Prehospital Use of Tranexamic Acid for Hemorrhagic Shock in Primary and Secondary Air Medical Evacuation

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Abstract

Introduction: Major hemorrhage remains a leading cause of death in both military and civilian trauma. We report the use of tranexamic acid (TXA) as part of a trauma exsanguination/massive transfusion protocol in the management of hemorrhagic shock in a civilian primary and secondary air medical evacuation (AME) helicopter EMS program.

Methods: TXA was introduced into our CCP flight paramedic program in June 2011. Indications for use include age > 16 years, major trauma (defined a priori based on mechanism of injury or findings on primary survey), and heart rate (HR) > 110 beats per minute (bpm) or systolic blood pressure (SBP) < 90 mmHg. Our protocol, which includes 24-hour online medical oversight, emphasizes rapid initiation of transport, permissive hypotension in select patients, early use of blood products (secondary AME only), and infusion of TXA while en route to a major trauma center.

Results: Over a 4-month period, our CCP flight crews used TXA a total of 13 times. Patients had an average HR of 111 bpm [95% CI 90.71-131.90], SBP of 91 mmHg [95% CI 64.48-118.60], and Glasgow Coma Score of 7 [95% CI 4.65-9.96]. For primary AME, average response time was 33 minutes [95% CI 19.03-47.72], scene time 22 minutes [95% CI 20.23-24.27], and time to TXA administration 32 minutes [95% CI 25.76-38.99] from first patient contact. There were no reported complications with the administration of TXA in any patient.

Conclusion: We report the successful integration of TXA into a primary and secondary AME program in the setting of major trauma with confirmed or suspected hemorrhagic shock. Further studies are needed to assess the effect of such a protocol in this patient population.

Introduction

Massive hemorrhage remains a leading cause of preventable death in both military and civilian realms. Multiple strategies exist to mitigate the morbidity and mortality associated with such trauma, including both medical and technical interventions and the early deployment of surface and air ambulances to rapidly transport patients to advanced medical and surgical aid. Most recently, attention has been refocused on the use of antifibrinolytic agents as one of many medical strategies to mitigate the effects of massive hemorrhage.1 In the highly pragmatic series, the clinical randomization of an antifibrinolytic in significant hemorrhage-2 (CRASH-2) trial investigators observed a mortality benefit in those patients administered tranexamic acid (TXA) if they had actual or potential indicators of massive hemorrhage based on the mechanism of injury or presenting physiology. There are some methodologic considerations to the CRASH-2 trial one must consider before generalizing to other populations; however, this article was instrumental in thrusting TXA into the spotlight as a cost-effective, lifesaving, medical adjunct in the management of trauma-induced hemorrhagic shock. After the publication of the CRASH-2 trial and a review of the current literature on the use of antifibrinolytics for controlling or minimizing surgical bleeding, our group believed that there was sufficient evidence for the introduction of TXA into the prehospital arena as an adjunct in combating the effects of major blood loss before arrival to definitive care. In this report, we describe the integration of TXA as part of a trauma exsanguination/massive transfusion protocol in the management of hemorrhagic shock in a civilian, primary, and secondary air medical evacuation (AME) helicopter emergency medical services program.

Methods

The British Columbia Ambulance Service’s (BCAS) AirEvac and Critical Care Operations provides emergency medical
services for the province of British Columbia, covering 944,735 square kilometers (364,800 sq mi) and servicing a population of just under 5 million people (approximately 2.5 million in the Greater Vancouver area). The BCAS AirEvac and Critical Care Operation performs approximately 8,000 missions per year, via both fixed and rotary wing aircraft (KingAir 350, Lear 31A, and Sikorsky S76C+, respectively). TXA was introduced into our Critical Care Flight Paramedic (CCP) program in June 2011. Indications for the administration of TXA include age older than 16 years, major trauma (defined a priori based on the mechanism of injury or findings on primary survey per BCAS Code 99 Trauma Triage Protocols), and heart rate greater than 110 beats per minute or systolic blood pressure less than 90 mm Hg. Our protocol includes 24-hour online medical oversight and early activation of helicopter scene response (BCAS Autolaunch Program described online at www.bcas.ca), and emphasizes rapid initiation of transport, permissive hypotension in select patients (e.g. penetrating torso injury), and early use of blood products (secondary AME only based on the referring facility blood product availability). Guidelines for the timing of TXA administration include early infusion after transport has been initiated to a level 1 trauma center and as soon as possible after the time of injury (ideally <1 hour from the time of injury).3-6 Our guidelines includes a loading dose of 1 g TXA administered over 10 minutes followed by a 1-g infusion over 8 hours, which is similar to the CRASH-2 trial;7 however, both the loading and maintenance doses can be adjusted at the discretion of online medical oversight and/or by the accepting physician or trauma surgeon.3-6

Results

Over a 4-month period, our CCP flight crews used TXA on a total of 13 patients. Patient demographics and mission descriptors are summarized in Table 1. All patients had clinical criteria suggestive of actual or potential massive hemorrhage (Table 2) with a mean Revised Trauma Score of 5.96.7

For primary AME (scene response, N = 8), the average response time (from takeoff to patient side) was 33 minutes (95% confidence interval [CI], 19.03-47.72), the average scene time was 22 minutes (95% CI, 20.23-24.27), and the average time to TXA administration was 32 minutes (95% CI, 25.76-38.99) from first contact with the patient. Blood products (packed red blood cells) were transfused in 4 patients. All patients received an initial loading dose of 1 g TXA over 10 minutes and infusions started or prepared; it is unknown if accepting trauma centers continued the TXA infusion because our air medical program has a separate governance and data archiving system than the trauma receiving hospitals. There were no reported complications with the administration of TXA in any patient.

Discussion

In this report, we have described the integration of TXA into a massive hemorrhage/trauma exsanguination protocol as a medical addition to current standard practice. Based on the available evidence for the use of antifibrinolytics and the mechanism of action, these adjuncts are best used early in the clotting process and, thus, best administered in the prehospital setting provided all other basic principles of advanced trauma life support (ATLS) have been addressed.

Recent trauma literature has focused on damage control or hemostatic resuscitation.8-14 In fact, many other terms have been proposed to describe the paradigm shift in the management of major trauma, away from large volumes of crystalloids and the restoration of normal blood pressure, and more toward maintaining minimally acceptable perfusion and facilitating clot formation (or minimizing clot disruption). Regardless of what terms are used to describe the approach, what is most striking is the attention to the pathophysiology at a cellular level, with a de-emphasis on less sensitive parameters, such as systolic blood pressure or response to volume resuscitation. In particular, the concept of acute traumatic coagulopathy or acute coagulopathy of trauma shock underscores the potential value of prehospital antifibrinolytics (Fig. 1).15-18 Endothelial dysregulation driven by hypoperfusion, hypothermia, and acidosis results in upregulated thrombomodulin expression, tissue plasminogen activator, and activated protein C activity. Acute traumatic coagulopathy is characterized by these early and exaggerated effects of activated protein C on top of dysregulated activity of tissue plasminogen activator and, hence, increased fibrinolysis. This interaction between endogenous anticoagulants and hyperfibrinolysis results in impaired hemostasis completely unrelated to the dilutional coagulopathy that has historically been implicated with large-volume crystalloid resuscitation.9,10,11,19

The downstream effects include disruption of early clot formation. As such, it is postulated that the stabilization of these early clots is what may confer the morbidity and mortality

### Table 1. Patient Characteristics (N = 13)

| Age: 43 years (mean) | Sex: male 70% |
| Mechanism of injury | Motor vehicle incident: 9 |
| | Fall from height: 3 |
| | Other: 1 (industrial incident) |

### Table 2. Physiologic Variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean or Median&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI or IQR&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>111 beats per minute</td>
<td>90.71-131.90</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>16 beats per minute</td>
<td>11.16-22.24</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>91 mm Hg</td>
<td>64.48-118.60</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3,12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

IQR = interquartile range.

<sup>a</sup>IQR was calculated.

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**Footnotes:**

1. These adverse effects include increased coagulation, decreased fibrinolysis, and enhanced platelet aggregation.2-5
2. TXA can also be administered through the intravenous line or intubation tube.2-5
3. TXA can be administered with or without the use of antifibrinolytic agents.2-5
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17. TXA can be administered with or without the use of antifibrinolytic agents.2-5
18. TXA can be administered with or without the use of antifibrinolytic agents.2-5
19. TXA can be administered with or without the use of antifibrinolytic agents.2-5

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**References:**

benefit seen in the CRASH-2 trial, where they observed in their subgroup analyses a trend toward increased survival if TXA was given 1 hour or less from the time of injury.\textsuperscript{1,2}

As such, we emphasize the earliest possible administration of TXA after the time of injury, which underscores the value of having this adjunct available in the prehospital setting.

With these biochemical observations in mind, the administration of antifibrinolytics should occur as soon as possible after the injury and should not be delayed until the patient arrives at a trauma center. In our series, there was an average of a 10-minute interval from the initiation of rapid transport to a trauma center and the administration of a loading dose of TXA. What is explicit to our CCP training and practice and only made implicit in the methodology section is that TXA is not used by our CCPs until the primary survey is complete, critical interventions executed, and transport initiated. Exceptions might include if the trauma patient is trapped and extrication prolonged. Also, our training program does not overplay the role of TXA; specifically, an emphasis is placed on the fundamentals of ATLS. During the process of data review, it was noted that on several missions in which patients met the criteria for TXA administration, TXA was not administered because individual practitioners determined that there were other priorities that required their attention as they balanced critical interventions, resuscitation, and short flight times. For our traumatized patient population in shock, the use of TXA is one of several other strategies as part of our damage control resuscitation paradigm. Other strategies in our program, for example, include permissive hypotension (eg, in penetrating torso injury), minimizing crystalloid intravenous fluid (IVF) resuscitation to minimize the effect of clotting factor dilution, and the use of pH neutral crystalloid solutions (eg, PlasmaLyte; Baxter Healthcare Corporation, Deerfield, IL) to avoid the hyperchloremic metabolic acidosis associated with large-volume normal saline resuscitation. For secondary AME, we also use blood products, including packed red blood cells, fresh frozen plasma, and platelets in a 1:1:1 ratio, as local resource availability and time constraints allow for rapid transport to definitive surgical care. We also aggressively prevent further heat loss of our patients and actively warm them when needed using heat blankets, in-line IVF, and blood-warming devices. Finally, although our TXA dosing reflects what is currently reported in the trauma literature, the optimal dose of TXA has yet to be elucidated because higher doses (upward of 10 mg/kg) are often used in other clinical settings.\textsuperscript{1-6,20-22} In this case series, no patient received doses larger than 1 g, but our guidelines do allow for the use of larger or repeat doses to reflect 10-mg/kg dosing in larger individuals or when out-of-hospital times are prolonged with limited blood product availability or limited means to control hemorrhage during transport.

Important limitations exist to this case series presentation. Because of the small sample size and lack of database linking with trauma receiving hospitals, we are not in a position to report any robust signals on important outcome measures, such as mortality. With that in mind, we believe the current evidence as previously reported has sufficiently shown a favorable mortality benefit and safety profile to justify the use of TXA in other settings; instead, the goal of this series is to thrust the use of TXA into the spotlight for prehospital use. Also, all patients have continuous monitoring during AME and during drug or blood product administration, and though we did not report any adverse events with the use of TXA, we cannot report if the patient had any idiosyncratic drug reaction or other complications (eg, venous thromboembolism) during their hospital stay. Having said that, the safety profile of TXA seems well established, and, as noted, our CCPs did not observe or report any patient-related sequelae associated with its administration in the prehospital setting.

### Conclusion

In summary, we report the successful integration of TXA into an out-of-hospital primary and secondary air medical evacuation program in the setting of major trauma with confirmed or suspected hemorrhagic shock. We believe our experience with this pharmacologic intervention reflects the most up-to-date pattern of practice for major hemorrhage in trauma. Provided that other basic principles of prehospital care are adhered to, including rapid transport and those principles espoused by ATLS, we believe that TXA is an appropriate and important out-of-hospital adjunct for the management of major hemorrhage in trauma and can safely and effectively be incorporated into an air medical evacuation program.
References


