths of stay                            |            |            |        |
| Hospital-free days                         | 13 (0, 19) | 0 (0, 11)  | 0.089  |
| Intensive care unit-free days              | 24 (0, 25) | 12 (0, 24) | 0.170  |
| Ventilator-free days                       | 27 (3, 28) | 22 (0, 27) | 0.230  |
| In-hospital mortality                      |            |            |        |
| Deaths                                     | 1 (6%)     | 7 (33%)    | 0.049  |
| Cause of death                             |            |            | 1.000  |
| MOf/Sepsis                                 | 0 (0%)     | 1 (14%)    | –      |
| Stroke                                     | 0 (0%)     | 0 (0%)     | –      |
| Traumatic brain injury                     | 0 (0%)     | 0 (0%)     | –      |
| Respiratory failure                        | 0 (0%)     | 1 (14%)    | –      |
| Transition to comfort care                 | 1 (100%)   | 5 (71%)    | –      |

This trial was limited by its narrow scope, small size and a failure to accrue the targeted sample size. This trial focused on a very specific group of patients—those for whom surgeons had equipoise for DEF and DCL. Before planning this trial, there was significant variation in the use of DCL at our institution. The 3 years of work leading up to this study led to the stakeholder-driven creation of acceptable inclusion criteria and sample size estimation. This work also changed the practice around DCL at our institution, namely use of consensus-based absolute and relative indications for DCL, which led to the decreased utilization of DCL from 39% to 17%. In addition to these internal changes, external events negatively affected enrollment. For unknown reasons, there was a temporary decrease in emergency laparotomies being performed at the trauma center, an occurrence that has now reversed. The trial was also limited by an imbalance of baseline characteristics in randomized groups and a lack of blinding. Inability to blind was addressed by having objective
definitions for outcomes and using independent surgeons for the evaluation of those that were more subjective. Lastly, the trial was stopped due to funding having ended and futility in accruing the estimated sample size within another 12 months.

In conclusion, our single-center pilot RCT was inconclusive and failed to provide definitive evidence to support our hypothesis. DCL was not worse than DEF and may have been beneficial. In the absence of any other RCT of DCL, our pilot trial indicates that a larger, multicenter trial is both feasible and necessary to compare DCL and DEF for patients with severe abdominal trauma. Until such a trial can confirm or refute the findings of this first RCT of DCL, we plan to liberalize our indications for DCL.

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Contributors Trial design: JAH, JET, CEW and JBH. Drafting/Critical revision of manuscript: JAH, SDA, S-IMD, KDI, CP, CEG, JET, EAT, DEM, LJM, LM, RA, MKM, LSK, CEW and JBH. Final approval of manuscript: JAH, SDA, S-IMD, KDI, CP, CEG, JET, EAT, DEM, LJM, LM, RA, MKM, LSK, CEW and JBH. Agreement to be accountable for work: JAH, SDA, S-IMD, KDI, CP, CEG, JET, EAT, DEM, LJM, LM, RA, MKM, LSK, CEW and JBH.

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Competing interests JBH is a co-founder and on the Board of Directors of Decisio Health, on the Board of Directors of QinFlow and Zibiro, a Co-inventor of the Functional Emergency Tourniquet Tool, an advisor to Safeguard, Arsenal Medical, Cellphire, Spectrum, CSL and PotentialMetrics.

Patient consent for publication Not required.

Ethics approval The McGovern Medical School Institutional Review Board approved this trial allowing for exception from informed consent with delayed patient or legally authorized representative consent (HSC-GEN-16-0104).

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ORCID iD John A Harvin http://orcid.org/0000-0002-2081-6256

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