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A Randomized Controlled Trial on Intra-Abdominal Irrigation during Emergency Trauma Laparotomy; Time for Yet Another Paradigm Shift

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Received: September 28, 2017

Revised: January 17, 2018

Accepted: January 20, 2018

► ABSTRACT

Objective: To determine the optimal volume of abdominal irrigation that will prevent surgical site infections (both deep and superficial), eviscerations and fistula formations; and improve 30-day mortality in trauma patients.

Methods: We conducted a three-arm parallel clinical superiority randomized controlled trial comparing different volumes of effluent (5, 10 and 20 liters) used in trauma patients (both blunt and penetrating) age 14 and above undergoing an emergency laparotomy between April 2002 and July 2004 in a busy urban Level 1 trauma center.

Results: After randomization, a total of 204 patients were analyzed. All patient groups were comparable with respect to age, gender distribution, admission injury severity score, and mechanism of injury, estimated blood loss and degree of contamination. The mortality rate overall was 1.96% (4/204). No differences were noted with respect to contamination, wound infection, fistula formation, and evisceration. The twenty liter group (Group III) showed a trend toward an increased incidence of deep surgical site infections when compared to the five liter (Group I) ($p=0.051$) and ten liter (Group II) ($p=0.057$) groups. This did not however reach statistical significance.

Conclusion: The old surgical adage “the solution to pollution is dilution” is not applicable to trauma patients. Our results suggest that using more irrigation, even when large amounts of contamination have occurred, does not reduce post-operative complications or affect mortality; and it may predispose patients to increased incidence of abscess formation.

(Trial registration number: ISRCTN66454589)

Keywords: Intra-abdominal irrigation; Intra-abdominal abscess; Sepsis; Randomized clinical trial; Peritoneal lavage.

Please cite this paper as:

Mashbari H, Hemdi M, Chow KL, Doherty JC, Merlotti GJ, Salzman SL, Singares ES. A Randomized Controlled Trial on Intra-Abdominal Irrigation during Emergency Trauma Laparotomy; Time for Yet Another Paradigm Shift. *Bull Emerg Trauma*. 2018;6(2):100-107. doi: 10.29252/beat-060203.

Introduction

The trauma laparotomy has undergone several revolutionary changes over the past few decades. Spleen preservation, nephron sparing techniques, angio-embolization, the introduction of laparoscopic explorations to rule out diaphragmatic injuries and, above all else, the paradigm shift that entail the Damage Control approach and management of open abdomen have already made significant improvements in the morbidity and mortality of this patient population [1, 2]. The use of evidence-based techniques has the potential to unlock additional benefits this cohort of individuals. This entails the re-examination and further appraisal under more controlled, rigorous conditions of traditional, time honored surgical maneuvers during the trauma laparotomy. One of these maneuvers is the use intraoperative irrigation.

As some trauma patients present with ongoing peritonitis from bowel injury they will require control of the source of contamination, since intestinal perforation and soiling of the peritoneal cavity is associated with high morbidity and mortality [3]. The use of irrigation for washout after the conclusion of an emergency abdominal procedure in a trauma patient is a logical, ubiquitous maneuver taught and practiced for over one hundred years, and considered to meet the standard of care; especially in the setting of abdominal contamination with enteral contents. There is, however, no quality evidence that supports it, and some data that may indicate it is potentially deleterious [4]. Factors that may potentially impact the desired effect include the volume of the effluent, where significant variability exist. There are several studies that specifically address this issue [5-8], but few of them meet criteria to be considered Level I human evidence. Therefore, no specific recommendations are currently available to guide decision making in the operating room, and existing literature seems to suggest a dose-effect relationship with the desired outcome [6-9]. Additional variables include the temperature of the effluent, the type of fluid utilized, the use of antimicrobials as additives and the source of contamination.

Thus, a single center, parallel, clinical superiority randomized prospective study was designed to compare three different volumes of irrigation with respect to complication rates and mortality, using 1:1:1 allocation ratios for each arm. After conclusion of the study the manuscript was revised and reformatted to conform to the CONSORT statement of 2010, using the published checklist [10].

Materials and Methods

Study Population

The original study protocol was reviewed and approved by the Advocate Institutional Review Board. To assure compliance with accepted best

practices for the conduction and reporting of clinical trials, this study was registered on a publicly accessible database. The trial registration number is ISRCTN66454589, and the registration, protocol and intervention information can be accessed at <http://www.isrctn.com/ISRCTN66454589>. Once the enrollment period began, all patients brought to the adult ER aged 14 and above requiring an emergent exploratory laparotomy for trauma were evaluated over a 2-year period (April 2002 to July 2004) for participation in the study. Inclusion criteria at that point included clinical or radiological evidence (i.e. CT scan, FAST exam or plain X-rays of the abdomen) of intrabdominal injuries (i.e. acute abdomen & clinical signs of peritonitis, free air, hemoperitoneum, evidence of peritoneal violation associated with a penetrating mechanism or the presence of retained missiles). Exclusion criteria at this stage included the need for concomitant extra-abdominal surgery, the presence of a pelvic fracture and severe TBI (GCS <6 noted during the primary survey). All eligible patients (or their representatives if unable to give consent) were approached in the Emergency Department for informed consent to participate in the study. Once entered into the study, patients were allocated a unique identifying number and transported expeditiously to the Operating Room (OR) for surgery.

Study Protocol

Patients underwent exploratory laparotomy with a standard midline incision with subsequent repair of all traumatic injuries identified. Additional exclusion criteria at this juncture included using the open abdomen technique, intrabdominal vascular implants (but not primary repairs) and the presence of diaphragmatic injuries. Enteral contamination of the surgical field was subjectively graded by the operating surgeon as Not Significant (either absent or localized and easily removable) or Significant (noticeable to generalized soiling). Once all operative repair was completed (including restoring intestinal continuity) and a decision to perform primary closure of the abdomen was made, the patients underwent random assignment to one of three treatment groups: Group I, assigned to receive 5L of Intra-Abdominal Irrigation (IAI); Group II, assigned to receive 10L of IAI; and Group III assigned to receive 20L of IAI (for replication purposes and following accepted guidelines [11], additional description of the treatment groups may be found at the trial registration site, below). The surgical team was notified of the result of the randomization procedure in the operating room, and the abdomen was irrigated with the designated volume of sterile, 37.8 C (100 F) 0.9% Sodium Chloride Irrigation USP (Baxter Healthcare Corp, Deerfield, IL) bottles. The designated volume was pulled one liter at the time from the OR Storage Console Warming Cabinet (Steris Corp. Mentor OH) and poured into the patient to avoid temperature

loss. Once irrigation was concluded the fascia was closed primarily and the skin was approximated if no colon injury was identified. Patients who died in the OR before randomization were excluded from the study. All patients received a standardized antibiotic regimen consisting of pre-operative Cefoxitin (Mefoxin, Bioniche Pharma, Lake Forest IL) 2 gm IV followed by 1 gm every eight hours for a period of 24 hours. Patients with known or suspected penicillin or cephalosporin allergy received Ciprofloxacin (Bayer Healthcare, Berlin, Germany) 400mg /Metronidazole (Pfizer, New York NY) 500mg IV for the same duration of the therapy.

Outcome and Measures

After the assigned intervention was completed patients were followed up during their inpatient stay and after discharge, for up to 30 days. Additional late follow up was provided in the Trauma clinic as needed or as indicated, according to the non-study interventions the patients received.

Operative findings, gender, age, Injury Severity Score, estimated intra-operative blood loss and the attending surgeon's subjective assessment of the amount of contamination were all recorded and entered into a database. Post-operative complications including 30 day mortality, intra-abdominal abscess, wound infection, fistula formation, and evisceration were also recorded. The diagnosis of intra-abdominal abscess required radiographic identification by computed tomography or ultrasonography, and confirmation of infection by open or percutaneous drainage and culture. Wound infection was defined as the presence of localized swelling, tenderness,

erythema or purulence from the surgical wound. Evisceration was defined as complete separation of all layers of the abdominal wall with exposure of intra-peritoneal organs.

Randomization and Intervention

The randomization was performed in a different room from where surgery was being conducted, and where study personnel not assigned to clinical duties (and blinded to the patient's identity and injuries) would pull a pre-marked envelope with the group assignment on it, from an urn containing equal numbers of envelopes for the three arms of the trial, which was under the custody of one of the authors (SLS) at all other times.

Statistical Analysis

Our sample size was calculated using the available contemporary (i.e. at the time of the original sample calculation) English biomedical literature to query the known incidence of the complications of interest after a trauma laparotomy which could be theoretically preventable by the use of abdominal irrigation [12-20], and cross referenced with current literature for continued relevancy (Table 1). The compiled risks of incidence were then used to make the calculation, using a power of 80% and two-sided 5% significance level (and aiming for clinical superiority), performing a Bonferroni adjustment for three comparisons per variable, and selecting the largest (which was abscess formation) resulting in a sample size of 68 subjects per arm (after adjustments for possible 2% crossover between groups). Data analysis was performed using the Statistical Package

Table 1. Complications of interest and their incidence according to available sources.

| Complication | Blunt Mechanism | Penetrating Mechanism | Original Sources | Updated Sources |
|-----------------------|-----------------|-----------------------|------------------|-----------------|
| Intrabdominal Abscess | 10.6% | 45% | 12,13,14,15 | 42,43,45,47,49 |
| Wound Infection | 19% | 13.4% | 12,13,15,16 | 43,45,47,48,49 |
| Fistula Formation | 1.1% | 0.4% | 14,15,17,18 | 44,45,46,48,50 |
| Evisceration | 5% | 2.4% | 16,18,19,20 | 45,46,49,50 |
| 30-day Mortality | 25% | 18.3% | 15,16,17,20 | 42,45,46,49 |

Table 2. Demographics and other information collected before treatment group assignment.

| IAI Treatment Groups: | 5 Liters | 10 Liters | 20 Liters | p values |
|--------------------------------|------------|------------|------------|----------|
| Demographics | | | | |
| N | 72 | 68 | 64 | |
| Male | 90.3% (65) | 89.7% (61) | 90.6% (58) | 0.985 |
| Female | 9.7% (7) | 10.3% (7) | 9.4% (6) | |
| Mechanism of Injury | | | | |
| Penetrating | 83.3% (60) | 79.4% (54) | 92.2% (59) | 0.113 |
| Blunt | 16.7% (12) | 20.5% (14) | 7.8% (5) | |
| Pre-operative Variables | | | | |
| ISS (Mean±SD) | 18.04±9.51 | 18.31±9.34 | 17.72±9.38 | 0.937 |
| Age (Mean±SD) | 28±10 | 30±12 | 27±10 | 0.261 |
| Operative Variables | | | | |
| EBL (Median mL) | 400 | 400 | 300 | |
| Significant Contamination | 50% (36) | 60.3% (41) | 56.3% (36) | 0.140 |

for the Social Sciences (SPSS) v.15.0 (Chicago IL). Group data was expressed as Mean I Standard Error of the Mean (S.E.M.). Substantial comparisons between groups were performed using ANOVA with post-hoc test for parametric data and Chi-Square analysis for non-parametric data. Statistical significance was defined as $P < 0.02$ after the Bonferroni correction.

Results

Overall 204 patients were analyzed in the study (Figure 1). Baseline demographic data is included in Table 2. All three patient groups were comparable with respect to age, gender distribution, admission Injury Severity Score, mechanism of injury (blunt vs penetrating), estimated blood loss (as recorded in the operative report), and degree of contamination. The overall mortality rate was 1.96% (4/204) with no significant differences among the three groups.

Among the survivors, no differences were noted within the groups with respect to contamination, wound infection, fistula formation, and evisceration rates (Table 3). The twenty liter group demonstrated a trend toward an increased incidence of intra-abdominal abscess formation when compared to the five liter ($p=0.051$) and ten liter ($p=0.057$) groups. However, this did not reach statistical significance. A post hoc analysis (Table 4) using the Bonferroni procedure was performed; and it provided confirmation of this findings.

Discussion

For a surgical trainee and (to a lesser degree) a general surgeon who takes occasional call for trauma, there are few more daunting experiences than a modern trauma laparotomy. This highly protocolized intervention is, ironically, the closest

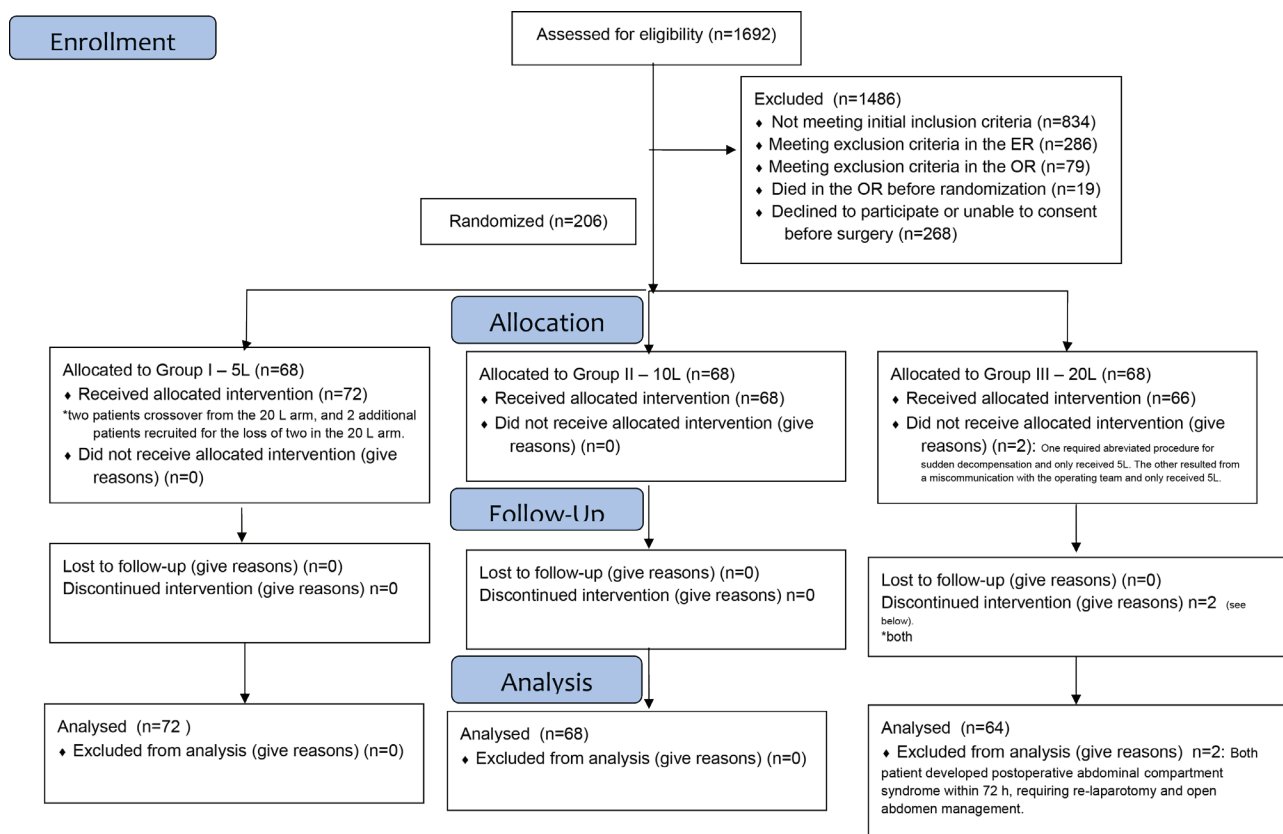


Fig. 1. CONSORT 2010 Flow Diagram

Table 3. Results after randomization by treatment group.

| Treatment Group | Mortality | Wound Infection | Fistula Formation | Evisceration | Abscess |
|------------------|-----------------------|-----------------|-------------------|----------------|----------------|
| 5 Liters (n=72) | 1.4% (1) ^a | 4.2% (3) | 1.4% (1) | 1.4% (1) | 1.4% (1) |
| 10 Liters (n=68) | 0% (0) | 7.4% (5) | 7.4% (5) | 2.9% (2) | 1.5% (1) |
| 20 Liters (n=64) | 4.7% (3) ^b | 4.7% (3) | 0% (0) | 7.8% (5) | 9.4% (6) |
| p-value | p=0.140 | p=0.678 | p=0.027 | p=0.139 | p=0.025 |

^aPulmonary embolism; ^bTraumatic Brain Injury, Severe ARDS, Pulmonary embolism. No significance differences found between the groups with respect to complications and mortality, after Bonferroni adjustments for 3 comparisons per variable ($p=0.02$)

Table 4. Post Hoc Comparisons between treatment groups.

| Outcome Measure | Comparison groups | p value |
|--------------------------|-------------------|---------|
| Mortality | 5L vs 10L | 1.000 |
| | 5L vs 20L | 0.500 |
| | 10L vs 20L | 0.159 |
| Wound Infection | 5L vs 10L | 1.000 |
| | 5L vs 20L | 1.000 |
| | 10L vs 20L | 1.000 |
| Fistula Formation | 5L vs 10L | 0.108 |
| | 5L vs 20L | 1.000 |
| | 10L vs 20L | 0.037 |
| Evisceration | 5L vs 10L | 1.000 |
| | 5L vs 20L | 0.165 |
| | 10L vs 20L | 0.450 |
| Abscess | 5L vs 10L | 1.000 |
| | 5L vs 20L | 0.051 |
| | 10L vs 20L | 0.057 |

to chaos a modern operating room will get. Severely injured patients arrive to the operating theatre either physiologically compromised or already in shock, with ongoing gross enteric contamination (in multiple places and from multiple sources) and sometimes with combined solid organ and vascular injuries that require hemorrhage control and immediate restoration of blood flow to compromised viscera and extremities. Every maneuver must be fast, deliberate, and geared towards the critical goals of damage control: stop the bleeding, resume distal perfusion, source control for enteric spillage and metabolic resuscitation with prevention of hypothermia. Consideration is then given for restoration of intestinal continuity and abdominal closure. After a decision has been made for primary closure, large volumes of warm saline irrigation are widely used to remove gross soiling and prevent surgical site infections and wound complications that arise from them.

Intraoperative abdominal irrigation was first formally described as a strategy for the management of peritonitis by Mikulicz [21] and Rhen [22] in 1902, and by Price *et al.*, [23] in 1905 (in the pre-antibiotic era), where peritoneal cleansing was able to decrease the mortality rate by 38%. It has since become part of the algorithm for any laparotomy, including the operative management of abdominal trauma. Multiple case reports and contemporary experts' opinions have been lodged in the biomedical literature over the course of the subsequent century, with subsequent variable and sometimes conflicting recommendations [3, 5, 9, 24]. All however share (with little more than anecdotal evidence to support those claims) the same purported benefit: decreased bioburden on the peritoneal surface, by either mechanical removal of bacteria and other soiling or supposed bacteriolytic properties of the effluent, to prevent intrabdominal abscess formation. The volume of irrigation recommended (as recently as 2009) averaged 25-30 liters. As we ushered the antimicrobial epoch, the rationale for continuing the

use of this intervention was not updated.

During the last decade of the twentieth century (and in some more recent literature [25-32]) animal and other experimental studies began addressing the question of which fluid and how much [8, 25-27, 33-40]. It was during this period that the potential adverse effects of the use of abdominal washouts were described: upregulation of pro-inflammatory mediators, damage to peritoneal mesothelial cells and polymorphonuclear neutrophil membranes, promotion of postoperative adhesions, documented instances of bacterial translocation, failure to effectively decrease peritoneal bacterial counts, and potential adverse effects on final hemostasis (through technical or chemical issues) [7, 33]. This was also a time when evidence began to accumulate regarding the use of antimicrobial and antiseptics as additives to the irrigation fluid [26, 33, 34]. A few systematic reviews have recently tried to provide some answers to this issue; but the evidence-base used has clear problems, i.e. the studies pooled are greater than 14 years old in more than 60% of the cases (in fact only 4 studies were more recent than the year 2010, only 2 of which are focused on the peritoneal cavity) [28-31]. Our interpretation of these meta-analyses and systematic reviews is in line with the conclusions reached by our own study; in that there is no benefit to large volume intra-peritoneal lavage with normal saline and, in fact, larger volumes can potentially increase complications rates. Finally, since the advent of damage control surgery, one of the purported benefits of the modern use of irrigation is the prevention (and reversal) of hypothermia. While the benefits of said prevention are well documented in the trauma literature, it is less clear how effective intrabdominal irrigation with warm fluids is to achieve that goal [35, 37].

We have shown that the use of larger volumes of intraoperative peritoneal irrigation offered no mortality benefit, regardless of the mechanism of injury, or the presence or severity of abdominal contamination as determined by the operating surgeon. This confirms similar findings in other populations (as stated above), and is a significant departure from the original evidence for its use at the beginning of the previous century [3-5, 21-24]. The reason for this discrepancy is unclear, factor possibly involved include the use of antibiotics, improvements in surgical technique and the advent of critical care units. In addition, the use of larger volumes of intraoperative peritoneal irrigation render no additional benefit for the prevention of intra-abdominal sepsis, wound complications (including wound infections and evisceration episodes), or anastomotic dehiscence and enterocutaneous fistula formation events. This is also in line with the most current literature on the subject [41-50].

In designing our trial, we attempted to elucidate which irrigation volume would provide the highest purported benefit of the intervention, while avoiding

the potential pitfalls, in a previously unreported population (trauma patients). The volumes selected were taken directly from those used in clinical practice at the time and the literature supporting those choices has been provided. When selecting the outcomes to be studied, we attempted to eliminate confounding factor by consistently warming the administered volumes and eliminating those patients that would benefit more from an open abdomen strategy (i.e. intraoperative evidence for abdominal compartment syndrome, massive resuscitation with swelling or intestinal discontinuity). Two patients that developed abdominal compartment syndrome after surgery were excluded (and replaced with new subjects) from the analysis as well. Finally, we design the trial for clinical superiority, with the intention of detecting even small advantages by using large volumes in regard to the selected outcomes.

When attempting to explain the findings, one may be tempted to borrow anecdotal evidence from unrelated studies, where the hypothesis was the use of large amounts of intra-abdominal irrigation may dilute or spread the contamination throughout the peritoneal cavity and lead to the formation of intrabdominal abscesses. It is also possible that a larger amount of irrigation negates the possible benefits of the intervention through a yet unknown mechanism. While there is experimental evidence of at least one benefit to the use of irrigation in trauma victims [39], our results strongly suggest an upper limit of 5L for the effluent. This has relevance for today's practice, since epidemiological evidence exist for the current use of Intraoperative Peritoneal Lavage for this indication in surgical practice [41-50].

Our trial has several limitations: Since damage control techniques were utilized when indicated (as per the contemporary accepted standard of care) it is very possible that the potential benefits and/or harms (or lack thereof) that the intervention has in this population remain unknown. Only the sickest patients undergo damage control, and they stand to receive the most benefit (if any) of a decrease in wound complications or the number of intrabdominal abscesses. As per accepted recommendations, all

colonic injuries were treated with the skin left open, negating the possible preventative effect of increased abdominal irrigation on the incidence of wound infections and abdominal wound dehiscence that would allow for the skin to be closed.

Since the Operating team, the SICU and the floor groups caring for the study subjects in the postoperative period were not blinded to the allocation group as per design, this introduced a possible source of bias in the interpretation of the clinical symptoms of the patients and the diagnostic workup. Additionally, the interpretation of the degree of enteral contamination was left to the operating surgeon, introducing a source of imprecision. Given the widespread use of Intraoperative Peritoneal lavage (as stated above) in current surgical practice, we believe it would have been unethical to include a group with no lavage. As such, we are unable to determine differences by using smaller volume irrigations.

The trial has been registered retrospectively (that is, after conclusion). The reason for that is that the trial was conceived, planned, executed and completed before registration was compulsory or even possible. Every effort has been made to comply with current best practices for the reporting of clinical trials.

The present study reflects the first randomized prospective clinical trial concerning the use of intrabdominal irrigation in the trauma setting. Our results suggest that the practice of irrigating the abdomen with large volumes of saline should be avoided in trauma patients. Furthermore, based upon the absence of any significant differences in complication rates between the 5L and 10L groups, we recommend a maximum of 5L volume of intrabdominal irrigation in all patients regardless of injury and amount of contamination.

Acknowledgement

The authors wish to acknowledge the contributions of the following individuals for their valuable contributions to the original trial.

Conflicts of Interest: None declared.

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