Massive transfusion policies at trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program

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BACKGROUND: Massive transfusion protocols (MTPs) have been developed to implement damage control resuscitation (DCR) principles. A survey of MTP policies from American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) participants was performed to establish which MTP activation, hemostatic resuscitation, and monitoring aspects of DCR are included in the MTP guidelines.

METHODS: On October 10, 2013, ACS-TQIP administration administered a cross-sectional electronic survey to 187 ACS-TQIP participants.

RESULTS: Seventy-one percent (132 of 187) of responses were analyzed, with 62% designated as Level I and 38% designated as Level II ACS-TQIP trauma centers. Sixty-nine percent of sites indicated that they have plasma immediately available for MTP activation. By policy, in the first group of blood products administered, 88% of sites target high (≥1:2) plasma–to–red blood cell (RBC) ratios and 10% target low ratios. Likewise, 79% of sites target high platelet-to-RBC ratios and 16% target low ratios. Eighteen percent of sites reported incorporating point-of-care thromboelastogram into MTP policies. The most common intravenous hemostatic adjunct incorporated into MTPs was tranexamic acid (49%). Thirty-four percent of sites reported that some or all of their emergency medical service agencies have the ability to administer blood products or hemostatic agents during prehospital transport. There were minimal differences in MTP policies or capabilities between Level I and II sites.

CONCLUSION: The majority of ACS-TQIP participants reported having MTPs that support the use of DCR principles including high plasma-to-RBC and platelet-to-RBC ratios. Immediate availability of plasma and product use by emergency medical services are becoming increasingly common, whereas the incorporation of point-of-care thromboelastogram into MTP policies remains low. (*J Trauma Acute Care Surg*. 2015;78: S48–S53.

KEY WORDS: Massive transfusion protocol; survey; policy.

Traumatic injury is the leading cause of death for patients between the ages of 1 and 40 years,[1] with approximately 181,000 deaths per year in the United States.[1] Acute blood loss from injury can lead to hemorrhagic shock. Deaths as a result of hemorrhagic shock typically occur early, and patients usually succumb within the first 6 hours of injury.[2–5] Early hypoperfusion or shock has been demonstrated to promote coagulopathy.[6,7] Approximately 25% of patients with severe traumatic injury are coagulopathic on admission.[2,8,9] Presence of shock and coagulopathy on admission are independently associated with massive transfusion requirement and increased mortality.[10–13] Therefore, early identification of patients at risk of developing shock and coagulopathy and subsequent blood transfusion strategies to prevent, reverse, and control these processes may improve survival.[7,10,11,14,15]

The concept of damage control surgery for patients with severe trauma has significantly altered initial trauma care and reduced mortality.[16] Based on lessons learned from damage control surgery and resuscitation of military conflict casualties, principles of damage control resuscitation (DCR) have been developed. The main components of DCR are (1) rapid recognition of trauma-induced coagulopathy and shock; (2) permissive hypotension; (3) rapid surgical control of bleeding; (4) prevention/treatment of hypothermia, acidosis, and hypocalcemia; (5) avoidance of hemodilution by minimizing use of crystalloid intravenous fluid; (6) transfusion of red blood cells (RBC):plasma:platelets in a high unit ratio (≥1:2) or reconstituted whole blood in a 1:1:1 unit ratio; (7) early and appropriate use of coagulation factor concentrates; and (8) use of fresh RBCs and whole blood when available.

Massive transfusion protocols (MTPs) have been developed by trauma centers to effectively and rapidly implement DCR principles. The use of an MTP standardizes the resuscitative approach for patients with traumatic hemorrhagic shock. An MTP also provides guidance to the blood bank on what blood products will be expected and used during

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resuscitation, allowing them to plan appropriately to make blood products available immediately. Although many adult trauma centers have adopted MTPs to implement DCR principles, there are no data describing which DCR principles are commonly used at trauma centers in North America. The objective of this survey is to determine which MTP activation, hemostatic resuscitation, and monitoring aspects of DCR concepts have been incorporated into MTPs at trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP). ACS-TQIP works to increase the quality of care for trauma patients. The program uses risk-adjusted benchmarking to provide hospitals with accurate national comparisons, additional education, and training to improve the quality of institutions. ACS-TQIP accomplishes this task by collecting data from trauma centers, providing feedback about performance and implementing guidelines to improve patient outcomes.[17] ACS-TQIP published a guideline in November 2013 for massive transfusion in trauma. This survey will provide baseline information on MTP practices at ACS-TQIP participating centers.

PARTICIPANTS AND METHODS

Cross-sectional electronic surveys were distributed on October 10, 2013, by ACS-TQIP administration to 187 ACS-TQIP trauma centers in the United States, Canada, and Qatar. This survey was administered as part of a larger ACS-TQIP survey. Only one response from each trauma center was allowed, but the survey could be completed by either the trauma program directors or by a surrogate of their choice. Blinding of responses from ACS-TQIP centers was assured for all surveys. After survey dissemination, but before data analysis, it was determined that only US sites would be analyzed because there was only one Canadian site and one site from Qatar, and their inclusion would potentially reveal their identity. Before survey dissemination, three trauma surgeons at different institutions validated the survey questions for clarity and appropriateness. For the survey, terms such as hypotension and tachycardia were not defined; sites used local definitions and stated threshold parameters used to trigger the MTP. The questions are presented in Appendix A (http://links.lww.com/TA/A580). The institutional review board at Washington University in St. Louis determined that this survey qualified for a complete waiver.

Statistical Analysis

Survey data are presented using descriptive statistics; χ^2 and Fisher's exact tests were used to compare binomial data as appropriate. For more than two groups of data, analysis of variance or the Kruskal-Wallis test was used, as appropriate. Comparisons were considered significant if the two-sided value of $p < 0.05$. Analyses were performed using GraphPad Prism software (La Jolla, CA).

RESULTS

Of the 187 surveys distributed, 138 (74%) were completed. The Canadian site, the site from Qatar, and the 3% (4 of 138) of sites that reported not having an MTP policy were excluded. As a result, 132 responses were analyzed. A total of 76.5% (101 of 132) of the survey respondents were trauma program medical directors and 23.5% (31 of 132) of the respondents were delegated to respond on behalf of the trauma medical director. Sixty-two percent (82 of 132) of respondents were from Level I trauma centers and 38% (50 of 132) were from Level II trauma centers. Respondents indicated that the MTP policy at their institution was also used for nontraumatic bleeding at 89% (73 of 82) of Level I sites and 86% (43 of 50) of Level II sites ($p = 0.61$).

Prehospital Treatment

Two Level I sites and two Level II sites responded that they did not know if their emergency medical service (EMS) agencies had the ability to administer blood products or hemostatic agents during prehospital transport. Three Level I sites did not answer the questions pertaining to prehospital treatment. As a result, 125 sites were analyzed. Thirty-four percent (42 of 125) of sites reported that some or all of their EMS agencies have the ability to administer blood products or hemostatic agents during prehospital transport. Thirty-nine percent (30 of 77) of Level I trauma centers and 25% (12 of 48) of Level II trauma centers reported that some or all of their EMS agencies have the ability to administer blood products or hemostatic agents during prehospital transport ($p = 0.11$). The most commonly reported blood products or hemostatic agents available during transport were (1) RBCs 28% (35 of 125), (2) tranexamic acid (TXA) 15% (19 of 125), and (3) plasma 10% (12 of 125). See Table 1 for a complete list of blood products and hemostatic agents available for administration during prehospital transport. Interestingly, although the frequency overall was low, there was an increased use of platelets prehospital by Level II (6%) versus Level I trauma centers (0%) that approached significance.

TABLE 1. Blood Products and Hemostatic Agent Use by Emergency Medical Services Prehospital

Blood Products and Hemostatic Agents	All Trauma Centers (n = 125), %	Level I Trauma Center (n = 77), %*	Level II Trauma Center (n = 48), %**	*p*
RBCs	28.0	32.5	20.8	0.16
TXA	15.2	14.3	16.7	0.72
Plasma	9.6	9.1	10.4	1.00
Platelets	2.4	0.0	6.3	0.05
rFVIIa	1.6	2.6	0.0	0.52
Cryoprecipitate	0.8	0.0	2.1	0.38
Whole blood	0.0	0.0	0.0	1.00
PCC	0.0	0.0	0.0	1.00
Fibrinogen concentrates	0.0	0.0	0.0	1.00
Aminocaproic acid	0.0	0.0	0.0	1.00
Other	0.8	1.3	0.0	1.00

PCC, prothrombin complex concentrates; RBC, red blood cell; TXA, tranexamic acid.

*Two Level I sites responded that they did not know if their EMS agencies had the ability to administer blood products or hemostatic agents during prehospital transport. Three Level I sites did not answer any questions pertaining to prehospital treatment.

**Two Level II sites responded that they did not know if their EMS agencies had the ability to administer blood products or hemostatic agents during prehospital transport.

MTP Activation Criteria

To describe MTP activation criteria within respondents, we divided activation triggers into three categories: physician discretion, laboratory triggers, and vital sign triggers (Table 2). One hundred percent of sites surveyed use trauma surgeon judgment as a trigger for MTP activation. Vital signs are frequently used to trigger MTPs at both Level I and II trauma centers, with hypotension being used 56% (74 of 132) of the time. Administration of un–cross-matched blood products was as commonly used as hypotension to initiate an MTP (Table 2). Eighty-six percent (36 of 42) of all sites that use hypotension as an MTP trigger define hypotension as systolic blood pressure of 100 mm Hg or less, 81% (34 of 42) as 90 mm Hg or less, 17% (7 of 42) as 80 mm Hg or less, and 5% (2 of 42) as 70 mm Hg or less. Laboratory values are used as triggers in MTP policies infrequently. Only 28% (37 of 132) of respondents use at least one type of laboratory value to activate their MTP. When Level I centers are compared with Level II centers, 26% (21 of 82) versus 32% (16 of 50) use at least one laboratory value to activate their MTP by policy ($p = 0.43$). The higher use of viscoelastic monitoring (VEM) (thromboelastogram [TEG]/rapid TEG/rotational thromboelastometry) to activate MTP at Level I (10 of 21) versus Level II (2 of 16) sites was significant ($p = 0.04$).

BLOOD PRODUCT POLICIES AND AVAILABILITY

Plasma

One Level I site did not answer any questions pertaining to plasma. Plasma is immediately available (<5 minutes from time of ordering to transfusion) at 69% (90 of 131) of sites. Plasma is immediately available at 72% (58 of 81) of Level I sites compared with 64% (32 of 50) of Level II sites ($p = 0.36$). At Level I and II sites, where plasma is immediately available, the types of plasma used are 78% (70 of 90) thawed fresh-frozen plasma/plasma frozen within 24 hours, 16% (14 of 90) thawed fresh-frozen plasma/plasma frozen within 24 hours or liquid plasma, and 7% (6 of 90) liquid plasma. For centers with immediately available plasma, the locations are as follows: 63% (57 of 90) in the emergency department, 51% (46 of 90) in the operating room, 44% (40 of 90) in the intensive care unit, and 36% (32 of 90) in the blood bank. There was no difference in the location of immediately available plasma according to Level I versus Level II trauma centers.

Table 3 displays the target-specific plasma-to-RBC ratios in the first and subsequent packs of blood products available.

TABLE 2. MTP Activation Triggers

Trigger for MTP Activation	All Trauma Centers (n = 132), %	Level I Trauma Center (n = 82), %	Level II Trauma Center (n = 50), %	*p*
Trauma surgeon judgment	100.0	100.0	100.0	1.00
Anesthesia judgment	75.0	73.2	78.0	0.53
ED physician judgment	68.9	65.9	74.0	0.33
Unmatched blood products	56.1	52.4	62.0	0.28
Hypotension	56.1	54.9	58.0	0.73
Tachycardia	36.4	29.3	48.0	0.03
Other physician judgment	32.6	25.6	44.0	0.03
Mechanism of injury	22.0	23.2	20.0	0.18
Base deficit/lactate	19.7	15.9	26.0	0.16
Hgb/Hct	18.9	17.1	22.0	0.48
INR/PT/PTT	15.9	15.9	16.0	0.98
Massive Transfusion Prediction Score	11.4	12.2	10.0	0.78
GCS	7.6	6.1	10.0	0.50
TEG	7.6	11.0	2.0	0.09
Rapid TEG	5.3	6.1	4.0	0.71
Rotational thromboelastometry	2.3	3.7	0.0	0.29

TABLE 3. Target Plasma-to-RBC Ratios and Platelet-to-RBC Ratios in MTP Policies for First and Subsequent Packs of Blood

Plasma-to-RBC Ratio for First Pack	All Trauma Centers (n = 131), %	Level I Trauma Center (n = 81), %*	Level II Trauma Center (n = 50), %	*p*
1:1	57.3	55.5	60.0	0.44
1.5:1	13.7	19.8	4.0	0.02
2:1	13.0	12.3	22.0	0.14
3:1	2.3	1.2	4.0	0.56
Other	9.9	9.9	10.0	0.41
No target ratio	0.8	1.2	0.0	1.00
Plasma-to-RBC ratio for subsequent packs				
1:1	67.9	66.7	70.0	0.69
1.5:1	15.3	17.3	12.0	0.41
2:1	5.3	4.9	6.0	0.79
3:1	1.5	1.2	2.0	0.73
Other	4.6	4.9	4.0	0.80
No target ratio	5.3	4.9	6.0	0.79
Platelet-to-RBC ratio for first pack				
1:1	72.5	72.8	72.0	0.76
2:1	6.1	6.2	6.0	1.00
4:1	4.6	4.9	4.0	0.80
10:1	2.3	2.5	2.0	0.86
No target ratio	3.8	4.9	2.0	0.65
Other	3.1	2.5	4.0	0.83
No plasma available	7.6	6.2	10	0.42
Platelet-to-RBC ratio for subsequent packs				
1:1	81.7	82.7	80.0	0.70
2:1	7.6	8.6	6.0	0.74
4:1	1.5	0.0	4.0	0.14
10:1	0.8	0.0	2.0	0.38
No target ratio	3.8	4.9	2.0	0.65
Other	4.6	3.7	6.0	0.67
No plasma available	0.0	0.0	0.0	0.00

*One Level I site did not answer any questions pertaining to plasma or platelet ratios.

In the first pack of blood products available, 87.8% (115 of 131) target high (≥1:2) plasma-to-RBC ratios, 9.9% (13 of 131) target low (<1:2) plasma-to-RBC ratios, 0.8% (1 of 131) reported having no target ratio, and 1.5% (2 of 131) replied with "other." One site that reported "other" stated that their site uses goal-directed therapy with pathologist assistance, and one site reported that the ratio of products available in the first pack of blood products does not define how products are administered. In subsequent packs of blood packages, 90.1% (118 of 131) of sites target high plasma-to-RBC ratios, 1.5% (2 of 131) of sites target low plasma-to-RBC ratios, 5.3% (7 of 131) of sites have no target ratio, and 3.1% (4 of 131) of sites replied with "other." One site that reported "other" stated that the ratio of products delivered does not define how products are administered. Two sites that responded "other" stated that they use TEG to direct blood product administration, and one site that reported "other" stated that they use goal-directed therapy with pathologist assistance.

Platelets

Of the 132 respondents with MTPs, one Level I site did not answer any questions pertaining to platelets. Ninety-five percent (124 of 131) of sites reported that a specific ratio of platelets to RBC units was targeted. In the first pack of blood products available, 78.6% (103 of 131) of sites target a high (≥1:2) platelet-to-RBC ratio, 16.0% (21 of 131) of sites target a low (<1:2) platelet-to-RBC ratio, 3.8% (5 of 131) reported no target ratio, and 1.5% (2 of 131) sites replied with "other" (Table 3). One site that answered "other" reported that the ratio of products available in the first pack of blood products does not define how products are administered, and one site reported they that use goal-directed therapy with pathologist assistance. In subsequent packs of blood packages, 90.8% (119 of 131) of sites target high platelet-to-RBC ratios, 2.3% (3 of 131) target low platelet-to-RBC ratios, 3.8% (5 of 131) reported no target ratio, and 3.1% (4 of 131) sites replied with "other." One site that answered "other" reported that the ratio of products available does not define how products are administered. Two sites that answered "other" reported using TEG to direct blood product administration, and one site answered that they use goal-directed therapy with pathologist assistance.

Cryoprecipitate

Cryoprecipitate is incorporated into 49% (65 of 132) MTP policies at all hospitals. Forty-eight percent (39 of 82) of Level I trauma centers and 52% (26 of 50) of Level II trauma centers incorporate cryoprecipitate into their MTPs ($p = 0.62$). Dosages and timing of cryoprecipitate use were not queried in the survey.

Intravenous Hemostatic Agents Administered Within Hospital

Two Level I sites did not answer the questions pertaining to intravenous (i.v.) hemostatic agents administered within the hospital, and one Level I site responded that they did not know what products were administered within the hospital. Seventy-five percent (97 of 129) of surveyed hospitals' MTPs include i.v. hemostatic agents within their MTP policy (Table 4). Intravenous hemostatic agents incorporated into MTPs include TXA, rFVIIa, prothrombin complex concentrates, fibrinogen concentrates, and aminocaproic acid. The most common i.v. hemostatic agent incorporated into MTPs was TXA. Respondents indicated that 50% (65 of 129) of centers include antifibrinolytics as a group (TXA or aminocaproic acid) in their MTP policies. There were no differences in i.v. hemostatic agent use in MTP policies between Level I and II trauma centers.

TABLE 4. Intravenous Hemostatic Agents Within MTP Policies

Hemostatic Agent	All Trauma Centers (n = 129), %	Level I Trauma Center (n = 79), %*	Level II Trauma Center (n = 50), %	*p*
TXA	50.3	54.4	44.0	0.25
rFVIIa	34.1	36.7	30.0	0.43
Prothrombin complex concentrates	25.6	22.8	30.0	0.36
Fibrinogen concentrates	10.1	8.9	12.0	0.56
Aminocaproic acid	3.1	2.5	4.0	0.64
Other	3.1	1.3	6.0	0.30

*One Level I site did not know what products were administered within the hospital. Two Level I sites did not answer any questions pertaining to intravenous hemostatic agents administered within the hospital.

Point-of-Care TEG

Two Level I sites did not answer the questions pertaining to point-of-care (POC) TEG. Incorporation of POC TEG in MTP policies to direct transfusion is relatively low. Overall, POC TEG is incorporated within the MTP policy at 18% (23 of 130) of sites, with 23% (18 of 80) at Level I sites and 10% (5 of 50) at Level II sites using POC TEG ($p = 0.07$). For the hospitals that incorporate POC TEG testing within their MTP, the location of the POC TEG testing for both Level I and Level II hospitals is presented in Table 5. At Level I centers, the increased availability of POC TEG in intensive care units compared with Level II centers approached significance.

DISCUSSION

Based on our survey results, the implementation of MTP activation, hemostatic resuscitation, and monitoring aspects consistent with DCR principles by trauma centers participating in ACS-TQIP is high. However, there are considerable differences in these MTP policies and availability of resources to support DCR principles across all Level I and Level II verified trauma centers surveyed. This is the first comprehensive survey to assess the components of specific MTP policies and capabilities to provide certain aspects of DCR at US ACS-TQIP centers. The use of ACS-TQIP centers provided the infrastructure to survey a large number of trauma centers, which improves the generalizability of our results. Previous reports on MTP development have focused on implementation of MTPs and the cost-benefit analysis associated with a set protocol for product utilization.[18] Other studies have documented that blood utilization is reduced and outcomes are improved when MTP policies have been implemented at trauma centers

TABLE 5. Location of POC TEG Within Hospitals That Incorporate POC TEG Testing Within Their MTP

Location	All Trauma Centers (n = 23), %	Level I Trauma Center (n = 18), %	Level II Trauma Center (n = 5), %	*p*
Emergency department	63.6	66.7	40.0	0.34
Operating room	81.8	77.8	80.0	1.00
Intensive care unit	63.6	72.2	20.0	0.06
Laboratory	22.7	22.2	20.0	1.00
Other	4.5	0.0	20.0	0.22

Represents the percent of locations within the trauma centers that POC TEG testing is made available by policy for those centers that require its use.

Two sites did not respond to any questions pertaining to POC TEG location (n = 130). Of the remaining sites, 18% (23 of 130) of sites incorporate POC TEG testing within their MTP.

compared with historical controls.[19,20] Therefore, it is important to determine what the current standard practice is in the United States regarding MTPs and to eventually determine which aspects of DCR principles within MTPs are associated with improved outcomes and safety.

Our survey did provide some surprising results. It was unexpected that Level II trauma centers would have similar policies and capabilities to Level I trauma centers in almost every area examined. It was interesting that the use of VEM at all centers was substantially lower than expected. A recent meta-analysis report demonstrated that the use of VEM for hemorrhage is associated with reduced blood product utilization but not mortality.[21] Perhaps additional outcomes-based studies for trauma patients are required before VEM monitoring becomes more widely incorporated into MTP policies. Another explanation for our findings is that VEM testing may be performed routinely but not as a part of an MTP policy. We also did not expect the use of blood products and i.v. hemostatic adjuncts to be as common as reported for prehospital transport. It is possible that some may have misinterpreted the question and were answering that they can give blood and i.v. hemostatic agents that were initiated at a referring facility. Although the question stated "prehospital," we did not define this term further nor did we ask about administration during interhospital transport. Nonetheless, the recent dissemination of the concept of remote DCR (RDCR), which is the principle of providing DCR in the prehospital phase, may be spreading to US ACS-TQIP centers and becoming incorporated more rapidly than we perceived.[22] Large trials by the US Department of Defense examining the use of plasma and TXA prehospital are underway and will provide high-quality evidence on the efficacy and safety of these elements of RDCR.[23–27] It was interesting that more than 80% of TQIP centers target a high (>1:2) ratio of both plasma and platelets to RBCs. Recent completion of the PROPPR trial will provide high-quality evidence on the outcomes associated with trauma patients targeted to receive a 1:2 versus 1:1 ratio of plasma and platelets to RBCs. It is somewhat concerning that more than 85% of ACS-TQIP centers apply their MTP to patients with nontraumatic life-threatening bleeding. Very little data exist outside patients with traumatic injury regarding the efficacy and safety of DCR/RDCR principles. Additional studies are required in these nontrauma populations to determine the appropriateness of this practice.

The development of a prospective observational study of MTP activations would inform the trauma and transfusion medicine communities regarding the range and diversity of MTPs, typical range of practice regarding blood product use and dosages of i.v. hemostatic agents, the use of typical hemostatic agents, and POC TEG monitoring. This information would be invaluable for future trial design for patients with severe traumatic hemorrhagic shock. The Trauma Outcomes Group led by Holcomb, which collected data from 10 large trauma centers retrospectively for 1 year, performed this type of data collection 8 years ago. Numerous informative publications resulted from that effort.[28–30] It was limited by its retrospective nature and lack of external funding, which reduced the amount of data that could be collected. Trauma practice has also changed rapidly in the subsequent 8 years; as a result, another study and analysis are warranted. Future efforts will require prospective data collection to increase the amount and quality of information collected from a large number of institutions.

The challenge with developing large prospective trials in each of these populations, for each of the components of DCR/RDCR, is that (1) the frequency of patients is low; (2) there is still significant heterogeneity within patient categories, introducing confounders that cannot be accounted for; and (3) the significant cost of these trials. Instead of randomized controlled trials, it may be more feasible to perform large prospective observational studies incorporating comparative effectiveness research principles. There is substantial support for comparative-effectiveness research–related studies not requiring informed consent because of the minimal risks associated with participation and potential benefits for future patients. Not requiring informed consent would make comparative-effectiveness research–related studies for this even more feasible.[31] This would not be feasible under current regulations in the United States but is possible in other countries.

The limitations of our study include the potential for selection bias because of survey administration solely to ACS-TQIP centers. ACS-TQIP centers represent about half of all trauma centers in the United States, which may represent the "early adopters" and therefore increasing the risk of selection bias. Our survey was linked to another ACS-TQIP survey, which for practical purposes limited the number of questions we could ask. As a result, the survey did not ask some questions that would have been informative such as the dose of certain i.v. hemostatic agents, timing of empiric cryoprecipitate use, and the metrics used for auditing compliance to MTP policies.

CONCLUSIONS

The dissemination and implementation of some DCR and RDCR principles are reflected by the high frequency of their use within MTP policies at US ACS-TQIP centers. These widely practiced concepts must be studied in high-quality prospective trials to determine their efficacy and safety. This includes both trauma and nontrauma patients with massive hemorrhage because the vast majority of ACS-TQIP trauma centers use their MTP for all massively bleeding patients.

AUTHORSHIP

All authors are guarantors of the integrity of the entire study. All authors contributed to the study design, data acquisition, analysis and interpretation of data, statistical analysis, manuscript preparation, manuscript editing, manuscript revision/review and final version approval.

DISCLOSURE

The authors declare no conflicts of interest.

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