Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: An analysis of the Glue Grant database

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BACKGROUND: Evidence suggests that aggressive crystalloid resuscitation is associated with significant morbidity in various clinical settings. We wanted to assess whether aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients.

METHODS: Data were derived from the Glue Grant database. Our primary outcome measure was all-cause in-hospital mortality. Secondary outcomes included days on mechanical ventilation; intensive care unit (ICU) and hospital length of stay (LOS); inflammatory (acute lung injury and adult respiratory distress syndrome, or multiple-organ failure) and resuscitation-related morbidity (abdominal and extremity compartment syndromes or acute renal failure) and nosocomial infections (ventilator-associated pneumonia, bloodstream, urinary tract, and surgical site infections).

RESULTS: In our sample of 1,754 patients, in-hospital mortality was not affected, but ventilator days \( (p < 0.001) \) as well as ICU \( (p = 0.009) \) and hospital \( (p = 0.002) \) LOS correlated strongly with the amount of crystalloids infused in the first 24 hours after injury. Amount of crystalloid resuscitation was also associated with the development of adult respiratory distress syndrome \( (p < 0.001) \), multiple-organ failure \( (p < 0.001) \), bloodstream \( (p = 0.001) \) and surgical site infections \( (p < 0.001) \), as well as abdominal \( (p < 0.001) \) and extremity compartment syndromes \( (p = 0.028) \) in a dose-dependent fashion, when age, Glasgow Coma Scale (GCS), severity of injury and acute physiologic derangement, comorbidities, as well as colloid and blood product transfusions were controlled for.

CONCLUSION: Crystalloid resuscitation is associated with a substantial increase in morbidity, as well as ICU and hospital LOS in adult blunt trauma patients. (J Trauma Acute Care Surg. 2013;74:1215–1222. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level III.

KEY WORDS: Crystalloid; resuscitation; outcomes; blunt trauma; Glue Grant.

Despite the fact that significant advances in medical science have led to major breakthroughs against disease and unprecedented life expectancy and quality of life during the past few decades, resuscitation science has failed to keep pace, and the fluids most commonly used, namely, isotonic sodium chloride solution and lactated Ringer’s solution, have been used with little change since they were first introduced in the 19th century.1,2 Similarly, aggressive resuscitative strategies, which have constituted the cornerstone of early trauma management for decades, had not been challenged until recently, when data obtained in a prospective randomized fashion on patients with penetrating torso injuries suggested that restrictive resuscitation might improve morbidity and mortality,3 raising the question that perhaps resuscitative fluids themselves conferred additional morbidity. Since time-honored trauma resuscitation strategies were brought back into question, there has been mounting evidence that liberal crystalloid administration may be associated with adverse clinical outcomes in the pediatric,4–6 burn,7 neurosurgical,8 critically ill,9 and the blunt trauma population.10,11 The common denominator across these references is that the aggressive crystalloid resuscitation, likely owing to the worsening of acidosis,12–14 local endothelial disruption,15 and volume overload it confers,16–19 triggers an inflammatory response that substantially increases morbidity.

With the current project, we aimed to establish whether an association exists between clinically relevant outcomes and volume of crystalloid resuscitation in adult blunt trauma patients.

**PATIENTS AND METHODS**

**Data Collection**

Data were extracted from a prospectively collected multicenter cohort of severely injured blunt trauma patients in hemorrhagic shock, the Glue Grant initiative (National Institute of General Medical Sciences, Inflammation and the Host Response to Injury Collaborative Program, www.gluegrant.com). Enrollment criteria for the Glue Grant study include a blunt mechanism of injury, an Abbreviated Injury Scale (AIS) score of 2 or greater in any body region excluding the brain, and significant hemorrhage requiring blood product transfusion within 12 hours of injury or manifesting as prehospital or emergency department (ED) hypotension (systolic blood pressure < 90 mm Hg) or an elevated base deficit (BD) of 6 mEq/L or greater.
Trauma patients younger than 16 years or older than 90 years were excluded, and so were those with spinal cord injury, isolated brain trauma and thermal burns of greater than 20% of the total body surface area. An extensive data set was collected prospectively in all cohort subjects that were able to provide informed consent either directly or through a health care proxy during the course of 8 years. These data include demographics, mechanism and severity of injury, preexisting comorbid conditions, overall fluid and blood product resuscitation parameters, serial laboratories, and multiple clinically relevant outcomes. Standardized protocols were developed and implemented across all participating institutions to minimize variability in postinjury care, including initial trauma fluid and blood product resuscitation, mechanical ventilation and weaning; intensive care unit (ICU) insulin infusion, venous thromboembolism prophylaxis, and sedation and analgesia as indicated. After compilation and validation, deidentified data were included in the Glue Grant investigator-accessible database for secondary analyses. Data collection was approved by the regional institutional review boards of all participating centers, and secondary analysis was approved by the Partners Healthcare Institutional Review Board.

**Definition of Complications**

During the enrolled subjects’ stay in the ICU, multiple-organ dysfunction scores for renal, hepatic, cardiovascular, metabolic, respiratory, and neurologic systems were determined daily, and the diagnosis of multiple-organ failure (MOF) required a Marshall Multiple Organ Dysfunction score of greater than 5. Definitions of the outcomes of interest in the Glue Grant cohort, namely, acute lung injury (ALI) and adult respiratory distress syndrome (ARDS), abdominal and extremity compartment syndromes, acute renal failure (ARF), ventilator-associated pneumonia (VAP), as well as bloodstream (BSI), urinary tract (UTI), and surgical site infections (SSI) have been described extensively elsewhere.

**Hypothesis**

Our primary hypothesis was that volume of crystalloid resuscitation received in the first 24 hours after injury does not affect in-hospital mortality. Secondary outcomes included commonly used clinically relevant outcome measures, such as time on mechanical ventilation, ICU and hospital length of stay (LOS); inflammatory (ALI/ARDS and MOF) and resuscitation-related morbidity (abdominal and extremity compartment syndrome, ARF) and nosocomial infections (VAP, BSI, UTI, and SSI).

**Analysis**

Total volumes of crystalloid, colloid, and blood product (packed red blood cells [PRBCs] and fresh frozen plasma [FFP]) resuscitation were calculated for the first 24 hours after injury as resuscitative efforts were complete within this time frame in the overwhelming majority of patients. To simplify analysis and interpretation of results, blood product volumes were translated from the raw data from milliliters to average volumes of standard component therapy in units per the following conversion scheme: 1 U of PRBC = 350 mL and 1 U FFP = 250 mL. Multivariate logistic and linear regression analyses of our binary and continuous outcome measures were performed, respectively, controlling for age, scene Glasgow Coma Scale (GCS), Injury Severity Score (ISS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, comorbidities (using a Charlson comorbidity index), as well as colloidal and blood product (PRBC and FFP units) administration over the same time frame. Using a Kernel density distribution for the 24-hour crystalloid resuscitation, we divided our sample population in four clinically relevant and easily memorable volume groups and performed analysis of variance for the outcome measures, where crystalloid resuscitation was found to be an independent predictor. Adjusted odds ratios (ORs) were subsequently calculated for the binary outcomes for which 24-hour volume of crystalloid resuscitation had been identified as a predictor, after controlling for the aforementioned confounders.

**RESULTS**

From November 2003 to October 2011, a total of 2,002 blunt trauma patients were enrolled across all participating trauma centers nationwide. For our analysis, we excluded trauma patients that died within 48 hours or were discharged home within 72 hours to exclude those with irreversible hemorrhagic shock and nonsurvivable trauma, as well as those with minor injury burden. Adolescents younger than 18 years and patients with a combined penetrating mechanism were also excluded for a total sample size of 1,754 (Fig. 1), the characteristics of whom are summarized on Table 1. Overall, our sample was composed of fairly young (mean [SD] age, 43.5 [18] years) and otherwise healthy patients—90% of the entire cohort had a Charlson comorbidity index of 0 or 1. As expected from the inclusion criteria, injury acuity was very high, with 72% of the cohort having an ISS greater than 25. Systolic blood pressure averaged approximately 109 mm Hg, but BD and lactate levels were significantly deranged, −8.4 and 4.4 on average, respectively.
From our multivariable regression model, amount of crystalloid resuscitation administered in the first 24 hours after injury was not found to be an independent predictor of all-cause mortality, our primary outcome; therefore, we could not reject our null hypothesis. (Table 2). Not surprisingly, older age ($p < 0.001$), poorer neurologic status (lower scene GCS score, $p = 0.031$), as well as more severe injury (greater ISSs, and acute physiologic derangement (higher APACHE II scores, $p < 0.001$) were independently associated with higher mortality. Volume of crystalloid resuscitation was also found to be a predictor for number of days on mechanical ventilation ($p < 0.001$), as well as the ICU ($p = 0.009$) and hospital ($p = 0.002$) LOS (Table 2). An association was also noted between volume of crystalloids given and development of ALI/ARDS ($p < 0.001$), MOF ($p < 0.001$), abdominal ($p < 0.001$) and extremity ($p = 0.028$) compartment syndromes, and surprisingly enough, BSI ($p = 0.001$) and SSIs ($p < 0.001$).

To reach clinically meaningful and memorable conclusions from our study, we divided our cohort in 5-L volume subgroups and made comparisons between these groups. The baseline characteristics and incidence of complications across these volume groups are summarized on Table 3.

To avoid confounding from age and preexisting comorbidities, neurologic status, injury and physiologic derangement burden, and colloid and blood product administration, we controlled for those factors in our regression model and calculated the adjusted ORs for the binary outcomes we identified crystalloid resuscitation to be a predictor for. Volume of crystalloid resuscitation was noted to be associated with the development of ALI/ARDS, MOF, abdominal compartment syndrome, and SSI in a dose-dependent fashion (Table 4).

Patients who received greater than 15 L of crystalloids in the first 24 hours after injury had three times the odds of developing ALI/ARDS (adjusted OR, 2.9 [1.3–6.1], $p < 0.007$), or SSI (adjusted OR, 2.8 [1–8.2], $p < 0.005$) (Table 4, Fig. 2) compared with their counterparts who received less than 5 L of crystalloids in the first 24 hours after injury. The increase in risk was even more dramatic in the development of abdominal compartment syndrome as those who received between 10 L and 15 L of crystalloid resuscitation had five times the odds of developing this complication compared with the group who received 5 L to 10 L. The risk increased to almost 9 in patients who received greater than 15 L of crystalloids.

**DISCUSSION**

Despite ongoing advances in resuscitative medicine, the determination of the optimal methods and goals of resuscitation remain elusive and an area of intense controversy.\(^7,28\) As the concept of “damage-control resuscitation” has slowly but steadily grown in popularity during the past decade and a half, it has become increasingly clear that while immediate and aggressive fluid resuscitation of the injured victim may rapidly improve the vital signs of both patient and treating physician, the overall effect on outcome may be much less comforting.\(^7,29,30\) The physician in charge of the resuscitation efforts must remain mindful of the posttraumatic and dilutional coagulopathy,\(^10,31,32\) iatrogenic volume overload,\(^9,33\) and the myriad complications stemming from the physiologic and immunologic effects of large-volume resuscitation and massive blood product transfusion strategies.\(^16,17,19,27,30,34\)

As a growing body of evidence points to significant morbidity associated with even moderate volumes of crystalloid\(^4\) or blood component therapy\(^27,35\) in a variety of clinical settings, we aimed to determine the effect of crystalloid resuscitation on clinically relevant outcomes and complications in adult blunt trauma patients, the most frequent recipient of such resuscitation efforts. While we did not find an association between volume of crystalloid resuscitation and mortality, our primary outcome measure, significant associations were noted between crystalloid volume infused during the first...
postinjury day and highly morbid complications, such as ALI/ARDS, MOF, abdominal and extremity compartment syndromes, and even infectious complications, notably BSI and SSI, which we believe will form the first step toward abandoning overly aggressive resuscitation protocols from trauma practices worldwide. We were not able to identify an association between crystalloid volume and mortality even when we included all deaths in our exploratory analysis, as early mortality was noted to be primarily related to injury burden, and not resuscitation. However, all remaining associations became stronger as the denominator decreased—patients still alive at 48 hours (one would have to be alive to develop a complication).

While associative relationships between resuscitative components and adverse outcomes have been previously described, controversy persists over whether these relationships constituted a mere surrogate for injury severity or represented a truly causative effect. What has so far been unclear is whether sicker patients with greater injury burden went on to develop various complications as a result of their trauma-induced physiologic derangements and not by the massive resuscitation they received. To answer that question, we controlled for both injury severity and acute physiologic derangement, as well as preexisting comorbidities, age, and neurologic status, all well-recognized markers of unfavorable outcomes. We also controlled for colloid and blood component administration because these have been recently associated with adverse outcomes in trauma patients.

We elected to use the multi-institutional Glue Grant cohort for our secondary analysis because we believe it represents the most accurate, extensive, and well-validated prospectively collected dataset for the population of interest. In contrast to previously published efforts that have used 12-hour resuscitation volumes, we elected to analyze resuscitation administered over the first 24 hours. The rationale behind this approach is to capture the full extent of resuscitative efforts and to align with the typical duration of resuscitation in trauma patients.

### Table 3: Distribution of Injury Severity Across Crystalloid Volume Strata and Dose-Dependent Effect of Crystalloid Resuscitation on Morbidity

<table>
<thead>
<tr>
<th>24-h Crystalloid Resuscitation</th>
<th>&lt;5 L</th>
<th>5–10 L</th>
<th>10–15 L</th>
<th>&gt;15 L</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>87</td>
<td>475</td>
<td>574</td>
<td>618</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50.9 (21.4)</td>
<td>44.9 (19)</td>
<td>43.4 (17.3)</td>
<td>41.5 (17.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>GCS score, mean (SD)</td>
<td>11.1 (4.9)</td>
<td>11.6 (4.4)</td>
<td>11.3 (4.6)</td>
<td>11.0 (4.8)</td>
<td>0.332</td>
</tr>
<tr>
<td>ED SBT mean (SD), mm Hg</td>
<td>106 (32.8)</td>
<td>108 (27.5)</td>
<td>111 (31.5)</td>
<td>113 (31.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>ED HR, mean (SD), beats per minute</td>
<td>103.2 (26.7)</td>
<td>104.1 (25.9)</td>
<td>109.5 (26.4)</td>
<td>113.3 (27)</td>
<td>0.807</td>
</tr>
<tr>
<td>BD, mean (SD)</td>
<td>7 (5)</td>
<td>7 (4.3)</td>
<td>8 (4.1)</td>
<td>9 (4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/dL</td>
<td>11.4 (2.5)</td>
<td>11.6 (2.3)</td>
<td>11.5 (2.5)</td>
<td>11.3 (2.8)</td>
<td>0.105</td>
</tr>
<tr>
<td>ISS, mean (SD)</td>
<td>27.8 (12.9)</td>
<td>29.9 (12.6)</td>
<td>32.1 (13.6)</td>
<td>34.8 (13.4)</td>
<td>0.348</td>
</tr>
<tr>
<td>APACHE II, mean (SD)</td>
<td>23.9 (8)</td>
<td>26.1 (7.6)</td>
<td>27.6 (6.8)</td>
<td>30.6 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidity index, mean (SD)</td>
<td>0.6 (1.4)</td>
<td>0.5 (1.1)</td>
<td>0.4 (0.9)</td>
<td>0.3 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator days, mean (SD)</td>
<td>7.3 (7.9)</td>
<td>8.4 (9.2)</td>
<td>10 (11.4)</td>
<td>12.8 (11.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS, mean (SD), d</td>
<td>11.3 (8.7)</td>
<td>12.5 (12.1)</td>
<td>13.1 (12.2)</td>
<td>16.4 (13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS, mean (SD), d</td>
<td>19.6 (12.2)</td>
<td>21.6 (19.5)</td>
<td>23.8 (17.7)</td>
<td>30 (29.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALI/ARDS, %</td>
<td>11.5</td>
<td>14.1</td>
<td>23.3</td>
<td>37.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MOF, %</td>
<td>14.9</td>
<td>20.2</td>
<td>28.2</td>
<td>46.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal compartment syndrome, %</td>
<td>0</td>
<td>0.6</td>
<td>4.3</td>
<td>12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extremity compartment syndrome, %</td>
<td>1.1</td>
<td>1.7</td>
<td>3.6</td>
<td>5.7</td>
<td>0.005</td>
</tr>
<tr>
<td>BSI, %</td>
<td>8</td>
<td>9.9</td>
<td>12.9</td>
<td>20.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SSI, %</td>
<td>4.6</td>
<td>9.1</td>
<td>14.1</td>
<td>20.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR, heart rate; SBP, systolic blood pressure.

### Table 4: Adjusted ORs for the Binary Outcomes for Which Volume of Crystalloid Resuscitation in the First 24 Hours After Injury Was Identified to be a Predictor of

<table>
<thead>
<tr>
<th>5–10 L OR (95% CI)</th>
<th>p</th>
<th>&gt;15 L OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI/ARDS Reference</td>
<td>1.7 (0.71–3.9)</td>
<td>0.24</td>
<td>2.3 (1.5–5.4)</td>
</tr>
<tr>
<td>MOF Reference</td>
<td>1.5 (0.7–3.3)</td>
<td>0.29</td>
<td>1.9 (0.9–4.1)</td>
</tr>
<tr>
<td>Abdominal compartment syndrome</td>
<td>NA</td>
<td>reference</td>
<td>4.8 (1.4–16.4)</td>
</tr>
<tr>
<td>Extremity compartment syndrome</td>
<td>1.3 (0.2–10.5)</td>
<td>0.835</td>
<td>2.4 (0.3–18.9)</td>
</tr>
<tr>
<td>BSI Reference</td>
<td>1.5 (0.6–4)</td>
<td>0.398</td>
<td>1.9 (0.7–4.8)</td>
</tr>
<tr>
<td>SSI Reference</td>
<td>1.7 (0.6–5)</td>
<td>0.32</td>
<td>2.3 (0.8–6.6)</td>
</tr>
</tbody>
</table>

ORs controlled for age, GCS score, ISS and APACHE II score, comorbidities, colloid and blood product administration over the same time frame. CI, confidence interval, NA, not applicable.
decision was to ensure that acute resuscitation is complete and would be more indicative of future fluid-related complications, should such associations be identified, because a 12-hour window would be too narrow for such determinations, as frequently resuscitation is still ongoing, especially in the case of distant prehospital transfers or lengthy surgical interventions. We also elected to omit platelet transfusions from our analysis because the majority of the Glue Grant cohort did not receive any platelet component therapy and the majority of those who did received only 1 U. We also wanted to maintain power in our regression model to the extent possible, ensuring inclusion of well-recognized confounders associated with adverse outcomes, as well as other more commonly used blood component therapy, so their effect would be controlled for in our analysis. A separate outcomes analysis associated with blood component therapy in the blunt trauma population is currently under way.

After dividing our cohort into four distinct crystalloid volume groups so we could arrive at more meaningful and clinically memorable conclusions, we noted some differences between the baseline characteristics across the four groups. Interestingly enough, age and comorbidities seemed to be lower in the higher-volume resuscitation groups and the majority of those who did received only 1 U. We also wanted to maintain power in our regression model to the extent possible, ensuring inclusion of well-recognized confounders associated with adverse outcomes, as well as other more commonly used blood component therapy, so their effect would be controlled for in our analysis. A separate outcomes analysis associated with blood component therapy in the blunt trauma population is currently under way.

After dividing our cohort into four distinct crystalloid volume groups so we could arrive at more meaningful and clinically memorable conclusions, we noted some differences between the baseline characteristics across the four groups. Interestingly enough, age and comorbidities seemed to be lower in the higher-volume resuscitation groups, while severity of neurologic injury (scene GCS score) remained fairly constant across resuscitation groups. Although injury severity and acute physiology scores rose—as expected—across the four groups, the differences only in the latter reached statistical significance in our analysis of variance (Table 3). Moreover, although BD seemed to be significantly higher in the larger-volume groups, the differences were not necessarily clinically significant (BD difference between the <5 L and the >15 L groups was 2 points).

While the major difference in the baseline characteristics across the various volume groups was noted in APACHE II, ventilator days as well as ICU and hospital LOS were significantly higher in the subgroups that received larger crystalloid volumes (Table 3). Dramatic increases were also noted in the incidence of ALI/ARDS, MOF, compartment syndromes, BSI, and SSI in the higher-volume groups, and these differences did reach statistical significance on analysis of variance. Interestingly, even after controlling for the aforementioned confounders, the incidence of ALI/ARDS and MOF was significantly higher in the higher-volume groups, as was that of abdominal compartment syndrome, a complication well recognized to be tightly associated with higher resuscitation volumes. In fact, the OR for development of ALI/ARDS and MOF was three times higher in the group who received greater than 15 L, even after adjusting for severity of injury and physiologic derangement, as well as blood component therapy, likely suggesting a causative mechanism. It is likely that the highly acidic nature of the fluids most commonly used in acute trauma resuscitation (isotonic sodium chloride solution and lactated Ringer’s solution) trigger a dose-dependent acute inflammatory response that, not dissimilarly from other highly inflammatory conditions known to be associated with ALI/ARDS and MOF, may easily affect the pulmonary parenchyma as it spirals out of control.16–19 It is also possible that vascular

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Figure 2. Adjusted Odds Ratios for the development of ALI or ARDS, MOF, abdominal compartment syndrome and SSI across the four 24h crystalloid resuscitation volume groups.
overdistention from volume overload accentuates this phenomenon from local endothelial damage unrelated to the original traumatic insult.\textsuperscript{15}

Not surprisingly, incidence of abdominal compartment syndrome rose dramatically in the higher-volume groups, while extremity compartment syndrome lost significance in our controlled analysis, suggesting that for the development of the latter, voluminous fluid resuscitation must act synergistically with a primary local injury for the clinical syndrome to develop, unlike the case of abdominal compartment syndrome, where high volumes alone may lead to this extremely morbid complication.

One of the most intriguing findings in our study was the higher incidence of SSI and BSI in the larger crystalloid volume groups, although the latter barely missed statistical significance (\(p = 0.056\)) in our adjusted analysis. The incidence of the former rose from 8\% and 4.6\%, respectively, to 20.9\% with higher volumes of resuscitation, for an adjusted OR of nearly 3 in the subgroup that received greater than 15 L of crystalloids. Perhaps, higher volumes of resuscitation bear a previously unrecognized immunomodulatory or even immunocompromising effect that renders the body less capable of fighting infectious insults. It is interesting, however, that the elevated risk for infectious complications did not translate to significantly higher risk for VAP. Not surprisingly, the number of UTIs (13\%–15\%) and the incidence of ARF (0\%–2\%) remained rather stable across volume groups because larger fluid volumes improved filtration rates and bestowed a protective effect on the kidneys.

Despite the use of statistical models to the best of our ability to adjust for injury severity, baseline patient characteristics, and concomitant resuscitation with blood products, to fully account for the complex interactions between injury and outcome and the medical interventions in between, as previously described by Klein et al.,\textsuperscript{7} remains challenging. However, we believe this is a firm attempt at demonstrating the potential adverse outcomes excessive fluid resuscitation may confer because these complex interactions will continue to be in place and urge the medical community with the privilege to care for the injured to refrain from it, until well-designed randomized studies shed more light on the optimal method and goals of resuscitation and help develop optimal resuscitation strategies and protocols.

CONCLUSION

High volume of crystalloid resuscitation confers prolonged time on the ventilator, ICU, and hospital LOS in the adult blunt trauma population. It also seems to be associated in a dose-dependent fashion with a substantial increase in highly morbid complications, such as ALI/ARDS, MOF, abdominal compartment syndrome, and SSIs, even when baseline patient characteristics, trauma burden, and blood product transfusions are controlled for. The current guidelines for crystalloid resuscitation in adult blunt trauma warrant revisiting.

AUTHORSHIP

All authors have contributed significantly to and are willing to take public responsibility for one or more aspects of the study's design as well as the data acquisition, analysis, and interpretation.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES


DISCUSSION

Dr. Jason Sperry (Pittsburgh, Pennsylvania): The authors have performed a secondary analysis of a prospective derived Glue Grant database characterizing the relationship of crystalloid volume and outcomes associated with resuscitation following significant blunt injury in patients in hemorrhagic shock.

The authors use a well-published, robust dataset and demonstrate, as one might expect, associations between higher crystalloid volumes and overall poor outcome, including extended ICU requirements, length of stay, as well as dose-dependent relationships with ARDS, multiple organ failure, infectious complications, and compartment syndrome.

In the manuscript the authors admit that the ability to prove causality is difficult but suggest their statistical analysis provides a good basis for this.

Their findings add to prior literature using the same dataset and adds to recent and prior literature documenting similar detrimental outcomes attributable to overzealous crystalloid resuscitation.

Dr. Susan Rowell (Portland, Oregon): That was a very nice presentation. I have just a couple of questions.

First, did you account for prehospital fluid volume? Also, do you have information on AIS scoring and cause of death for these patients? Finally, did you notice any center clustering or variability among centers? And if so, how did you account for these patients? Finally, did you notice any center clustering for that? Thank you very much.

Dr. Joseph Cuschieri (Seattle, Washington): Just two quick questions and nice presentation. The first question: we just published a benchmarking paper from this data and there...
was a significant change in mortality over the study perioddid you look at and control for enrollment dates of these patients to see if that had an effect?

The second question is based on the crystalloid resuscitation itself. It would be apparent and obvious, that patients who are getting crystalloid are getting it for a reason. Was the degree of shock different between patients, thus the rate of crystalloid infusion different. In other words, did you look at the highest base deficit or highest lactate, or the reversal of acidosis at 24 hours and use that in your adjustment of your modeling which would add more information?

Dr. Peter Rhee (Tucson, Arizona): I think that because this is a retrospective study, by going back and looking at your data you can show there is an association with crystalloids and adverse outcome. I think it makes sense that if you infuse a lot of pro-inflammatory crystalloids which is harmful to patients, you will get some of these adverse clinical manifestations. So I agree with you and it’s nice that you demonstrated this.

The second, as Dr. Cushieri just mentioned, over time, as mortality decreased can you show that the use of crystalloids also decreased over time? Can you go back and take a look at that data?

Finally, did you notice what the cause of death was in these groups with the high volume versus the low volume crystalloid infusion? Thank you.

Dr. Sandro Rizoli (Toronto, Ontario, Canada): This is a very interesting study. The same adverse effects you demonstrated with crystalloids can be observed with blood transfusion. The more blood transfusions, more ARDS, more abdominal compartment syndrome and other similar complications are known to occur.

So maybe the problem is not on administering crystalloids or blood, but maybe the problem is circulatory overload. Maybe the problem is giving too much of any “resuscitation fluid”—crystalloids, colloids or blood. My first question: are the problems you demonstrated related to crystalloid or circulatory overload, which one is the problem?

The second question is: using your data can you tell when did you consider the amount of fluid administered “overzealous” and when you considered it appropriate? Thank you.

Dr. George Kasotakis (Boston, Massachusetts): Those are all great, well-thought out questions, let me say.

First, let me address Dr. Sperry’s questions. We did look at the time from injury to the final receiving ED, but not whether an in-between transfer has taken place, and the overwhelming majority of patients were in a participating trauma center within 2–3 hours at most, with very few outliers. When we looked at the amount of crystalloid given with regards to time-to-ED, we did not identify any significant association, which suggests that paramedic teams know when to slow down their LR drips.

With regard to the second question, in the last two years we have discovered that overly-aggressive crystalloid resuscitation triggers an inflammatory response by worsening acidosis, causing volume overload and leading to local endothelial disruption. This inflammatory response is cytokine-mediated, which means that it takes hours or even days to mount. Therefore, it is very unlikely for the early mortality to be resuscitation-related.

We also know this from the trimodal distribution of mortality after trauma, where the first two peaks occur at the scene and in the first 24- and 48-hours after injury and are directly associated with the trauma burden. It is the late morbidity and mortality in trauma that could potentially be iatrogenic and, hence, preventable. Now this time-honored notion was corroborated by our findings in our exploratory analysis, when we did not exclude any deaths: We found no correlation with any of our important clinical outcomes, because patients who died in the first 24-48 hours received large volumes of crystalloids, but never went on to develop complications because they had already died. And while there was no correlation between crystalloid resuscitation and mortality, there was a moderate inverse correlation between injury severity and time to death.

Now with regard to the third question, unfortunately, again, this is not a question that can be answered with this particular dataset because the Glue Grant database only includes information on whether somebody had a major operation or resuscitative procedure, but not how much later. However, because common protocols were utilized by all participating institutions, we could assume that similar algorithms were in place for all patients in our dataset.

Finally, with regard to the hypotensive patient who is being worked up in the trauma bay, while blood products are being prepared, we do not completely oppose crystalloid resuscitation. What we have found and are presenting here today is that it is massive crystalloid resuscitation that can prove harmful. So small to moderate amounts of crystalloids can be used, aiming for hypotensive resuscitation end-points.

To answer Dr. Rowell’s, Dr. Cushieri’s and Dr. Rhee’s questions, yes, prehospital fluids were included in our analysis, as we looked at total volume of resuscitative fluids administered within the first 24 hours after injury. With regards to the maximum non-head injury AIS, over 96% of the subjects had scores between 3 and 5, so this is a pretty significantly injured group. Regarding cause of death, it was not in the scope of our study to perform such an analysis, and neither was the clustering across different institutions or across various timesframes that data collection took place. When we looked at amount of crystalloid resuscitation and base deficit and lactate in our univariate analyses, we noted a weak correlation, and that is why we elected to omit those from our regression model.

To answer Dr. Rizoli’s questions, I could not agree more. I do think that circulatory volume overload definitely plays a role, but in addition to that, I believe that the unique chemical composition of the most commonly used resuscitative fluids, that are highly acidic, may exacerbate that effect. We are currently conducting similar analyses looking at various other fluids and blood products, so we hope we will have a better answer to this question soon. With regard to whether fluid resuscitation was overzealous or not, again, there was only a weak correlation between amount of crystalloids administered and highest base deficit or lactate levels, so at least some proportion of the resuscitation was overzealous, even though we did not specifically tailor our analysis to answer this question. Those are all great suggestions that could potentially trigger excellent future research projects.
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