

# Prehospital synergy: Tranexamic acid and blood transfusion in patients at risk for hemorrhage

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| <b>BACKGROUND:</b>        | Growing evidence supports improved survival with prehospital blood products. Recent trials show a benefit of prehospital tranexamic acid (TXA) administration in select subgroups. Our objective was to determine if receiving prehospital packed red blood cells (pRBC) in addition to TXA improved survival in injured patients at risk of hemorrhage.   |
| <b>METHODS:</b>           | We performed a secondary analysis of all scene patients from the Study of Tranexamic Acid during Air and ground Medical Pre-hospital transport trial. Patients were randomized to prehospital TXA or placebo. Some participating EMS services utilized pRBC. Four resuscitation groups resulted: TXA, pRBC, pRBC+TXA, and neither. Our primary outcome was 30-day mortality and secondary outcome was 24-hour mortality. Cox regression tested the association between resuscitation group and mortality while adjusting for confounders.  |
| <b>RESULTS:</b>           | A total of 763 patients were included. Patients receiving prehospital blood had higher Injury Severity Scores in the pRBC (22 [10, 34]) and pRBC+TXA (22 [17, 36]) groups than the TXA (12 [5, 21]) and neither (10 [4, 20]) groups ( $p < 0.01$ ). Mortality at 30 days was greatest in the pRBC+TXA and pRBC groups at 18.2% and 28.6% compared with the TXA only and neither groups at 6.6% and 7.4%, respectively. Resuscitation with pRBC+TXA was associated with a 35% reduction in relative hazards of 30-day mortality compared with neither (hazard ratio, 0.65; 95% confidence interval, 0.45–0.94; $p = 0.02$ ). No survival benefit was observed in 24-hour mortality for pRBC+TXA, but pRBC alone was associated with a 61% reduction in relative hazards of 24-hour mortality compared with neither (hazard ratio, 0.39; 95% confidence interval, 0.17–0.88; $p = 0.02$ ). |
| <b>CONCLUSION:</b>        | For injured patients at risk of hemorrhage, prehospital pRBC+TXA is associated with reduced 30-day mortality. Use of pRBC transfusion alone was associated with a reduction in early mortality. Potential synergy appeared only in longer-term mortality and further work to investigate mechanisms of this therapeutic benefit is needed to optimize the prehospital resuscitation of trauma patients. ( <i>J Trauma Acute Care Surg.</i> 2022;93: 52–58. Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.)  |
| <b>LEVEL OF EVIDENCE:</b> | Therapeutic/Care Management; Level III.  |
| <b>KEY WORDS:</b>         | Tranexamic acid; prehospital; blood; mortality; resuscitation.   |

Hemorrhage is the leading cause of early preventable death after injury. Minimizing time to resuscitation is critical to curtail early mortality and improve long-term survival.<sup>1</sup> Death from hemorrhage often occurs within the first few hours from time of injury and one-third of exsanguinating deaths occur prehospital.<sup>1,2</sup> Damage-control resuscitation has become the standard in-hospital strategy; however, prehospital resuscitation is not optimized to mitigate hemorrhage. Prior literature demonstrates

inflammation and coagulopathy ensue within minutes of injury underscoring the need for prompt and targeted resuscitation strategies in the field.<sup>3,4</sup>

Crystalloid remains the most widely used resuscitation fluid in the prehospital setting due to its availability and durability. Blood product administration in the field is limited by storage challenges and cost. Recent progress adopts the tenets of damage-control resuscitation, adding blood products and limiting large volume crystalloids in the field.<sup>5–7</sup> The benefits of prehospital blood product resuscitation were demonstrated in military practice<sup>8–11</sup> and confirmed to be safe and effective in civilian trauma for patients in hemorrhagic shock.<sup>12–18</sup>

Important resuscitative and hemostatic adjuncts including antifibrinolytics have emerged in advanced resuscitative strategies. Antifibrinolytics aid in hemostasis as demonstrated in elective surgical cases.<sup>19</sup> Trauma-induced coagulopathy can manifest as a hyperfibrinolytic phenotype in some patients, and is associated with poor outcomes.<sup>20,21</sup> Administration of tranexamic acid (TXA) reduces mortality in bleeding trauma patients when provided at the receiving hospital.<sup>22</sup> Extrapolating these data, subsequent guidelines incorporated TXA into prehospital resuscitation algorithms.<sup>23,24</sup> Recent studies further demonstrate safety and efficacy for select prehospital populations and dosing regimens.<sup>25,26</sup>

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As prehospital resuscitation capabilities become more sophisticated, the impact of combining multiple advanced prehospital resuscitation interventions is unclear. We previously demonstrated combining prehospital packed red blood cell (pRBC) and plasma had a greater mortality benefit than either alone among patients in hemorrhagic shock.<sup>16</sup> However, outcomes associated with the combination of prehospital TXA with other prehospital resuscitation products represents a knowledge gap. Our objective was to determine if receiving prehospital pRBC in addition to TXA reduced mortality in injured patients at risk of hemorrhage. We hypothesized the combination of pRBC and TXA will be associated with reduced mortality in this population.

## METHODS

### Trial Design

We conducted a secondary analysis of the Study of Tranexamic Acid during Air and ground Medical Prehospital transport (STAAMP) trial. The details of the STAAMP trial have been previously published.<sup>25</sup> Briefly, the STAAMP trial was a multicenter pragmatic double-blind placebo-controlled trial which randomized patients undergoing emergency medical services (EMS) transport after injury to receive a 1-g TXA bolus or placebo in the prehospital setting. Patients receiving TXA were further randomized in-hospital to three dosing regimens, including an abbreviated regimen with additional placebo bolus and infusion, a standard regimen with placebo bolus and TXA infusion, and a repeat regimen with additional TXA bolus plus TXA infusion.

In the STAAMP trial, 24 EMS bases enrolled and transported patients to four Level I trauma centers. Among these, 12 EMS bases (all air medical transport agencies), provided pRBC as standard of care for prehospital resuscitation when indications were met (Fig. 1). This configuration of EMS bases led to

four prehospital resuscitation groups for purposes of this study: (1) patients receiving prehospital TXA (TXA only group), (2) patients receiving prehospital pRBC and placebo (pRBC only group), (3) patients receiving prehospital pRBC and TXA (pRBC+TXA group), and (4) patients receiving placebo only (neither group). Of note, all EMS bases provided crystalloid resuscitation to the above four groups.

### Study Population

Inclusion criteria for the STAAMP trial were patients with at least one episode of hypotension (systolic blood pressure [SBP] <90 mm Hg) or tachycardia (heart rate >110 beats per minute) within 2 hours of injury. Patients were excluded if older than 90 years or younger than 18 years, lack of intravenous or intraosseous access, isolated fall from standing, documented cervical cord injury, known prisoner or pregnancy, traumatic arrest of more than 5 minutes, penetrating brain injury, isolated drowning or hanging, objection to study voiced at scene, or wearing a STAAMP study opt-out bracelet.

For the current study, we restricted the study population to patients transported directly from the scene of injury. This was done as there were limited data available about resuscitation products and volumes received when initially transported to a referring hospital, which might introduce unmeasured confounding.

### Statistical Analysis

The primary outcome was 30-day mortality. Given the potential influence of multiple downstream in-hospital factors that might obscure the impact of prehospital interventions on 30-day mortality, we also assessed a secondary outcome of 24-hour mortality, an endpoint more proximate to the interventions of interest. We used Cox proportional hazard regression to evaluate the association with mortality outcomes and the four prehospital resuscitation groups. The proportional hazards assumption was

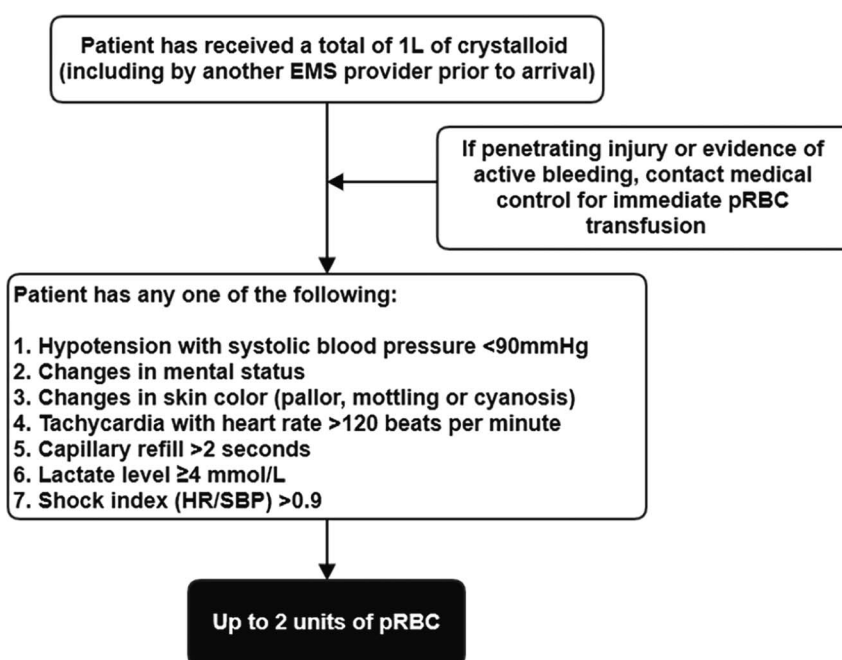


Figure 1. Emergency medical services protocol for prehospital pRBC transfusion on scene.

evaluated by testing for difference from a nonzero slope of Schoenfeld residuals, with a significant test indicating violation of this assumption. The neither group, receiving neither prehospital pRBC nor TXA, was used as the reference category for reporting hazard ratios. Based on the results from the original trial, receiving prehospital pRBC was a clear marker of more severe injury and not randomized as the TXA groups were. Thus, we calculated a propensity score that reflected the likelihood of receiving prehospital pRBC based on the protocols for administering prehospital pRBC (Fig. 1) and prehospital variables that potentially could influence this decision. This propensity score included age, Injury Severity Score (ISS), mechanism of injury, prehospital SBP, prehospital heart rate, prehospital Glasgow Coma Scale, prehospital time, prehospital intubation, prehospital crystalloid volume, and head, chest, and abdominal Abbreviated Injury Scale (AIS). The propensity score was then used as a covariate in our models. This allowed us to mitigate selection bias, as well as limit the number of variables included in the model to prevent overfitting given the small sample and number of outcome events. Propensity score distributions were examined. We also performed a sensitivity analysis weighted for the maximal overlap in propensity scores (Supplemental Methods, <http://links.lww.com/TA/C482>).

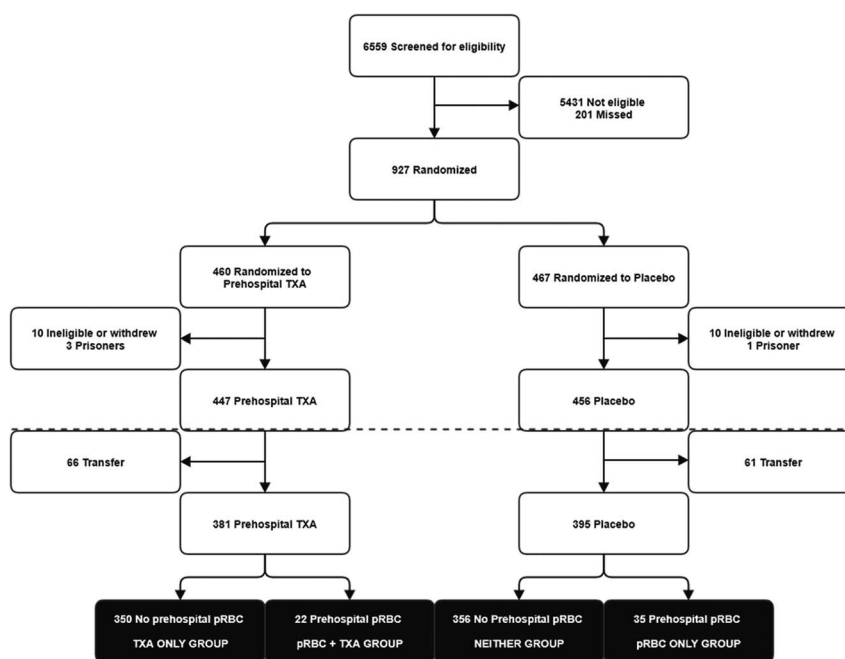
As the resuscitation groups were not randomized by design, in addition to the propensity to receive prehospital pRBC, we also adjusted the models for intensive care unit admission, emergent/urgent surgical procedures within 24 hours, and TXA in-hospital dose. Tranexamic acid in-hospital dose was included as it was part of the treatment of interest; however, patients could receive a second bolus plus infusion, infusion alone, or no further in-hospital TXA, representing a potential confounder. Covariates were selected a priori based on clinically relevant predictors of mortality in trauma and retained in the final models if they

changed the primary treatment effect of interest coefficient by greater than 10%.<sup>27</sup> Multiple organ failure, defined by Denver criteria, was included as a covariate in the 30-day mortality model but not the 24-hour mortality model given that it is calculated after 24 hours. Robust variance estimators were used to account for clustering by site. To evaluate potential differential effects of the resuscitation groups on mortality outcomes, we also tested several interactions, including prehospital SBP and heart rate, prehospital time, lactate level, ISS, and AIS for head, chest, and abdominal regions.

Data analysis was conducted using Stata v17MP (StataCorp; College Station, TX). Continuous data are presented as median (interquartile range [IQR]). Continuous data were compared using Wilcoxon rank-sum tests, and categorical data compared using  $\chi^2$ . Cox proportional hazard model discrimination was assessed using Harrell's C-statistic and global goodness-of-fit assessed using the Groennesby and Borgan test. All included variables met the proportional hazards assumption by evaluation with Schoenfeld residuals. The overall fraction of missing data was low at 1% and addressed using multiple imputation as described in the original trial. A two-tailed *p* value of 0.05 or less was considered significant. The University of Pittsburgh Institutional Review Board approved this study. Reporting of this study follows the STROBE guidelines for cohort studies (Supplemental Digital Content, <http://links.lww.com/TA/C483>).

## RESULTS

A total of 763 patients were included from the 903 patients in the original STAAMP trial. There were 350 (46%) patients in the TXA only group, 35 (5%) patients in the pRBC only group, 22 (3%) patients in the pRBC+TXA group, and 356 (46%) patients in the neither group (Fig. 2). Patients in the pRBC only



**Figure 2.** Study participant selection and resuscitation groups from the STAAMP trial. Participant selection below dotted line indicates cohort selection beyond the original trial population for this study.

and pRBC+TXA groups were sicker with higher ISS, lower SBP, and higher unadjusted 24-hour and 30-day mortality than patients in the TXA only or neither groups (Table 1). The distribution of propensity scores among the four resuscitation treatment groups are shown in eFigure 1, <http://links.lww.com/TA/C482>.

In the primary outcome model for 30-day mortality, resuscitation with pRBC+TXA was associated with a 35% relative decrease in the hazards of mortality compared with the neither group (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.45–0.94;  $p = 0.02$ ). There was no association between the hazards of 30-day mortality and resuscitation with TXA only or pRBC only when compared with the neither group (Table 2). Model diagnostics demonstrated excellent discrimination with Harrell’s C-statistic of 0.81, and acceptable calibration with non-significant Groennesby and Borgan test ( $p = 0.324$ ). The proportional hazards assumption was not violated ( $p = 0.259$ ). Analysis weighted toward maximal overlap of the propensity score demonstrated similar overall results (eTable 1, <http://links.lww.com/TA/C482>).

In the secondary outcome model for 24-hour mortality, resuscitation with pRBC-only was associated with a 61% relative reduction in the hazards of mortality compared with the neither group (HR, 0.39; 95% CI, 0.17–0.88;  $p = 0.02$ ). There was no association between the hazards of 24-hour mortality and resuscitation with TXA only or pRBC+TXA when compared with the neither group (Table 3), although the pRBC+TXA group was associated with a strong reduction in the point estimate of 24-hour mortality hazards with a  $p$  value of 0.06. Model diagnostics demonstrated good discrimination with Harrell’s C-statistic of 0.72, and acceptable calibration with nonsignificant Groennesby

**TABLE 2.** Cox Proportional Hazard Regression Resuscitation Group Results for 30-Day Mortality

|                     | HR        | 95% CI       | <i>p</i> |
|---------------------|-----------|--------------|----------|
| Resuscitation group |           |              |          |
| Neither             | Reference | —            | —        |
| TXA only            | 0.99      | 0.39–2.51    | 0.986    |
| pRBC only           | 1.05      | 0.57–2.00    | 0.842    |
| pRBC+TXA            | 0.65      | 0.45–0.94    | 0.022    |
| ICU admission       | 1.13      | 0.75–1.69    | 0.552    |
| MOF                 | 1.95      | 1.38–2.75    | <0.001   |
| Urgent procedure    | 1.24      | 1.17–1.33    | <0.001   |
| TXA dose            | 0.96      | 0.74–1.24    | 0.768    |
| Propensity score    | 76.67     | 50.43–122.72 | <0.001   |

ICU, intensive care unit.

and Borgan test ( $p = 0.472$ ). The proportional hazards assumption was not violated ( $p = 0.181$ ). Analysis weighted toward maximal overlap of the propensity score demonstrated similar overall results, although the pRBC+TXA group did reach statistical significance in the association with reduced hazards of 24-hour mortality (eTable 2, <http://links.lww.com/TA/C482>).

Several variables were significant in interaction testing. The pRBC+TXA group had significant interactions with prehospital SBP ( $p < 0.001$ ), lactate level ( $p < 0.001$ ), and AIS abdomen ( $p < 0.001$ ). All resuscitation groups had significant interactions with prehospital heart rate ( $p \leq 0.001$ ), AIS head ( $p < 0.001$ ), and AIS chest ( $p \leq 0.01$ ). Finally, the pRBC only and pRBC

**TABLE 1.** Patient Characteristics by Resuscitation Group

|                      | TXA (n = 350)        | pRBC (n = 35)        | TXA + pRBC (n = 22)  | Neither (n = 356)   | <i>p</i> |
|----------------------|----------------------|----------------------|----------------------|---------------------|----------|
| Age, y               | 39 (26–52)           | 53 (40–69)           | 39 (31–56)           | 37 (25–55)          | <0.001   |
| Sex (male)           | 254 (73%)            | 23 (66%)             | 11 (50%)             | 262 (74%)           | 0.090    |
| Blunt mechanism      | 305 (87%)            | 28 (80%)             | 18 (82%)             | 323 (91%)           | 0.130    |
| PH time, min         | 37 (28–46)           | 41 (31–63)           | 41 (34–49)           | 36 (30–45)          | 0.068    |
| PH SBP, mm Hg        | 128 (90–147)         | 84 (74–95)           | 86 (68, 102)         | 128 (89, 148)       | <0.001   |
| PH heart rate, bpm   | 118 (112, 128)       | 112 (90, 120)        | 115 (99, 140)        | 118 (112, 125)      | 0.074    |
| PH GCS score         | 14 (12, 15)          | 13 (3, 15)           | 15 (8, 15)           | 14 (12, 15)         | 0.120    |
| PH crystalloid, mL   | 400 (110, 850)       | 1,000 (700, 2,000)   | 910 (300, 1,400)     | 400 (0, 750)        | <0.001   |
| PH intubation        | 81 (23.1%)           | 17 (48.6%)           | 9 (40.9%)            | 85 (23.9%)          | 0.003    |
| ED SBP, mm Hg        | 130 (110, 144)       | 98 (82, 108)         | 95 (88, 110)         | 132 (110, 150)      | <0.001   |
| ED HR, bpm           | 105 (91, 117)        | 101 (89, 113)        | 109.5 (89, 129)      | 106 (91, 120)       | 0.590    |
| ED GCS               | 15 (11, 15)          | 11 (3, 15)           | 12.5 (3, 15)         | 15 (10, 15)         | 0.003    |
| ISS                  | 12 (5, 21)           | 22 (10, 34)          | 22 (17, 36)          | 10 (4, 20)          | <0.001   |
| 24-h pRBC, units     | 0 (0, 0)             | 5 (1, 11)            | 5 (2, 10)            | 0 (0, 0)            | <0.001   |
| 24-h plasma, units   | 0 (0, 0)             | 2 (0, 7)             | 0 (0, 5)             | 0 (0, 0)            | <0.001   |
| 24-h crystalloid, mL | 2,650 (1,100, 5,000) | 6,048 (3,900, 7,729) | 4,663 (2,000, 7,600) | 2,434 (1,010–4,925) | <0.001   |
| MOF                  | 24 (7%)              | 9 (26%)              | 4 (18%)              | 26 (7%)             | <0.001   |
| 3-h mortality        | 5 (1%)               | 3 (9%)               | 1 (5%)               | 4 (1%)              | 0.007    |
| 6-h mortality        | 8 (2%)               | 3 (9%)               | 1 (5%)               | 6 (2%)              | 0.066    |
| 24-h mortality       | 10 (3%)              | 5 (14%)              | 3 (14%)              | 9 (3%)              | <0.001   |
| 30-d mortality       | 24 (7%)              | 10 (30%)             | 4 (19%)              | 24 (7%)             | <0.001   |

Continuous variables presented as median (IQR).

Categorical variables presented as n (%).

PH, prehospital; ED, emergency department; MOF, multiple organ failure.

**TABLE 3.** Cox Proportional Hazard Regression Resuscitation Group Results for 24-Hour Mortality

|                     | HR        | 95% CI         | <i>p</i> |
|---------------------|-----------|----------------|----------|
| Resuscitation group |           |                |          |
| Neither             | Reference | —              | —        |
| TXA only            | 1.00      | 0.71–1.40      | 0.990    |
| pRBC only           | 0.39      | 0.17–0.88      | 0.024    |
| pRBC+TXA            | 0.33      | 0.10–1.08      | 0.068    |
| ICU admission       | 0.11      | 0.06–0.20      | <0.001   |
| Urgent procedure    | 1.58      | 0.89–2.81      | 0.081    |
| TXA dose            | 0.97      | 0.60–1.58      | 0.916    |
| Propensity score    | 991.57    | 475.57–2067.46 | <0.001   |

+TXA groups had significant interactions with prehospital time ( $p < 0.01$ ) and ISS ( $p < 0.001$ ). Overall, for the pRBC only and pRBC+TXA groups, patients with lower SBP, higher heart rate, higher lactate, more severe anatomic injuries, and longer prehospital time derived greater mortality benefit than less severely injured patients receiving similar prehospital resuscitation.

## DISCUSSION

We found that prehospital resuscitation with the combination of pRBC and TXA reduces the hazards of mortality at 30 days for injured patients at risk for hemorrhagic shock. Notably, there was no 30-day mortality benefit for patients that received either product in isolation. In addition, resuscitation with pRBC alone was associated with reduced mortality at 24 hours, consistent with prior literature,<sup>15</sup> while no early benefit was shown for TXA alone. There was a strong point estimate association of reduced 24-hour hazards for the pRBC+TXA; however, the  $p$  value was 0.06. This may reflect an underpowered analysis given the low numbers in this group, especially as our weighted sensitivity analysis showed the pRBC+TXA group to be significantly associated with a reduction in the hazards of 24-hour mortality.

Amidst the push of advanced resuscitative techniques into the prehospital setting, pRBCs are the most commonly available blood products, and almost exclusively through air medical transport agencies.<sup>28</sup> Prior reports demonstrate feasibility, safety<sup>29</sup> and a growing body of evidence supports a mortality benefit.<sup>9,14,15,30–32</sup> This was initially demonstrated in the literature from recent military conflicts wherein improved survival was observed for severely injured patients that received advanced prehospital care, including pRBC transfusion.<sup>9,30</sup> More recent civilian-based studies demonstrated a reduction in early mortality, as well as biochemical improvements in coagulopathy for those that received prehospital pRBC.<sup>14</sup> A large propensity-matched, single-center study matched severely injured patients that received prehospital pRBC to those that did not and, similarly, found a reduction in early mortality at 24 hours.<sup>15</sup>

Given the logistical challenges and relatively limited availability of prehospital blood products, it is important that we continue to pursue adjunctive hemostatic therapies. Tranexamic acid has greater shelf life than blood products and can be widely deployed in ground and air EMS agencies. Tranexamic acid impairs the biochemical conversion of plasminogen to plasmin, and at higher concentrations, inhibits plasmin, serving as potent adjunct

in resuscitation efforts as an inhibitor of fibrinolysis.<sup>33</sup> Our finding of 30-day but not 24-hour survival benefit of adding prehospital TXA to pRBC in the main analysis could suggest its antifibrinolytic mechanism may not be the only property responsible for its effects in recent trials. Notably, plasmin carries proinflammatory effects by activating endothelium and platelets, and also has a role in innate immune signaling.<sup>34,35</sup> Plasmin induces chemotaxis of monocytes and dendritic cells with release of proinflammatory cytokines.<sup>35,36</sup> Thus, the benefit of TXA observed in the current study may be through inhibition of plasmin and attenuation of inflammation, ischemia-reperfusion, and complement activation.<sup>37–40</sup>

Tranexamic acid effectively reduces surgical bleeding<sup>19</sup> and following the CRASH-2 trial<sup>22</sup> is increasingly utilized in prehospital care. This trial demonstrated a reduction in mortality from bleeding with early administration from time of injury at the receiving hospital, as compared with placebo, with the greatest benefit observed for those that received TXA within 1 hour of injury. Subsequently, the CRASH-3 trial compared TBI patients and in-hospital head-related mortality at 28 days for those that received in-hospital TXA within 3 hours of injury vs. placebo. Although a negative trial for the primary outcome, head-related mortality was reduced in the TXA arm at 24 hours and in sensitivity analysis for those with mild to moderate TBI, without observed differences in vasoocclusive or seizure events.<sup>41</sup> Morrison and colleagues<sup>42</sup> thereafter conducted a retrospective military study comparing hospital TXA versus no TXA in combat injuries for patients requiring pRBCs. They also demonstrated improved survival for the most severely injured patients with an associated improvement in coagulopathy.

Extrapolating this evidence to the field, EMS systems implemented TXA protocols<sup>43,44</sup> and retrospective studies demonstrate reduced fibrinolysis, a safety profile marked by venous thromboembolism, mixed results on early outcomes, and a paucity of long-term data.<sup>23,45,46</sup> The STAAMP trial addressed this evidence gap and showed a reduction in mortality in patients with TXA  $\leq 1$  hour, 3-gram total dose, and those with SBP of 70 mm Hg or lower, with no differences in seizure or thrombotic complications.<sup>25</sup> In another secondary analysis of STAAMP, for patients at greatest risk of hemorrhage, receipt of early TXA 1 hour or less was associated with a reduction in 30-day mortality risk.<sup>47</sup> A prehospital trial by Rowell et al.<sup>26</sup> investigated the impact of prehospital TXA on long-term neurologic function for patients with TBI. The authors found no difference in 6-month neurologic outcomes; however, there was lower 28-day mortality among patients that received a 2-g bolus only dosing regimen.

Taken together, the current body of literature indicates that TXA is safe and effective but should be administered in appropriately selected patient cohorts as evidenced by the subgroup analyses of several of these trials.<sup>22,25,41</sup> In the present study, we demonstrate the best outcomes for patients that received combined therapy with pRBC and TXA transfusion and similar to the original trial, the greatest benefit is observed for those most severely injured with severe shock and high ISS. A secondary analysis of the PAMPer trial also corroborates best outcomes for patients receiving combination prehospital therapies.<sup>13</sup> Severely injured patients in hemorrhagic shock who received combined prehospital pRBC and plasma showed the greatest mortality benefit.<sup>16</sup>

Trauma and severe shock cause early coagulopathy, endotheliopathy, and systemic inflammation that is difficult to reverse.<sup>48</sup> Our findings have important implications for improving the prehospital phase of trauma care. Optimal management requires prehospital, early, and multimodal resuscitation to ameliorate the complex pathophysiologic insult of injury. Early prehospital use of TXA may benefit patients who require prehospital pRBC resuscitation. Future investigations should aim to delineate the mechanisms responsible for combined resuscitation strategy benefits, as well as further define the injured patient populations most likely to benefit from prehospital TXA. The PATCH multicenter trial is currently underway and evaluates prehospital TXA in severe trauma.<sup>49,50</sup> Results of this trial will supplement the available evidence as we work to improve prehospital care of trauma patients at risk of exsanguination.

This study has several important limitations to acknowledge. First, this was a secondary analysis of a randomized trial with a hypothesis that differed from that of the original design. This resulted in relatively small sample sizes within our defined resuscitation groups. In particular, there were only 22 patients in the pRBC+TXA group, potentially making some of our analyses underpowered to find an effect, again such as no association with 24-hour mortality. Efforts to explore sensitivity analyses and better elucidate significant interactions led to unstable models. In addition, the majority of our patients sustained blunt trauma and were treated in mature trauma systems of four participating trauma centers by trial protocol. This may limit the generalizability of our findings for those with penetrating injury or patients served in differing trauma systems without access to advanced prehospital resuscitation. As noted, prehospital pRBC are limited in availability currently, although advances, such as freeze-dried products, may make prehospital blood products more readily available.

## CONCLUSION

For injured patients at risk of hemorrhage, prehospital resuscitation with a combination of pRBC and TXA is associated with a reduction in the risk of 30-day mortality. Prehospital pRBC transfusion alone was associated with a reduction in the risk of early mortality. Prehospital professionals with the capability to provide both pRBC and TXA should consider administering TXA to any patient meeting criteria for prehospital pRBC transfusion. Potential synergy appeared most robustly in longer-term mortality and further work to investigate mechanisms of this therapeutic benefit is needed to optimize the prehospital resuscitation of trauma patients.

## AUTHORSHIP

A.-P.D., L.H., J.B.B. participated in the literature search. A.-P.D., J.B.B. participated in the study design. A.-P.D., J.B.B. participated in the data collection. A.-P.D., J.B.B. participated in the data analysis. All authors participated in data interpretation. A.-P.D., L.H., S.L., J.B.B. participated in the writing of the article. All authors participated in the critical revision of the article for important intellectual content.

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## DISCLOSURE

The authors declare no conflicts of interest.

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