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REVIEW ARTICLE

Is there a role for antifibrinolytics in pelvic and acetabular fracture surgery?

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Abstract
Background Pelvic and acetabular fractures are rare, complex injuries associated with significant morbidity. Fixation of these injuries requires major orthopaedic surgery which in itself is associated with substantial blood loss owing to the extensile operative approach and prolonged operating time required to address the complex fracture anatomy. In order to reduce morbidity, a multifactor approach to blood conservation must be adopted.
Current role of antifibrinolytics in orthopaedic surgery The use of antifibrinolytics to reduce operative blood loss is well documented in many surgical specialties, including orthopaedic surgery. Elective spinal surgery and joint arthroplasty have benefited from the introduction of antifibrinolytics; however, their role in trauma and fracture surgery is not fully defined. Pelvic and acetabular fracture surgery would benefit from further investigation on the benefit and safety of these agents.
Conclusion Routine use cannot be recommended at this time but agents may be considered on a case-specific basis.

Keywords Pelvic and acetabular fracture · Tranexamic acid · Antifibrinolytics · Blood conserving strategy

Pelvic and acetabular fractures amount for 3–8 % of all skeletal injuries, with the majority occurring as a result of high velocity trauma [1]. As a result of both the severity of the injury and the required major surgical reconstruction, the reported morbidity rates are high. The management of these injuries is extremely challenging due to the complex fracture anatomy, surrounding major neurovascular structures, the large degree of displacement and the associated high-energy trauma.

One of the major contributory factors to the high morbidity and mortality of these patients is blood loss, both from the initial injury and the major surgical intervention required for reconstruction. Some authors have argued that early surgical intervention leads to a greater blood loss in patients [2, 3]. This classical teaching has been disproven in recent years with recent studies demonstrating no significant increase in blood loss with early intervention in patient with acetabular fractures [4, 5]. Further studies have shown that early intervention leads to a greater accuracy of reduction, less morbidity and shorter length of stay [6–8]. Thus, the current practice is to intervene earlier than traditionally advocated, and an emphasis is placed on strategies to reduce blood loss and transfusion requirements. Total volume lost from these operations has been reported to be as high as 1232 to 2818 mL [9, 10]. Intra-operative haemorrhage increases surgical risk by affecting safe surgical exposure and prolonging operating time. The haemorrhage in combination with surgical dissection and blood transfusion can lead to significant coagulopathy developing. This coagulopathy may require blood transfusion and substitution coagulation products. Transfusion is required in 24 % of isolated pelvic fractures, 35 % of isolated acetabular fractures and 57 % of combination injuries, with a mean transfusion of 4.81 units [11]. The required allogeneic blood products carry the risk of infection (bacterial contamination and/or viral transmission), blood group mismatch, transfusion related lung injury and haemolytic and allergic reactions [12, 13]. In elective cardiac surgery,

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this has an impact on patient morbidity, length of stay and subsequently healthcare cost [14]. In trauma patients, the development of coagulopathy is multifactorial due to the dilution, consumption and dysfunction of platelets and coagulation factors. Trauma-induced coagulopathy has a significant mortality and can be present in up to a third of severely injured trauma patients [15]. Thus, in order to reduce perioperative morbidity, and subsequently healthcare cost, a multimodal approach to blood conservation involving surgical, anaesthetic and pharmacological factors must be adopted [12].

The fibrinolytic system can be used as a potential target when trying to reduce intra-operative blood loss. Fibrinolysis is a physiological process in which the products of the coagulation cascade are broken down by activated plasminogen. The inactive proenzyme plasminogen is converted to the active enzyme plasmin by the action of tissue-type plasminogen activators (t-PA) and urokinase-type plasminogen activator (u-PA). Plasmin then degrades fibrin into soluble fibrin degradation products [16]. Inhibiting this process prevents fibrin break up, thus maintaining clot stability and preventing excessive blood loss. Inhibition of this pathway via pharmacological methods has been shown to reduce bleeding in surgical patients [12, 17]. The use of antifibrinolytics has also been shown to reduce the rate of blood transfusion [13]. In acute severe trauma, there is an increase in fibrinolysis, which leads to early coagulopathy. This coagulopathy then in turn adversely affects the mortality rate [18, 19]; it is in this period that antifibrinolytics are the most effective. In later phase of severe trauma, patients can develop thrombotic disseminated intravascular coagulation, which would be a contraindication to antifibrinolytic use and thus the timing of administration in trauma patients is crucial. Safety concerns exist, however, that these drugs produce a hypercoagulable state by inhibiting the natural defence against thrombosis [17], thus increasing the risk of post-operative thrombosis complications. Venous thromboembolism following trauma is a well-known complication, and has been estimated to occur in 61 % with pelvic fractures without prophylaxis [20]. With prophylaxis, the prevalence ranges from 2–33 % [21, 22]. The CRASH-2 study identified no increase in the risk of vascular occlusive events. The authors, however, were cautious with their conclusions as events may be have been under-reported, and thus, they would not excluded an increased risk of vascular occlusive events with the use of tranexamic acid in trauma patients [23]. Aprotinin, Tranexamic acid and epsilon-aminocaproic acid are widely available and commonly used antifibrinolytics. These agents are used in scenarios where there is activation or dysregulation of the fibrinolytic system. Aprotinin is derived from bovine lung and is a non-specific serine protease inhibitor, which is thought to act by inhibiting the seine protease plasmin and preventing its attachment to fibrin via lysine residues on the target molecules [12]. First used in clinical practice in the 1950s, it became widely used and the most popular antifibrinolytic. It was shown to significantly reduce intra-operative bleeding and rate of transfusion in cardiac surgery [24, 25]. However, recent studies by Mangano et al. [26] and the BART trial [27] have demonstrated an increase in mortality and morbidity associated with renal failure, myocardial infarction and heart failure. Its licence has been withdrawn secondary to these findings but ongoing research in this area may see it return to clinical practice. Tranexamic acid and epsilon-aminocaproic acid are synthetic lysine analogues which are used widely across a number of specialities including orthopaedics. Both act by reversibly binding to plasminogen, preventing its activation to plasmin and thus fibrinolysis [17]. Unlike aprotinin, these lysine analogues have not been shown to have an increased risk of myocardial infarction and there are to date no definitive data proving that they have a detrimental prothrombotic effect [12]. As such, they have been adopted into routine practice in several surgical specialities including orthopaedics, and the antifibrinolytic effect is also beneficial in the hyperfibrinolysis state associated with acute traumatic coagulopathy.

The use of antifibrinolytics is still relatively new and their role is yet to be fully defined in the context of orthopaedic surgery. Major orthopaedic operations are associated with significant blood loss and provide a challenge in blood conservation. Though further study is needed in the area, the benefit of these agents and their safety has been proven in the context of both spinal surgery and joint arthroplasty (Table 1). With regard to spinal surgery, benefit has been shown with their use in both the adult and paediatric setting. A Cochrane review on their use in paediatric scoliosis surgery concluded that there was a significant reduction in both total blood loss and the amount of transfused blood required by patients. No adverse events were recorded in the patient group in the study [28]. In adult spinal surgery, Wong et al. demonstrated a 25 % reduction in blood loss in patients undergoing spinal fusion surgery [29]. Gill et al. conducted a meta-analysis and their conclusions support the evidence that these agents reduce both blood loss and transfusion requirements [30]. In terms of knee and hip replacement surgery, a meta-analysis by Zufferey et al. demonstrated a reduction in the rate of blood transfusion with aprotinin and tranexamic acid [13]. There was no such benefit with epsilon-aminocaproic acid and the authors felt there was insufficient data for a safety assessment available. Three years later, a second meta-analysis showed more favourable results. Kagoma et al. [31] concluded that antifibrinolytics reduced bleeding and transfusion requirements

Table 1 Summary of antifibrinolytics in spine surgery and total joint arthroplasty

	Author	Year	Type	Main finding
Spine	Tzortzopoulou et al. [28]	2008	Cochrane review	In paediatric scoliosis surgery, antifibrinolytics reduced the amount of transfused blood (−327 mL; 95 % CI −469.04 to –185.78) and the amount of blood loss (−427 mL; 95 % CI −602.51 to −250.56)
	Wong et al. [29]	2008	RCT	Tranexamic acid reduced blood loss by 25 % in adult spinal fusion patients but had no impact on perioperative transfusion and length of hospital stay
	Gill et al. [30]	2008	Meta-analysis	Antifibrinolytic agents reduce levels of total blood loss and transfusions associated with spine surgery. The effect size for total blood loss ranged from −0.668 (95 % CI, −0.971 to −0.365) to −0.936 (95 % CI, −1.240 to −0.632). The effect size for total blood transfusions ranged from −0.466 (95 % CI, −0.764 to −0.167) to −0.749 (95 % CI, −1.046 to −0.453)
Total joint arthroplasty	Zufferey et al. [13]	2006	Meta-analysis	Tranexamic acid reduced the rate of blood transfusion (OR 0.17; 95 % CI 0.11–0.24). Aprotinin was also of benefit (OR 0.43; 95 % CI 0.28–0.64) but ε-aminocaproic acid was not beneficial
	Kagoma et al. [31]	2009	Systematic review	Antifibrinolytics reduce the need for blood transfusion after total hip and knee joint arthroplasty, without increasing the risk of thromboembolic events

significantly in patients undergoing primary hip and knee arthroplasty surgery. Analysis of the 26 randomized clinical trials included demonstrated that the routine use of these agents reduced bleeding by at least 300 mL and reduced the need for transfusion by 52 %. With regard to venous thromboembolic events, there was no difference in risk with the use of antifibrinolytic agents. However, the authors were cautious of this conclusion due to the small number of events reported and lack of systematic investigation and reporting of theses complications.

Multiple studies have demonstrated the benefit of antifibrinolytics in elective spinal and joint replacement surgery. Extrapolating the potential use of these agents in trauma patients from elective surgery studies is not justified due to the unique aspects of post-traumatic coagulopathy and as such their role in trauma surgery is less defined. Acute traumatic coagulopathy is preset in 10–25 % of patients following major trauma [32] which has been associated with a 3–4 times increase in patient mortality [33]. Mitra et al. identified that post-traumatic coagulopathy was associated with early death post-trauma in an Australian population, and that it was independent of demographics, injury severity, the use of blood products and surgical intervention [34]. A recent Cochrane review looked at "Antifibrinolytic drugs for acute traumatic injury" and concluded that antifibrinolytics imparted a 10 % reduction in the risk of death, and that they did not affect the need for blood transfusion or surgery, and there was no evidence of an increased risk of vascular occlusive events [35]. However, this review was largely based on the CRASH-2 trial data alone. CRASH-2 trail was a multicentre randomized placebo-controlled trial of 20,211 patients in 40 countries, which examined the role of a loading dose of tranexamic acid followed by an infusion over 8 h. The CRASH-2 trial demonstrated a significant reduction in all-cause mortality, and in deaths due to bleeding in trauma patients [23]. However, this benefit was seen primarily if administered in the first 3 h and these agents are most effective within the first hour where the risk of death due to bleeding can be decrease from 7.7 to 5.3 %, but outside of this window there was an increase in mortality [36]. The need for blood transfusion was not significantly affected by the administration of tranexamic acid with 50.4 % of patients (mean 6.06 units) in the intervention group requiring transfusion compared with 51.3 % of patients (mean 6.29 units) in the placebo group [36]. With regard to vascular occlusive events, there was no increase risk observed during the study period, with 204 (1.01 %) patients experiencing a venous occlusive event (pulmonary embolism or deep vein thrombosis) and 200 (0.99 %) experiencing an arterial occlusive event (myocardial infarction or stroke). Eighty-one (0.4 %) patients died secondary to their vascular occlusive event. Further analysis of the CRASH-2 data demonstrated that patients with more severe bleeding, which was assessed by the predicted risk of death due to bleeding, had a significantly increased risk of all type of vascular occlusive events [37]. Following on from their findings, the CRASH-3 study is currently ongoing to assess tranexamic acid's role in traumatic brain injury [23]. In combat trauma patients, the Military Application of Tranexamic Acid in Trauma and Emergency Resuscitation (MATTERs) study investigated the use of Tranexamic acid in combat injury and its effect on total blood product use, thromboembolic complications and mortality. The MATTERs study showed a lower mortality in the treatment group, those who received

tranexamic acid, despite patients being more severely injured [38]. This benefit was not observed until after 48 h and authors suggested that the benefit of tranexamic acid may be an anti-inflammatory effect. Coagulation, fibrinolysis and inflammation are interwoven pathophysiological processes and it is difficult to separate them. The MATTERs study found a relative reduction in mortality of 23 % in the first 24 h after administration of Tranexamic Acid, and though this did not reach statistical significance, this may be secondary to the study size rather than a lack of association. Such a reduction in the first 24 h would imply that the tranexamic acid effect is on coagulation and not inflammation. The anti-inflammatory effect of tranexamic acid has not been investigated to date by a randomized control trial and thus cannot be excluded [39].

To date, there is paucity of data investigating the use of antifibrinolytics in pelvic and acetabular trauma surgery. McMichan et al. examined the use of Aprotinin in trauma patients with hypovolemic shock and major fractures of the lower limb and or pelvis [40]. There was no difference between patient mortality and need for surgical intervention in the study; however; there was no data reporting on the venous thromboembolism rate or transfusion requirements [40]. Logically, these pharmacological agents could be of significant benefit in this orthopaedic subspecialty and it is currently under investigation. Elements of their use that have yet to be fully defined included the dose regime, which lacked heterogeneity in the above studies, as well as the optimal timing of administration of agents. The short half-life of these agents, approx 2 h, also raises the question of benefit from multiple dose regimens to further reduce blood loss. A randomized double-blinded clinical trial is ongoing in the University of Missouri-Columbia investigating "Hemostasis in open acetabulum and pelvic ring surgery using tranexamic acid" [41]. Its primary outcome measure will be intra-operative blood loss, but secondary outcome measures will included total blood loss, transfusion requirements, hospital costs and the occurrence of complications including venous thromboembolism (VTE), infection, and need to return to the operating room. Patients will receive 10 mg/kg TXA loading dose approximately 15 min before surgical start time and then 1 mg/kg/h TXA infusion over 10 h; the placebo group will receive normal saline in the same dose. The outcome of this RCT will be eagerly anticipated, and the expected completion date is August 2016.

In the presence of a severely injured patient, resuscitation and diagnosis must be performed in tandem. As stated previously, there is a high incidence of acute traumatic coagulopathy in the severely injured patient and also a significant mortality. Traditionally, the diagnosis and monitoring of coagulopathy is performed via routine plasma-based test such as prothrombin time (PT), activated partial thromboplastin time (APTT) and the international normalisation ratio. However, studies have shown that they do not help predict the extent of bleeding in the critically ill and trauma patient [42] and are inappropriate in the trauma setting [43]. One solution may be the use of thromboelastography (TEG®), which is a viscoelastic whole blood assay, which evaluates clot strength in real time that can help target therapy to facilitate haemostasis. In observational studies, TEG has been shown to aid in the early diagnosis of acute trauma coagulopathy and help predict blood product transfusion and mortality but randomized control trials have not to date proven its effect on blood product transfusion, mortality and other patient outcomes [44]. TEG can identify patients with significant hyperfibrinolysis but the role of thromboelastography-directed antifibrinolytic therapy in trauma patients to identify which patients should receive antifibrinolytics warrants further study.

In conclusion, antifibrinolytic agents have a benefit in major orthopaedic surgery with regard to decreasing blood loss and transfusion requirements. Antifibrinolytics are widely available and inexpensive techniques in blood conservation. While there is a theoretical risk of thrombosis with the use of these agents due to their mechanism of action, this has not been proven to occur in the clinical studies discussed. The routine use of these agents with regard to pelvic and acetabular fracture surgery cannot be endorsed at this time, and the outcome of the ongoing clinical trial is awaited. Regardless these agents remain a viable option in a multimodal approach to blood conservation in orthopaedic surgery and there use may be considered on a case-specific basis by the operating surgeon and anaesthetist.

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