ORIGINAL ARTICLE

Administration of tranexamic acid for victims of severe trauma within pre-hospital care ambulance services (PHCAS) in Malaysia

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ABSTRACT

Introduction: Trauma is a Global threat and the 5th highest cause of all-cause mortality in Malaysia caused predominantly due to road traffic accidents. Majority of trauma victims are young adults aged between 21-40 years old. In Malaysia, 24 out of 100,000 population die annually due to trauma, rating us amongst the highest in South East Asia. These alarming figures justify aggressive preventive and mitigation strategies. The aim of this paper is to promote the implementation of evidence-based interventions that will reduce the rate of preventable death because of trauma. Tranexamic acid is one of the few interventions in the early management of severe trauma with level-one evidence. Tranexamic acid has been proven to reduce all causes of mortality and mortality due to bleeding. Evidence proves that it is most effective when administered early, particularly within the 1st hour of trauma. This proposed guideline is formulated based upon quality evidence from multicentre studies, clinical practices in other countries and consideration of the local demographic factors with the intent of enabling an easy and simple pathway to administer tranexamic acid early in the care of the severely injured.

Conclusion: The guideline highlights select pre-hospital criteria's and the methods for drug administration. The authors recognise that some variants may be present amongst certain institutions necessitating minor adaptations, nevertheless the core principles of advocating tranexamic acid early in the course of pre-hospital trauma should be adhered to.

KEY WORDS:
Hemorrhage Control, CRASH 2, PATCH-Study, Trauma Management, Emergency Medicine

INTRODUCTION

Trauma is a global threat. A recent study in 2013 reported that 973 million people suffered injuries globally with 4.8 million fatality. The study also reported that 30% of all-cause injury related to death was due to road traffic accidents.[1]

Trauma ranks 5th highest of all-cause mortality in Malaysia, representing 9.74% of principal causes of death in Ministry of Health hospitals.[2] Motor vehicle crashes remain the predominant cause of deaths related to trauma,[3] evidenced by 24 deaths per 100,000 population annually.[4] This differs from neighbouring South East Asian countries such as Indonesia, Philippines and Singapore where a lesser incidence of 15.3, 10.5 and 3.6 deaths/100,000 population respectively.[4]

The majority of trauma victims who succumb to trauma in Malaysia were between the ages of 21-40 years.[3] This age group represents a large portion of the nation's youth and human resource. Such loss of lives not only represents a calamity for families and friends but causes a significant reduction to the national socio-economic and human capital resource. The current statistics justify the introduction of a new evidence-based policies and guidelines that can mitigate these alarming figures. Effective strategies should focus on the development of an improved trauma system coupled with the provision of evidence based clinical practice. It is therefore important that clinical stakeholders strategize, and address trauma related preventable deaths.

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Priority should be given to early effective management of exsanguinating traumatic haemorrhage. If evidence-based interventions are administered early during the pre-hospital phase, there will be a significant reduction in mortality. The administration of tranexamic acid is one of the few interventions for haemorrhage in the early management of trauma with level one evidence. We have outlined a comprehensive guideline that is applicable to the pre-hospital setting for early administration of tranexamic acid for victims of severe trauma.

The reduction in mortality demonstrated from the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2)[15] study suggests that trauma systems within the low- and middle-income countries would stand to benefit the most. Therefore, a clear and delineated guide to early administration of tranexamic acid should prove beneficial in Malaysia. This document will entail the provision of tranexamic acid for severe trauma victims in the Malaysian pre-hospital care system (PHCAS).

What is Tranexamic Acid?

Tranexamic Acid [trans-4-(aminomethyl) cyclohexanecarboxylic acid] is a synthetic derivative of amino acid lysine, a potent anti-fibrinolytic which is clinically proven to inhibit breakdown of fibrin clots. It has no proven pro-thrombotic effects but promotes the stability of the already formed fibrin clot. Hence, it is a vital adjunct in the clinical management of severe traumatic haemorrhage and haemorrhage attributed to surgery, intra-partum and post-partum haemorrhage.

Tranexamic Acid: Mechanism of Action

Tranexamic Acid competitively inhibits the activation of plasminogen to plasmin by binding to the plasminogen kringle domains. These lysine-binding sites are important for the binding of fibrin. This action reduces the conversion of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, pro-coagulant factor V, VII and other plasma proteins.[5,6] Tranexamic Acid, in a similar manner, competitively inhibits the activation of plasminogen-activator which is absorbed to the fibrin.[5] In much higher concentrations, tranexamic acid acts as a non-competitive inhibitor of plasmin. Actions of Tranexamic Acid are similar to Aminocaproic Acid but with 10 times more potency in vitro. Compared to Aminocaproic Acid, tranexamic acid binds more strongly to both the strong and weak receptor sites of the plasminogen molecule.[6] Recent studies relating to perioperative administration of tranexamic in cardio pulmonary bypass surgery suggest that tranexamic acid plays a pivotal role in reducing the subsequent systemic inflammatory response, associated with reduction in circulatory pro-inflammatory cytokines IL-6 and IL8. It is also believed that there is a strong correlation between the systemic inflammatory response and the haemostatic cascade, in which tranexamic may play an extended role beyond just inhibiting fibrinolysis.[7-9]

Tranexamic Acid: Adverse Reactions

Tranexamic acid is a drug with a high safety profile. However, due to its anti-fibrinolytic properties, caution should be emphasized in patients with previous history of thrombo-embolic disease or suspected active intra-vascular clotting.[6] Incidence of convulsions has been associated with high doses of tranexamic acid (>80-100mg/kg).[10,11] Rapid intravenous administration may induce reflex hypotension. Reproduction studies performed in animals have not revealed evidence of impaired fertility or adverse outcomes on the foetus. It is a pregnancy category-B drug and therefore should be used in pregnancy only if indicated. Other reported adverse reactions range from gastrointestinal disturbances (nausea, vomiting and diarrhoea) and giddiness. However, these symptoms are un-common in low doses.[6]

Methodology of Creating this Proposed Guideline

The development of this proposed guideline was initiated by members of the Trauma Special Interest Group, College of Emergency Physicians of Malaysia. The members developed a steering committee which consisted of senior Emergency Physicians and Trauma Physician Subspecialty Fellows. The committee set out to describe the main objectives and goals of preparing these guidelines. A web-based literature search was conducted to identify evidence[8,9,12-15] as well as existing guidelines[16-22] for the use of tranexamic acid in pre-hospital severe trauma. Utilizing the evidence and research findings, the committee then created an initial draft of the proposed guideline based upon the unique demographics relevant to the Malaysian Emergency Trauma Services. The drafted guideline was then distributed to 6 different pre-hospital trauma services in Malaysia. The draft was peer reviewed by Emergency Physicians and the pre-hospital team members. Feedback was provided via a standard pro forma utilizing the Likert Scale and a section for free comment. Based upon the feedback and recommendations, the committee then produced the final version of this proposed guideline.

Evidence Based Recommendations and Efficacy of Tranexamic acid

The use of Tranexamic acid has been widely demonstrated to reduce morbidity and mortality in patients with major bleeding. It has been shown to reduce bleeding and transfusion requirements in patients undergoing elective surgeries[8,9,23-25] and in patients with post-partum haemorrhage.[26,27] CRASH-2 was the largest randomised multi-centre placebo controlled trial that analysed the effects of tranexamic acid in trauma patients with significant haemorrhage.[15] The study involved 274 hospitals spanning 40 countries involving 20,211 patients. CRASH-2 study conducted in 2010 demonstrated an all-cause mortality reduction with administration of tranexamic acid in victims of severe trauma. All-cause mortality was reduced from 16.0% to 14.5%, with an 1.5% absolute reduction, relative risk (RR) of 0.91, 95% confidence interval (95%CI): 0.85, 0.97, and number needed to treat (NNT) of 67, and the risk of death caused by bleeding was reduced from 5.7% to 4.9% (0.8% reduction, NNT 121). A sub-group analysis of the CRASH-2 study also identified that early administration of tranexamic acid is prudent in reducing the risk of death from bleeding.[14,28,29] Tranexamic acid administered ≤1 hour after injury was shown to be more protective (2.4% risk reduction, RR=0.68; 95%CI: 0.57, 0.82) when compared administering 1-3 hours after injury (1.3% risk reduction, RR=0.79; 95%CI: 0.64, 0.97; NNT=77). Comparatively tranexamic acid administered ≥3 hours after severe injury was associated with an increased risk of death from bleeding (1.3% increase risk, RR=1.44; 95%CI: 1.12, 1.84; NNH=77), but no difference in

all-cause mortality. The CRASH-2 study also found that there was no significant difference between incidence of fatal and non-fatal vascular occlusive events when compared between the tranexamic and placebo group (1.7% vs 2.0%, RR=0.84; 95%CI: 0.68, 1.02).[15]

The European guideline on the management of major bleeding and coagulopathy following trauma has recommended the administration of tranexamic acid as early as possible to the trauma patient who is bleeding or at risk of significant hemorrhage.[16] Tranexamic acid was recommended to be administered at a loading dose of 1gram infused over 10min, followed by an intravenous infusion of 1gram over 8-hour (Grade 1A). The guidelines also recommend that tranexamic acid be administered within 3-hour after injury (Grade 1B), preferably with the first dose administered en-route to the hospital (Grade 2C). Many ambulance services around the world have created protocols for the administration of tranexamic acid in major trauma including the UK Ambulance Services.[20,29] Although the CRASH-2 study did not particularly focus on pre-hospital administration of tranexamic acid, the evidence gathered was felt sufficient for its recommendation.[29] The PATCH-Trauma Study is another international, multi-centred, double blinded, placebo controlled trial which analyses the efficacy of pre-hospital tranexamic acid for the severely injured patients. The PATCH-Trauma study focuses on the cohort of patients at risk of traumatic coagulopathy within a framework of an advanced trauma system.[13] This study is currently on-going and is estimated to be completed in 2020. However, the authors of the PATCH-Study argue on the generalisation, applicability and predictability of the CRASH-2 recommendations in nations with advanced trauma systems, which have already achieved low rates of preventable trauma deaths. They go further to state that only <2% of the study population in CRASH-2 constituted centres with advanced trauma systems and therefore the blanket recommendation of its use in such centres may be somewhat premature.[30] It is also postulated that vaso-occlusive events in CRASH-2 tranexamic arm may have been under-detected due to less extensive use of diagnostic modalities such as CT-Scans and ultrasound.[30] The PATCH-Study also included clinical data sets that would further assist us in understanding the pathophysiology of acute traumatic coagulopathy and the effects of tranexamic upon the haemostatic and systemic inflammatory system.[13, 30]

The PATCH-Trauma Study utilises a different approach in administering the initial tranexamic bolus. The 1gram initial dose (100mg/ml concentration in 10mls vial) is administered using a "slow push of the syringe" method[13] as compared to the 1gram (1gram tranexamic acid diluted in 100ml of 0.9% normal saline solution) "infused over 10 minutes method" utilised in the CRASH-2 study. Hypotension has been observed when tranexamic acid is administered in a rapid bolus and therefore, caution should be emphasized during this phase.[6]

Tranexamic Acid in Paediatric Trauma

The role of tranexamic acid in paediatric surgery has been well documented.[31] There has been strong evidence to demonstrate the reduction in blood loss and transfusion requirements in cardiac, scoliosis and craniosynostosis surgery.[32-34] The use of tranexamic acid in paediatric scoliosis and cardiac surgery demonstrated no increase in thromboembolic rates and the drug has a high safety profile even in dosing regimens approaching 100mg/kg.[17] However, unlike in adults, there is inadequate research to offer a strong level of evidence to show the benefit of tranexamic in paediatric major trauma.[31] Nevertheless, major surgery and trauma are known to trigger a similar haemostatic host response, both posing a challenge to homeostasis. Recognising this, the Royal College of Paediatrics and Child Health (RCPCH) United Kingdom has issued an evidence statement proposing the use of tranexamic acid for all children sustaining major trauma.[17] Denying this adjunctive care to severely injured children simply due to the lack of trauma trials and evidence is unfounded, given the ample evidence available in other paediatric settings and clear mortality benefit seen in adult trauma. The RCPCH and Neonatal and Paediatrics Pharmacist Group (NPPG) Medicines Committee (UK) has rolled out a recommended dosing consensus based on paediatric age.[31] Adolescents aged 12 and above are recommended to have similar doses as adults. For children <12 years of age, the loading dose is recommended at 15mg/kg (max 1gram) diluted in a convenient volume of sodium chloride 0.9% or glucose 5% and given over 10 minutes. Subsequently a maintenance infusion is administered at a dose of 2mg/kg/hour for at least eight hours or until bleeding stops. Suggested maintenance dilution is 500mg in 500ml of sodium chloride 0.9% or glucose 5% given at a rate of 2ml/kg/hour. The Hospital for Sick Children, Ontario Canada has proposed tranexamic acid as part of the massive haemorrhage protocol and that it be provided for children with any one of the following criteria, i) Systolic blood pressure (<80mmHg for <5 years and <90mmHg for >5 years); ii) poor blood pressure response to crystalloid 20-40ml/kg; and iii) obvious significant bleeding.[18]

Despite strong supporting evidence and recommendations for use in paediatric trauma, the authors recognise the difficulties involved in administering the drug for paediatric patients in the primary healthcare services. The potential task relies on the out of hospital preparation and dilution of drugs, administration of weight specific drug dose, attempts and time spent on securing potentially failed or unnecessary intravenous access and the current number of paramedics/ambulance available during an emergency response. Such tasks may be less challenging for adolescent and adult patients who are given a standard 1gram regime dose and have easier intravenous access. The physiological parameters and response to injury differ according to age, adding further challenges to the team in identifying paediatric patient criteria for pre-hospital tranexamic acid. The authors propose severe trauma patients <12 years old are rapidly assessed, stabilised, transported to the most appropriate facility and tranexamic acid be considered early during trauma reception. However, the focus should be given to administering the drug <3 hours from injury. For individual institutions that have specifically trained personnel and adequate resources, tranexamic acid administration in children may be considered based upon readily available local institutional guidelines and protocols. This current proposed guideline addresses the administration of pre hospital tranexamic for severe trauma in adolescents and adults only.

Table I: Pre-Hospital Severe Trauma Tranexamic Acid Administration Criteria

Trauma < 3 Hours and Age ≥ 12 Years Old	Inclusion Criteria	Suspected severe internal or external hemorrhage
		Systolic blood pressure < 100 mmHg with associated heart rate > 100 /min
		Traumatic amputation proximal to the wrist or ankle
		Penetrating trauma to the neck, chest, abdomen, pelvis or posterior trunk
	Consult Medical Direction	Heart rate > 120/min
		Entrapment
Exclusion Criteria		Isolated head injury
		Known hypersensitivity to tranexamic acid
		Known history of thromboembolic disease or suspected active intravascular clotting
		Priority required for continuous live saving intervention
		Cardio respiratory arrest

Criteria for Tranexamic Acid Administration

The pre-hospital care ambulance service team will administer 1gram of intravenous tranexamic acid for severe trauma victims based upon select criteria. These criteria consist of three categories, "exclusion criteria, "inclusion criteria" and "criteria requiring medical direction". Tranexamic acid will not be administered in the event the patient poses any one of the exclusion criteria. Pre-hospital tranexamic acid will be administered directly in the event that any one of the inclusion criteria are fulfilled. If there are no inclusion criteria, criteria requiring medical direction can be considered after discussing with either the medical officer or emergency physician in charge.

Exclusion Criteria

a) Trauma >3 hours or age <12 years
b) Isolated head injury; (await the results of the CRASH-3 trial)
c) Known or suspected hypersensitivity to tranexamic acid.
d) Known history of thromboembolic disease or suspected active intravascular clotting
e) Priority required for live saving intervention
f) Cardiorespiratory arrest

Inclusion Criteria

a) Suspected internal or external severe haemorrhage
b) Systolic blood pressure <100mmHg with associated heart rate >100/min
c) Traumatic amputation proximal to the wrist or ankle
d) Penetrating trauma to the neck, chest, abdomen, pelvis or posterior trunk

Criteria Requiring Medical Direction

a) Entrapment
b) Heart rate >120/min

Severe haemorrhage

Any patient with Class II-IV haemorrhage as defined by the Advanced Trauma Life Support (ATLS©) clinical classification of haemorrhage;

I) Suspected severe internal haemorrhage
When a medical responder is clinically suspicious that a trauma victim is experiencing severe concealed haemorrhage, (not pertaining to isolated intracranial haemorrhage) associated with but not limited to the following examples;

a. Severe abdominal pain associated with or without abdominal distension, suspicious of intra-abdominal bleeding
b. Clinically evident two or more long bone fractures
c. Severe tenderness over pelvic region suspicious of a pelvic fracture with associated retro-peritoneal haemorrhage

II) Suspected severe external haemorrhage
when a medical responder has clinically identified that a trauma victim is experiencing severe external haemorrhage associated with but not limited to the following examples;

a. Visible site of life-threatening bleed from any parts of the body
b. Visible evidence of recent active bleeding (visible blood clots over injury site and evidence of large amounts of blood at the scene) from any parts of the body
c. Whenever a tourniquet is required in the attempt to attain haemostasis of any injured limb
d. Evidence suggesting base of skull fractures with active ear or nasal bleed.

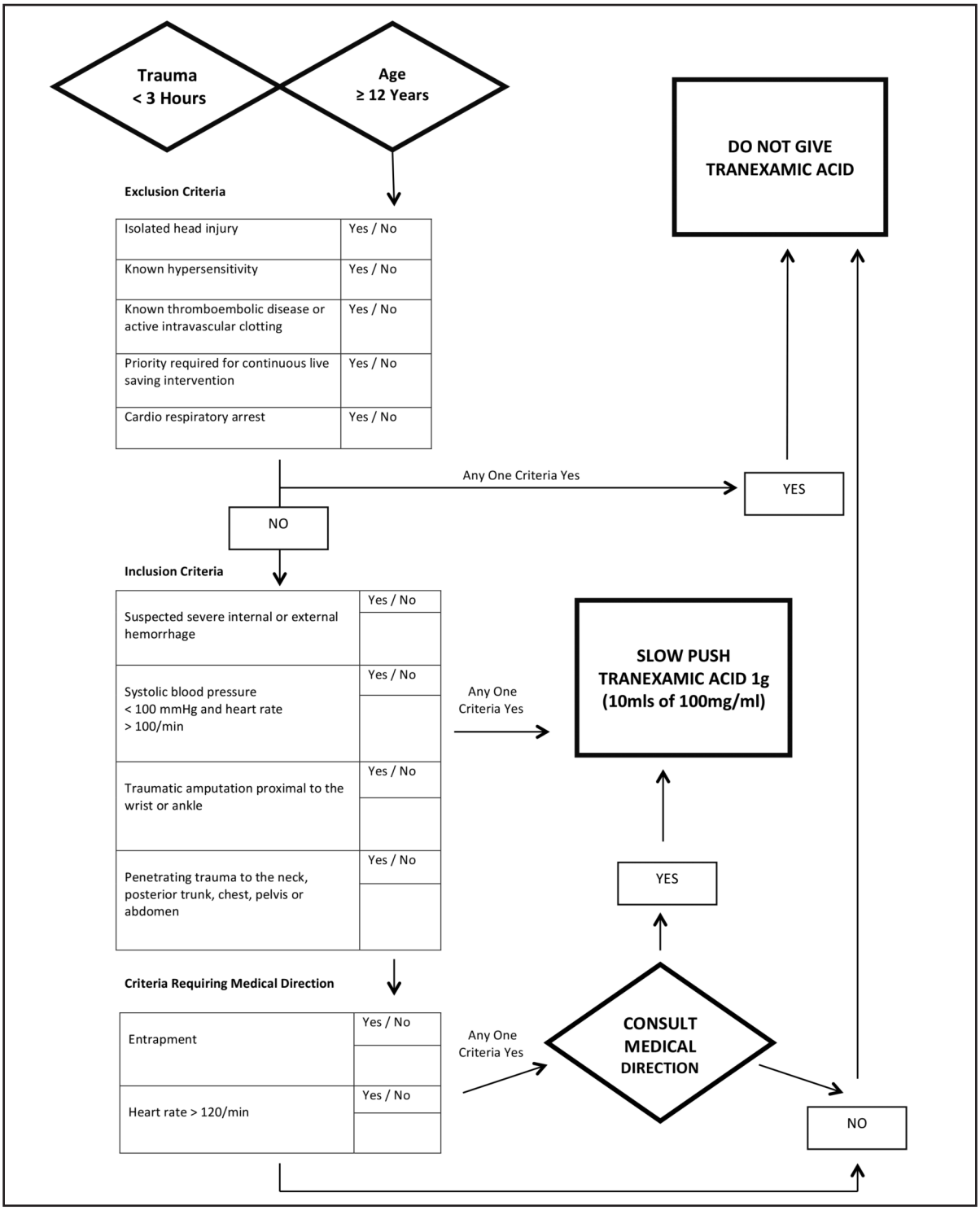

Fig. 1: Pre-Hospital Checklist: Administering Tranexamic Acid in Severe Trauma.

Entrapment

This is the state of being trapped in a damaged structural cavity either by injury or restrained by objects, requiring external mechanical assistance and >30minutes effort in rescue. Entrapment has been proven as one of the factors closely associated with acute traumatic coagulopathy.[19]

Important Considerations

The administration of tranexamic acid is an adjunct to the management of severe haemorrhage. The administration of tranexamic acid does not supersede the priorities of clinical interventions of haemorrhage control such as, direct compression, wound packing, tourniquet application, the use of haemostatic agents and others.

Administering Tranexamic Acid

i. A single dose of 1g (100mg/ml concentration in 10 ml vial) is administered intravenously using a slow push of the syringe.[13] Tranexamic acid initial dose is administered as early as possible, no later than 3 hours after trauma. Upon completion of the initial dose and arrival to hospital, 1g is infused over a period of 8 hours. (10ml ampoule containing 100mg/ml Tranexamic Acid added to 500ml 0.9% sodium chloride and the entire volume infused intravenously over 8 hours). Tranexamic acid Infusion may be ceased if the bleeding has been ceased.
ii. Tranexamic acid initial dose or infusion should be stopped immediately if the patient becomes combative, develops an anaphylactic reaction, seizure, profound hypotension or cardiorespiratory arrest.
iii. In the event that PHCAS paramedics are engaged with immediate lifesaving interventions, initial dose tranexamic acid administration should be deferred to arrival at hospital and administered during the early phase of trauma reception. Tranexamic acid should be administered preferably within the 1st hour post trauma and no later than 3 hours
iv. To administer tranexamic acid in a safe and timely fashion, the authors believe that it is reasonable for PHCAS paramedics to "pre-pack" tranexamic acid in sterile syringes and store in a sterile manner prior to each ambulance shift. Aside from being highly cost efficient [22,35] tranexamic acid is a stable drug and has been proven to be effective despite exposure to long durations of extreme temperatures (-20°c to 50°c).[12]

AUTHORS STATEMENT OF RECOMMENDATION

It is recommended that tranexamic acid is administered en-route and as soon as possible by pre-hospital care ambulance paramedics, to all adolescent and adult trauma victims bleeding extensively or at risk of severe haemorrhage.

CONCLUSION

Clinical guidelines can facilitate the translation of evidence into routine clinical practice. However, guidelines may need to be adapted to suit unique local demographics. The authors have created this proposed guideline based on quality evidence from multi-centred studies, clinical practices in other countries and consideration of local demographic factors. This proposed guideline is designed with the intent of enabling an easy and simple pathway to administer tranexamic acid early in the care of the severely injured. The authors recognize that some variants may be present amongst certain institutions necessitating minor adaptations, nevertheless the core principles of advocating tranexamic acid early in the course of pre-hospital trauma should be adhered to. Widespread implementation of such guidelines would be of benefit to Malaysian population in reducing trauma related mortality as well as the rate of preventable death from bleeding.

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