Hypothesis: A massive transfusion protocol (MTP) decreases the use of blood components, as well as turnaround times, costs, and mortality.

Design: Retrospective before-and-after cohort study.

Setting: Academic level I urban trauma center.

Patients and Methods: Blood component use was compared in 132 patients during a 2-year period following the implementation of an MTP; 46 patients who were treated the previous year served as historical control subjects.

Intervention: Introduction of an MTP that included recombinant factor VIIa for patients with exsanguinating hemorrhage.

Main Outcome Measures: The amount of each blood component transfused, turnaround times, blood bank and hospital charges, and mortality rates.

Results: After introduction of the MTP, there was a significant decrease in packed red blood cells, plasma, and platelet use. The turnaround time for the first shipment was less than 10 minutes, and the time between the first and second shipments was reduced from 42 to 18 minutes, compared with historical controls. The decreased use of blood products represented a savings of $2270 per patient or an annual savings of $200,000, despite increased costs for recombinant factor VIIa. There was no difference in mortality in either group; it remained around 50%. Thromboembolic complications did not increase, despite a significant increase in the use of recombinant factor VIIa.

Conclusions: The MTP resulted in a reduction in the use of blood components with improved turnaround times and significant savings. Mortality was unaffected. The use of recombinant factor VIIa did not increase thromboembolic complications in these patients.

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Massive transfusion is loosely defined as the transfusion of more than 10 units of packed red blood cells (PRBCs) in a 24-hour period. Although there have been reports of improved survival after massive transfusion during the last decade, it is unclear what factors are responsible. There is increasing evidence that the early coagulopathy seen in trauma patients should be treated aggressively during the initial resuscitation, particularly in those patients requiring massive transfusion. It has been suggested that a protocol designed to give red blood cells and coagulation factors (ie, plasma and platelets) in prespecified ratios can improve outcomes. Both military and civilian data suggest that a ratio of 1:1 to 1:2 of fresh frozen plasma to PRBCs is needed to adequately treat coagulopathy in patients undergoing massive transfusions.

We developed and instituted a massive transfusion protocol (MTP) at Parkland Health and Hospital System, Dallas, Texas, which was mainly designed for trauma patients with severe, active hemorrhage. The protocol includes giving prespecified amounts of PRBCs, thawed plasma (defined in the "Methods" section), cryoprecipitate, and platelets, as well as the recombinant factor VIIa (rFVIIa). The rationale of this protocol was to improve turnaround time, ie, the time between when the order for the products was received in the blood bank and when the products left the blood bank, as well as to provide component therapy in a more clearly defined proportion to prevent and treat coagulopathy and to reduce the waste that occurred with random product ordering.

We sought to examine our experience and outcomes among patients treated using this protocol. We hypothesized that an MTP would improve turnaround times, re-
duce the use of blood products and associated charges, and possibly decrease mortality.

METHODS

The Transfusion Service of Parkland Health and Hospital System collected data prospectively on patients who were treated using the MTP from June 1, 2004, to June 30, 2006. The data consisted of the amount and type of blood products transfused, the turnaround time for shipments, and the patient’s survival. The trauma team initiates the MTP with a phone call or a written order (survival. The trauma team initiates the MTP with a phone call and possibly decrease mortality.

Table 1. Massive Transfusion Protocol

<table>
<thead>
<tr>
<th>Shipment</th>
<th>PRBCs, Units</th>
<th>TP, Units</th>
<th>Platelet Dosea</th>
<th>Cryoprecipitate, Pooled Units</th>
<th>rFVIIa, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>5 0-Negative</td>
<td>2 AB</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1c</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>NA</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>2</td>
<td>NA</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>4.8</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>2</td>
<td>NA</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>2</td>
<td>NA</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PRBCs, packed red blood cells; rFVIIa, recombinant factor VIIa; TP, thawed plasma.

a One platelet dose equals a “6 pack” of pooled platelets or 1 apheresis unit.
b If blood type is unknown, the first shipment consists of 5 units of blood group O Rh-negative PRBCs and 2 units of blood group AB TP.
c If blood type is known, shipment consists of type-specific PRBCs and TP.

The figures given include a technical component to represent the costs of cross-matching, labeling, and processing, as well as the technicians’ time. Charges related to nursing time and administration of products were not included in these figures. Total hospital charges, which include all blood bank charges, were collected from the trauma registry.

Statistical analysis was performed using SPSS software, version 11 for Macintosh (SPSS Inc, Chicago, Illinois). Categorical data are expressed as proportions, and continuous data are given as means with standard deviations. Differences between proportions were tested using the Pearson χ² test and between means using the t test. Multivariate logistic regression analysis was used to account for possible confounders on mortality rate. Statistical significance was set at P < .05.

RESULTS

We calculated the dollar amount saved based on the amount the blood bank was charged for the various components by our suppliers. The figures given include a technical component to represent the costs of cross-matching, labeling, and processing, as well as the technicians’ time. Charges related to nursing time and administration of products were not included in these figures. Total hospital charges, which include all blood bank charges, were collected from the trauma registry.

Baseline demographic characteristics of the 2 patient populations are shown in Table 2. There were 132 patients treated in the 2 years after the introduction of the MTP. A historical control group consisted of 46 pa-
Patients treated the year before the MTP was introduced. There was no significant difference between groups in terms of age, sex, and mechanism of injury or Injury Severity Scores.

Patients in the MTP group received significantly fewer blood products during the first 24 hours (Table 3). There was an increase in the amount of rFVIIa given because it was included in the third shipment in our protocol; 37.1% (49/132) of patients in the MTP group received 1 or more doses of rFVIIa, vs 10.9% (5/46) in the historical control group. Despite the increased use of rFVIIa, there was no increase in the incidence of thromboembolic complications in the MTP group (0.8% in the control group). The turnaround time for dispensing blood products between the second and third shipments fell significantly in the MTP group vs the control group (Table 4).

There was no significant difference in mortality rates between groups, either in crude mortality rates, mortality stratified by time of death, mortality stratified by Injury Severity Score, or mortality adjusted for age, sex, mechanism of injury, Injury Severity Score, Glasgow Coma Scale score taken in the emergency department, blood pressure taken in the emergency department, days spent in the intensive care unit, and comorbidities using regression analysis (Table 5).

There were considerable savings associated with adoption of the MTP. Using the figures given for blood component charges in Table 6, we calculated that there was a savings per patient of $2270. This was despite the increased use and expense of rFVIIa. Because the MTP is currently activated for approximately 2% of 4500 trauma patients we see per year at our institution, this represents an annual savings of around $200,000. Although overall hospital charges were reduced from $163,173 to $125,531, this difference was not statistically significant.

Institution of an MTP at our hospital resulted in a significant decrease in the number of blood components transfused. Although we postulate that this is owing to a decrease in the presence or degree of dilutional coagulopathy, we cannot prove that there is a causal link. Our protocol was designed specifically not to track nor depend on any measured coagulation variables during the massive hemorrhage treated by our MTP. The turnaround time for coagulation testing is 30 to 40 minutes, and, therefore, in a patient who is exsanguinating, the results of any coagulation tests do not truly represent the current hemostatic profile, but rather the patient’s state of hemostasis 30 to 40 minutes earlier. We wished to avoid treatment decisions based on inaccurate data, and we instead chose to transfuse blood and components in predefined ratios that have already been shown in the literature to be effective. This concept takes into account the increasing evidence that more plasma should be given around time for coagulation testing is 30 to 40 minutes, and, therefore, in a patient who is exsanguinating, the results of any coagulation tests do not truly represent the current hemostatic profile, but rather the patient’s state of hemostasis 30 to 40 minutes earlier. We wished to avoid treatment decisions based on inaccurate data, and we instead chose to transfuse blood and components in predefined ratios that have already been shown in the literature to be effective. This concept takes into account the increasing evidence that more plasma should be given earlier to prevent the early coagulopathy of trauma. In addition, these patients are often hypothermic, and coagulation tests that are run at 37°C in vitro do not represent the coagulation status of a hypothermic patient in vivo.14,15

Despite the decrease in blood transfusions, there was no improvement in mortality seen in any analyzed subgroup during the study period. This may be for a number of reasons. First, these patients had severe injuries. For some patients, the MTP may improve their coagulation status, but they have suffered nonsurvivable injuries, and their probability of survival cannot be improved. Second, our sample sizes may be too small to show a difference, especially in the historical control group. Other investigators have shown a higher mortality rate in their historical control group and subsequently have achieved an almost identical mortality rate of approximately 50% after starting a similar transfusion protocol. Previous studies have shown a difference in mortality when increased volumes of plasma are transfused. However, the mean PRBC:plasma ratio in our study rose only from 1.7

### Table 3. Differences in Units of Blood Component Transfused Between Groups

<table>
<thead>
<tr>
<th>Component</th>
<th>Pre-MTP</th>
<th>MTP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBCs</td>
<td>15.5 (15.5)</td>
<td>11.8 (11.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thawed plasma</td>
<td>8.7 (6.9)</td>
<td>5.7 (5.4)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Platelets</td>
<td>3.8 (5.2)</td>
<td>1.1 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0.7 (0.9)</td>
<td>0.6 (0.8)</td>
<td>.32</td>
</tr>
<tr>
<td>rFVIIa, mg</td>
<td>0.63 (1.8)</td>
<td>1.91 (2.5)</td>
<td>&lt;.002</td>
</tr>
</tbody>
</table>

Abbreviations: MTP, massive transfusion protocol; PRBCs, packed red blood cells; rFVIIa, recombinant factor VIIa.

\(a\) Data are given as mean (SD).

### Table 4. Turnaround Time Between Shipments

<table>
<thead>
<tr>
<th>Shipment</th>
<th>Pre-MTP, min</th>
<th>MTP, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start to first</td>
<td>NA</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>First to second</td>
<td>42 (30)</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>Second to third</td>
<td>44 (31)</td>
<td>29 (1.7)</td>
</tr>
<tr>
<td>Third to fourth</td>
<td>NA</td>
<td>26 (1.6)</td>
</tr>
</tbody>
</table>

Abbreviations: MTP, massive transfusion protocol; NA, not applicable.

\(b\) P < .05.

### Table 5. Mortality in Pre- and Post-MTP Patient Populations

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Pre-MTP, %</th>
<th>MTP, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>50.0</td>
<td>52.3</td>
</tr>
<tr>
<td>OR</td>
<td>15.2</td>
<td>25.8</td>
</tr>
<tr>
<td>First 24 h</td>
<td>19.6</td>
<td>20.5</td>
</tr>
<tr>
<td>After 24 h</td>
<td>13.0</td>
<td>5.3</td>
</tr>
<tr>
<td>With ISS &lt;9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>With ISS 9-15</td>
<td>62.5</td>
<td>100</td>
</tr>
<tr>
<td>With ISS 16-24</td>
<td>41.7</td>
<td>58.6</td>
</tr>
<tr>
<td>With ISS ≥25</td>
<td>45.8</td>
<td>49.4</td>
</tr>
</tbody>
</table>

Abbreviations: ISS, Injury Severity Score; MTP, massive transfusion protocol; OR, operating room.

\(a\) No statistically significant differences were noted between groups.
among historical controls to 2.0 in the MTP cohort, which is unlikely to influence mortality.\textsuperscript{17} This suggests that the lack of coagulation factors was not a significant problem before initiation of the protocol, so mortality could not be improved in this way. We did not attempt to analyze for unexpected survivors using a predictive model based on the Trauma and Injury Severity Score, as others have done, which may have demonstrated a survival benefit. Finally, initiation of a protocol may not affect mortality, but may still have a beneficial effect on morbidity, which we did not measure in this study, as well as the benefits already described.

In light of the controversy surrounding rFVIIa, it was interesting to note that there was no increase in the incidence of thromboembolic complications. This is in contrast to recent reports, especially in the media, and in light of its continued use in the ongoing Iraq conflict.\textsuperscript{18,19} In contrast to those military patients, our patients were unlikely to have been dehydrated before injury and would have received significant volumes of crystalloid as well as blood components before receiving rFVIIa for continued hemorrhage. There may also be a difference because of the whole blood that is primarily used in the military setting.\textsuperscript{20}

We noted a significant improvement in the timeliness of blood transfusion after introduction of the MTP, which is to be expected with the design of the protocol, in which the next shipment is prepared automatically and is then ready to be picked up, rather than waiting for a request to be made by a physician. This enables the medical staff to concentrate on the resuscitation of the patient, rather than trying to ascertain what products are needed, in what quantities, and how soon. Although there is a wealth of evidence detailing the need for increased and early use of plasma and clotting factors in exsanguinating hemorrhage, it appears that this practice has yet to be universally adopted. A protocol that sends blood components in specified ratios that are designed to be transfused as they arrive is intended to take the guesswork out of preventing and treating the coagulopathy of massive transfusion.

A final advantage to the introduction of the MTP is the significant cost savings that can be achieved. Although there was an increase in the use of rFVIIa after the introduction of our protocol, this was offset by the decrease in the amount of blood products transfused. Blood and blood components are scarce resources that need to be managed efficiently. Other institutions have seen decreases in the amount of blood products transfused subsequent to developing a protocol, even without the use of rFVIIa.\textsuperscript{20} We did see a reduction in overall hospital charges in the MTP population, but this was not statistically significant.

Transfusion of blood and blood components is also not without risk, and in the current climate, with concerns regarding transfusion-related acute lung injury and unknown blood-borne diseases, a protocol that reduces unnecessary transfusions should be welcome.\textsuperscript{21,22} We believe that there are a number of advantages to an MTP, the most important of which is the increased speed of delivery of blood products. Other potential benefits may include decreased amounts of crystalloid infusion and avoidance of coagulopathy. In addition, ours is the first study to show that there was a net reduction in blood-bank charges following the introduction of an MTP.

There are some limitations associated with this study that should be acknowledged. The data were a combination of retrospective registry data and prospectively collected data; as such, the study suffers from the drawbacks of all retrospective registry reviews, because it relies on the accuracy of the data abstracters and it is not possible to control for unknown confounders. As this was a clinical protocol, end points for the MTP were based on clinical factors, such as surgical site bleeding and patient physiological characteristics, rather than set goals for hematocrit levels, coagulation profiles, or base deficit. As such, it is possible that during the 3-year period, individual and institutional transfusion practices may have changed in ways that we could not detect and that would affect our results. Although our goal was also to raise awareness of the problem of dilutional coagulopathy in trauma patients undergoing massive transfusion, it is possible that some of our observed improvement was owing to the Hawthorne effect.

We used historical controls treated during the year before the initiation of the MTP, and there may have been treatment changes during the study period that could have accounted for some of the differences seen between groups. Also, the historical control group was just more likely to have received significant volumes of crystalloid as well as blood components before receiving rFVIIa for continued hemorrhage. There may also be a difference because of the whole blood that is primarily used in the military setting.\textsuperscript{20}
results in favor of the protocol. The similarity of mean Injury Severity Scores in both groups suggests that this was not the case. Despite our best efforts, we may not have been able to detect every thromboembolic complication because of the retrospective nature of the data extraction and because our institution does not routinely screen for deep vein thrombosis.

Finally, although we did not perform this analysis, because doing so would have reduced our numbers significantly, a case-control design may be a more appropriate way of comparing these groups, rather than a pre- and post-MTP period, so confounding factors could have been more appropriately matched. The nature of our data would make this a challenging undertaking. The small number of patients receiving rFVIIa may have made it difficult to detect a difference between the 2 groups.

In conclusion, an MTP offers a number of benefits, including fewer blood product transfusions, improved time to transfusion, and decreased blood bank and hospital charges. This is another example of a quality-driven protocol that removes variable decision making from the equation and leads to an improvement in the quality of care.

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Author Contributions: Drs O’Keeffe and Sarode had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tchorz, Forestner, and Sarode. Acquisition of data: O’Keeffe, Refaaai, Forestner, and Sarode. Analysis and interpretation of data: O’Keeffe, Refaaai, and Sarode. Drafting of the manuscript: O’Keeffe, Refaaai, and Sarode. Critical revision of the manuscript for important intellectual content: O’Keeffe, Tchorz, Forestner, and Sarode. Statistical analysis: O’Keeffe and Refaaai. Administrative, technical, or material support: O’Keeffe and Tchorz. Study supervision: Tchorz and Sarode.

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Additional Contributions: Raymond Morris, MT (ASCP); Venita Dasch, RN; Jarred McDaniel, BS; Julia Napper, RN; Johnathan Baker, MD; Mohammed Alsammak, MD; Marty Koch, MT (ASCP); James Burner, MD; Scott Hampton, MT (ASCP); and Jennifer Parks, MPH; assisted with development of the MTP as well as data collection.

REFERENCES


in bleeding patients with severe injuries. As mortality rates range from one-third to one-half of these massively transfused individuals, heroic new measures are aggressively sought after and easily embraced.

In this article, the authors describe the use of blood and blood components of a new MTP. When the data from MTP from the year prior to implementation of the new algorithm were compared with the 2 years following its utility, a number of observations were made: total number of MTP activations per year nearly doubled, the mean use of red blood cells per patient decreased by about 4 units or 25%; blood and blood component availability in the trauma resuscitation area improved, but mortality remained the same at 50%.

I have a number of concerns and questions about this retrospective study. First, how was the decision made to activate the MTP? It is doubtful that the number of yearly admissions of severely ill trauma patients with coagulopathy doubled at Parkland during the 3-year study period. Is it possible that the authors actually were diagnosing impending coagulopathy in patients who were subtly less sick? Maybe the reduction in blood product use without change in mortality demonstrates that this MTP harms patients who were less ill and did not need it.

Second, how did the authors validate the ratios of various products used and the timing of administration? Why not guide your correction of coagulation factors by tests that could be available in the emergency department, such as thrombelastography and prothrombin time?

Third, the data supporting the use of factor VIIa are controversial, so why include this procoagulant at all? For example, did you give factor VIIa to patients who were profoundly acidotic, where it is not active?

Finally, what other factors were altered during the 3 years of this study that may have changed blood product use? Did the faculty change during those 3 years of the study, or the seniority of the responding residents, and I am not aware of there being any changes in the standards of responsibilities or the seniority of responding residents, and I could control these factors retrospectively, as unfortunately our staff do not routinely record which person makes the decision to initiate the MTP. There were no changes in the responsibilities or the seniority of responding residents, and I am not aware of there being any changes in the standards of fluid resuscitation institution-wide at that time.

Financial Disclosure: None reported.