Tranexamic Acid in the Management of Non-variceal Upper Gastrointestinal Bleeding

Muhammad Reza[1], Saskia Aziza Nursyirwan[2]
[1]Faculty of Medicine, Universitas Indonesia
[2]Internal Medicine Department, Cipto Mangunkusumo National General Hospital, Faculty of Medicine, Universitas Indonesia

Corresponding author:
Muhammad.reza814@ui.ac.id, +6281271037612, Jl. Jati Padang Raya no. 52, Pasar Minggu, Jakarta Selatan, DKI Jakarta 12540

ABSTRACT

Background: *Non-variceal upper gastrointestinal bleeding (UGIB) is a common case of emergency in daily clinical practice with a fairly high mortality rate. The use of tranexamic acid, which has been recommended in managing trauma bleeding, may serve as an alternative pharmacological therapy to manage bleeding in non-variceal UGIB. This evidence-based case report aims to evaluate the impact of tranexamic acid on managing bleeding, risk of mortality, and thromboembolic event in non-variceal UGIB patients.*

Methods: *A systematic literature search was conducted on 4 databases: CDSR, EMBASE, PubMed, and Scopus for meta-analyses. Studies were selected based on inclusion and exclusion criteria formulated a-priori with subsequent critical appraisal according to the OCEBM critical appraisal tools.*

Result: *Meta analyses by Kamal, et al (2020) and Twum-Barimah, et al (2020) were included in our report. Kamal, et al shows no significant difference in mortality in tranexamic acid use compared to placebo (RR 0.84; 95%CI 0.63–1.11; I^2=2%). Similarly, although Twum-Barimah reported tranexamic acid reduced risk of mortality compared to placebo (RR 0.45; 95%CI 0.23–0.88; p=0.02; I^2 = 0%), none of the RCTs included shows significant result when observed individually. In addition, Kamal, et al also reported increased risk of vein thromboembolic events in high-dose tranexamic acid administration (RR 2.21; 95%CI 1.32–3.69; I^2=0%) compared to low-dose administration, in UGIB patients.*

Conclusion: *Tranexamic acid is not recommended to be used in managing bleeding in patients non-variceal UGIB patients and may increase the risk of thromboembolic event.*

Keywords: *Non-variceal gastrointestinal bleeding, placebo, tranexamic acid, UGIB*

ABSTRAK

Latar Belakang: *Perdarahan saluran cerna bagian atas (SCBA) non-variceal merupakan kasus kegawatdaruratan yang sering ditemukan dalam praktik klinis sehari-hari dengan angka kematian yang cukup tinggi. Penggunaan asam traneksamat, yang telah direkomendasikan dalam penanganan perdarahan trauma, berpotensi menjadi terapi farmakologis alternatif atau tambahan untuk mengelola perdarahan SCBA non-variceal. Evidence-based case report ini bertujuan untuk mengevaluasi dampak asam traneksamat dalam penatalaksanaan perdarahan, risiko mortalitas, dan kejadian tromboemboli pada pasien perdarahan SCBA non-variceal.*

Metode: *Dilakukan penelusuran literatur pada 4 database: CDSR, EMBASE, PubMed, dan Scopus untuk meta-analisis. Studi dipilih berdasarkan kriteria inklusi dan eksklusi, dan melalui penilaian kritis menggunakan Oxford Centre for Evidence Based Medicine critical appraisal tool*

Hasil: *Meta-analisis oleh Kamal, et al (2020) dan Twum-Barimah, et al (2020) dianalisis dalam laporan kami. Kamal, et al menunjukkan tidak ada perbedaan mortalitas yang bermakna pada penggunaan asam traneksamat dibandingkan dengan plasebo (RR 0,84; 95%CI 0,63–1,11; I^2=2%). Demikian pula, meskipun Twum-Barimah melaporkan asam traneksamat mengurangi risiko kematian dibandingkan dengan plasebo (RR 0,45; 95% CI 0,23–0,88; p=0,02; I^2=0%), tidak ada hasil signifikan pada RCT yang dianalisis ketika diamati satu per satu. Selain itu, Kamal, et al juga melaporkan peningkatan risiko kejadian tromboemboli vena pada pemberian asam traneksamat dosis tinggi (RR 2,21; 95%CI 1,32–3,69; I^2=0%) dibandingkan dengan pemberian dosis rendah, pada pasien perdarahan SCBA non-variceal.*

Kesimpulan: *Asam traneksamat tidak disarankan untuk digunakan dalam penatalaksanaan perdarahan SCBA non-variceal dan dapat meningkatkan risiko kejadian tromboemboli.*

Kata Kunci: *Asam traneksamat, placebo, perdarahan saluran cerna atas non-variceal, SCBA*

INTRODUCTION

Background

Upper gastrointestinal tract bleeding (UGIB) is a common case of emergency in daily clinical practice which causes a fairly high mortality rate. Patients with UGIB need medical help as quickly and as precisely as possible, otherwise the bleeding may lead to hypovolemic shock, or worse; death. In Indonesia, the number of mortality due to UGIB reached 14% in 2014, with an incidence of 160 cases per 100,000 population, in which 25% of the patient experienced recurrent bleeding events.[1] Along with the development of diagnostic and therapeutic endoscopic modalities, the incidence, recurrence, and mortality of UGIB patients is decreasing, but still far from optimal. With its high prevalence and its high risk of mortality, a more advanced management method to improve the outcome of patient with UGIB is greatly needed.

Based on its location and cause, UGIB is classified into variceal and non-variceal.[2] Variceal UGIB is caused by the rupture of dilated submucosal veins connecting the portal and systemic circulations, usually preceded by portal hypertension.[2] One example of variceal UGIB is ruptured esophageal varices in cirrhosis patient.[2] Meanwhile, non-variceal UGIB is caused by discontinuation of the inner lining of the GI tract because of gastric acid secretion.[3] Peptic ulcer disease (PUD) is an example for non-variceal UGIB.[3] To differentiate between variceal and non-variceal UGIB, physician should look for signs of chronic liver disease, such as stigmata of chronic liver disease or hepatitis infection marker.[2,4] If chronic liver disease sign is not found, the differential diagnoses will lean more to those of non-variceal UGIB, although the diagnosis still need to be confirmed using esophagogastroduodenoscopy (EGD).[3,4] Due to the differences of bleeding cause of variceal and non-variceal UGIB, the management between the two is far from being similar. Variceal upper GI bleeding is commonly treated using vasoactive agent or band ligation, while non-variceal upper GI bleeding is usually treated using proton pump inhibitor (PPI).[2,3]

Current standard pharmacological therapy for patients with non-variceal UGIB is the use of proton pump inhibitor (PPI) class drugs, such as omeprazole.[3] PPI works by blocking the proton pump in the gastric acid secretion cascade, greatly reducing the release of gastric acid, preventing further damage to the stomach lining.[5] Furthermore, inhibiting gastric acid release also provide suitable environment for blood clot to form, thus promote hemostasis.[5] On the other hand, tranexamic acid is classified as an antifibrinolytic drug, a preferred therapies for the management of bleeding due to trauma.[6] Tranexamic acid works by blocking lysin binding on plasminogen molecule, inhibiting the interaction of plasminogen with plasmin and fibrin, thus preventing the breakdown of blood clot.[6] Due to its mechanism of action, and similarity with PPI in supporting blood clot formation, antifibrinolytic agent is more suited to treat non-variceal UGIB compared to the variceal one.

Tranexamic acid is easily accessible with an affordable price, so that it can be used as an alternative or additional therapy of non-variceal UGIB. However, evidence supporting the role of tranexamic acid in controlling bleeding and preventing mortality in non-variceal UGIB patients is yet to be thoroughly explored. Available studies on the effectiveness of tranexamic acid therapy in UGIB patients shows varied results and discrepancies among expert are still present. Therefore, this evidence-based case report was made to find out about the effectiveness of tranexamic acid therapy in patient with UGIB and its role in controlling bleeding, as well as preventing mortality, based on evidence-based medical principles.

Table 1.1. PICO Framework

Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
Patients with non-variceal upper GI bleeding	Tranexamic acid	Placebo	Management of bleeding
Type of Clinical Question	Intervention		
Study Design	Meta-analyses		

CASE ILLUSTRATION

A 49-year-old man presented at the emergency unit of a hospital in Jakarta, Indonesia with a chief complaint of black stool since 4 days ago. The black stool is described as liquid, asphalt-colored, frequency of 3 – 4 times a day, volume around 300 cc, with no mucous. He also experienced upper abdominal pain, described as burning, come and go over time, and does not influenced by food consumption. Complaint of nausea and vomiting were denied. On the day of admission, the patient experienced pallor and general weakness, and was brought to the hospital after he fainted. He never experienced similar complaints before. Complaints of fever, jaundice, loss of appetite, and loss of weight were denied. He has a history of hypertension since 3 years ago. History of diabetes, heart disease, liver disease, and kidney disease were denied. History of smoking and alcohol consumption were denied. The patient has a habit of consuming traditional medicine commonly known as "*jamu*" to relieve muscle soreness.

The patient was found to be aware and cooperative. His heart rate of 68x/min, respiratory rate of 16x/minute, body temperature of 36.9 ^{o}C, and oxygen saturation of 99% on room air were within normal range. His blood pressure is elevated at 139/93 mmHg. The patient is obese with the BMI of 27.5 kg/m^2. Physical examination reveals pale conjunctiva and epigastrium tenderness. The presence of icteric sclera, gynecomastia, hepatosplenomegaly, ascites, caput medusae, spider nevi, palmar erythema, clubbing finger, leukonychia, ecchymosis, and flapping tremor were not found. Laboratory examination reveals anemia with the Hb of 4.4 (normal: 13 – 17% for male), low hematocrit at 14% (normal: 36 – 46%), and low erythrocyte count at 1.8x10^6/µL (normal 3.8 – 4.8 x10^6/µL).

The patient was suspected to have peptic ulcer and was planned to undergo esophagogastroduodenoscopy to confirm the diagnosis. The patient was given proton pump inhibitor (PPI) of omeprazole to relieve the epigastric pain and to prevent further erosion of the stomach lining. The physician ponders about the possibility of using tranexamic acid, an antifibrinolytic agent which has been recommended in the management of bleeding, such as bleeding due to trauma, but not yet for non-variceal upper gastrointestinal bleeding, such as peptic ulcer.

CLINICAL QUESTION

In response to the case reported, the following clinical question was proposed: "Is the use of tranexamic acid effective in the bleeding management of patients with non-variceal UGIB?". The framework of population, intervention, comparison, and outcome components (PICO) underlying this evidence-based case report is presented in **Table 1.1**

METHOD

Searching Strategy

This evidence-based case report was done based on protocols endorsed by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. A comprehensive systematic literature search across 4 online electronic databases was conducted on 28 June 2023 to identify all available studies to date investigating the role of tranexamic acid in non-variceal gastrointestinal tract bleeding management. Explored databases included Cochrane Database of Systematic Reviews (CDSR), EMBASE, PubMed, and Scopus. Relevant keywords, including MeSH terms, utilized in the literature search were based on the PICO framework described in Section I: "non-variceal upper gastrointestinal tract bleeding" or "tranexamic acid". Combinations of these main keywords were formulated using BOOLEAN terms "OR" and "AND". To rule out studies only involving variceal gastrointestinal bleeding, the keyword "varice*" was used alongside the BOOLEAN "NOT". Truncation (with suffix -*) was utilized to maximize studies found. A summary of electronic databases, search strategies utilised, and number of articles discovered may be noted in **Table 2**.1.

Table 2.1 Literature Search Strategy

Database	Time of Search	Search Strategy	Records Found
CDSR	28/06/2023 14.14	((("upper GI") OR ("upper-GI") OR (("upper") NEXT (("GI") OR ("gastrointestinal"))) AND (("bleed*") OR ("hemorrhage"))) NOT ("varice*")) AND ("tranexamic acid") Filter on meta-analysis and publication date for the last 10 years	1
EMBASE	28/06/2023 14.18	((upper AND gi) OR (upper gi) OR (upper AND (gi OR gastrointestin*))) AND (bleed* OR hemorrhag*) NOT varice* AND tranexamic acid AND [meta analysis]/lim AND ([english]/lim OR [indonesian]/lim) Filter on publication date for the last 10 years	10
PubMed	28/06/2023 14.20	(((upper GI) OR (upper-GI) OR ((upper) AND ((GI) OR (gastrointestin*))) AND ((bleed*) OR (hemorrhag*))) NOT (varice*)) AND (tranexamic acid) Filter on meta-analysis and publication date for the last 10 years	5
Scopus	28/06/2023 14.25	TITLE-ABS-KEY ((("upper GI") OR ("upper-GI") OR (("upper") AND ((GI) OR ("gastrointestin*"))) AND (("bleed*") OR ("hemorrhag*"))) AND NOT ("varice*")) AND TITLE ("tranexamic acid") Filter on reviews and publication date for the last 10 years	17

Table 2.2. Inclusion and Exclusion Criteria

Element	Inclusion Criteria	Exclusion Criteria
Study design/characteristic	- Meta-analysis of RCTs - Meta-analysis of systematic reviews of RCTs	- Not written in English or Bahasa Indonesia
Population	- Patients with upper GI bleeding	- Patients <18 years old of age - Analyses patients with variceal upper GI bleeding
Intervention	- Tranexamic acid	- Combination therapy
Comparator	- Placebo	- No placebo used in the control group
Outcome	- Mortality - Uncontrolled bleeding - Rebleeding - Need for transfusion - Thromboembolic event	

RCT: randomized controlled trial; GI: gastrointestinal.

Eligibility Criteria

Subsequent to identifying all published articles discovered from our search strategy, records were screened for suitability against a number of predefined inclusion and exclusion criteria (**Table 2.2**). Records included must be relevant to the clinical question and exhibit robust evidence by having a population of patients with non-variceal gastrointestinal tract bleeding; distinguished or presented separate data for vaiceal and non-variceal patients if both were studied; included results of tranexamic acid use compared to placebo as one of the drug choices studied; reported data concerning mortality, uncontrolled bleeding, rebleeding, need for transfusion, thromboembolic event, and/or clinical improvement; and was a meta-analysis of RCTs. Records were excluded if inclusion criteria were not met, full-text articles not retrievable, and/or the article was not written in English or Bahasa Indonesia. Afterwards, full reports were sought and retrieved to assess eligibility for inclusion as high-quality evidence in our report.

Data Extraction and Critical Appraisal

From studies included, various data were collected for synthesis: (1) authors; (2) year of publication; (3) study characteristics including study setting, intervention, comparator, and outcome parameters; (4) patient characteristics including sample size, age, gender, and diagnosis; and (5) mortality and/or bleeding outcomes. Lastly, validity, importance, and applicability were appraised with the Oxford Centre for Evidence-Based Medicine (OCEBM) critical appraisal tools for clinical trials and systematic reviews.[7] Furthermore, records were ranked according to their level of evidence (LoE) based on the 2011 OCEBM Level of Evidence guidelines (LoE).[8] Article selection, data extraction, and critical appraisal were conducted by one investigator (MR) and independently reviewed by another reviewer (SAN).

RESULT

Search Findings

A sum of 33 records were retrieved from CDSR (n=1), EMBASE (n=10), PubMed (n=5), and Scopus (n=17). A total of 11 duplicated were removed, leaving a total of 22 records to be screened based on title and abstract. Irrelevant titles (n=14) were immediately excluded in the initial screening – yielding a remainder of 8 articles to be sought for retrieval. During retrieval, two articles were found to be inaccessible, thus excluded. Following a thorough evaluation of eligibility based on our pre-formulated inclusion criteria, four studies were excluded due to not having satisfied the eligibility criteria of not performing subgroup analysis on non-variceal UGIB only (n=3) and uses combination therapy (n=1). Therefore, we included two meta-analyses by Kamal, et al. and Twum-Barimah, et al. to be utilized in our evidence-based case report. The study selection process and includes the detailed reason for exclusion is illustrated in **Figure 3.1.**

Study Characteristics of Selected Articles

Characteristics and main results of studies included may be observed in **Table 3.1** For Twum-Barimah, et al's meta-analysis, only the subgroup analysis of non-variceal UGIB patients treated with tranexamic acid (taken from 5 RCTs) was assessed to draw conclusions, while the total subject from Kamal et al.'s subgroup analysis is inaccessible.[9,10]

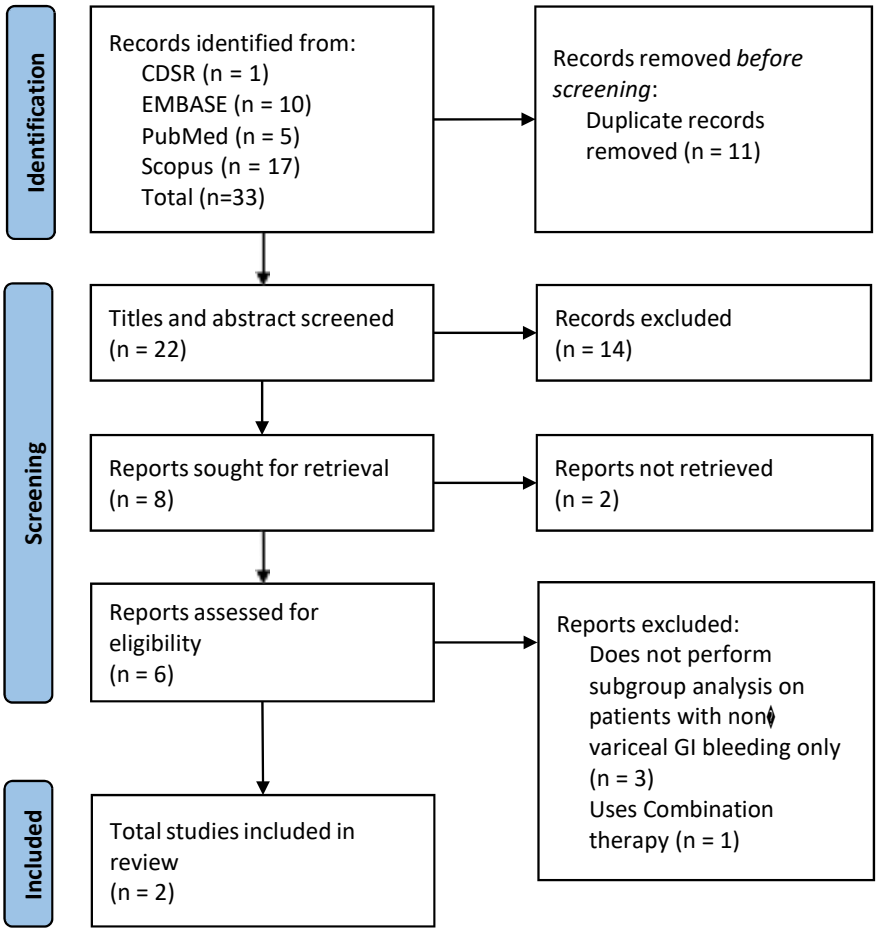

Figure 3.1. Study Selection Flowchart

Table 3.1. Study Characteristics of Selected Articles

No.	Author (year)	Size	Age (year)	Study design	Location	Inclusion criteria	Intervention (I)	Comparator (C)	Outcome parameters (O)	Main Result
1	Kamal, et al (2020)[9]	Total: 14100 patients from 12 RCTs	Patients under 18 years of age are excluded	Meta-analysis of RCTs	Albania, Australia, Egypt, Georgia, Ireland, Malaysia, Nepal, Nigeria, Pakistan, Papua New Guinea, Romania, Saudi Arabia, Spain, Sudan, and UK	RCTs that compared tranexamic acid with placebo in UGIB. Studies that only included patients under 18 years of age, non-randomized trials and review articles are excluded	Tranexamic acid, oral or IV, 2 – 4.5 g daily	Placebo	Non-variceal UGIB subgroup: Mortality	Subgroup analysis including only those patients with non-variceal bleeding showed no difference in mortality; (RR 0.84; 95% CI; 0.63–1.11, I^2 = 2%)
2	Twum-Barimah, et al (2019)[10]	Non-Variceal UGIB Subgroup: 829 patients from 5 RCTs	Include all age group, but analysis for the pediatric patients is separated	Meta-analysis of RCTs	Australia, Iran, Russia, Sweden, UK.	RCTs that compared tranexamic acid use in UGIB, either variceal or nonvariceal bleeding irrespective of the severity, to placebo across all age groups.	Tranexamic acid, oral or IV, 2.25 – 6 g daily	Placebo	Non-variceal UGIB subgroup: Mortality	Beneficial effect of tranexamic acid on mortality was seen in studies that investigated only patients with nonvariceal bleeding (RR 0.45; 95% CI 0.23-0.88, P = 0.02; I^2 = 0%)

Critical Appraisal

Selected studies were appraised based on the OCEBM critical appraisal tools for RCTs and systematic review. Both studies provide robust evidence based on their LoE of 1.[8–10] Quality of these studies were revealed to be sufficient by fulfilling OCEBM appraisal elements in terms of validity, importance, and applicability.[7] Both meta-analysis satisfied 7/8 yes-no appraisal elements with only 1 question being responded as "no", thus may be established as a high-quality study. In terms of applicability, both of the meta-analysis included a wide variety of patient populations, mostly from USA and Europe. However, both studies may be applicable to our patient's case due to similar condition of non-variceal UGIB, which presents in our patient. Thus, both articles were included in our evidence-based case report. Detailed results of appraisal and justification may be noted in detail in **Table 3.2.**

Table 3.2. Critical Appraisal of Included Systematic Review based on OCEBM

Appraisal Component	Kamal, et al (2020)[9]	Twum-Barimah, et al (2019)[10]	Comments
Level of evidence*	Level 1	Level 1	Both are systematic review of RCTs
VALIDITY			
Were the research question and PICO defined clearly	Yes	Yes	Kamal, et al (2020): PICO stated in methods. P: Adult patients with UGIB. I: Tranexamic acid. O: Placebo. O: Efficacy and adverse events Twum-Barimah, et al (2019): PICO stated in methods. P: Patients with UGIB. I: Tranexamic acid. O: Placebo. O: Efficacy and adverse events
Is it unlikely that important, relevant studies were missed?	Yes	Yes	Kamal, et el (2020): Included Pubmed & MEDLINE, Embase, Web of Science Core Collection and CENTRAL up to June 25, 2020 using specific keywords clearly stated and MeSH words, without restrictions of publishing time and language. Twum-Barimah, et al (2019): Included PubMed, Embase, CINAHL and CENTRAL up to December 10, 2019 using specific keywords clearly stated and MeSH words, without restrictions of publishing time and language. Hand searching was done for gray literature.
Were the criteria used to select articles for inclusion appropriate?	Yes	Yes	Kamal, et al (2020): Clearly stated inclusion criteria and appropriate for PICO: only RCTs that compared tranexamic acid with placebo in UGIB. We excluded studies that only included patients under 18 years of age, non-randomised trials and review articles. Twum-Barimah, et al (2019): Randomised controlled trials (RCTs) that compared tranexamic acid use in upper gastrointestinal bleeding to other treatment modalities for upper gastrointestinal bleeding across all age groups were eligible for inclusion. Participants of the primary studies were patients with either variceal or nonvariceal bleeding irrespective of the severity of bleeding.
Were the included studies sufficiently valid for the type of question asked?	Yes	Yes	Both studies: Quality of studies included were assessed using the Cochrane tool for bias risk assessment by two investigators. Non-randomized, non-blinded, incomplete outcome data, and selective outcome reporting.
Were the results similar from study to study?	Yes	Yes	Kamal, et el (2020): Heterogeneity between studies were low for outcomes of mortality in UGIB patients (I^2 =12%) and non-variceal UGIB patients only subgroup analysis (I^2 = 2%). Twum-Barimah, et al (2019): Heterogeneity between studies were low for outcomes of mortality in UGIB patients (I^2 =0%) and non-variceal UGIB patients only subgroup analysis (I^2 = 0%).
IMPORTANCE			
What is the result?	Kamal, et el (2020): **Figure 3.2** showcases the forest plot of the meta-analysis by Kamal, et al. which shows the analysis for 14,107 UGIB patients from 12 RCTs which revealed tranexamic acid use does not had a clinically beneficial impact on patients' outcome with the (RR 0.84; 95% CI: 0.63–1.11; I^2 = 2%). The study also provides subgroup analysis for non-variceal UGIB patients which revealed tranexamic acid use does not had a clinically beneficial impact on patients' outcome with the (RR 0.84; 95% CI: 0.63–1.11; I^2 = 2%). However, the table was not accessible. Twum-Barimah, et al (2019): **Figure 3.3** showcases the forest plot of the meta-analysis by Twum-Barimah, et al. which shows the subgroup analysis for 829 non-variceal UGIB patients from 5 RCTs which revealed tranexamic acid use had a clinically beneficial impact on reducing mortality in non-variceal UGIB patients (RR 0.45; 95% CI: 0.23-0.88, p = 0.02; I^2 = 0%)		

Appraisal Component	Kamal, et al (2020)[9]	Twum-Barimah, et al (2019)[10]	Comments
APPLICABILITY			
Were the study patients similar to your own?	Yes	Yes	Both studies included patients with general UGIB, but provided subgroup analysis for non-variceal UGIB patients. Both studies also included data from various sites, mostly from USA and Europe. However, some RCTs included in the studies does not have separate analysis on non-variceal UGIB patient only.
Is the treatment feasible in my setting?	Yes	Yes	Both studies use tranexamic acid as the treatment, which is readily available in Indonesia.
Will this evidence make a clinically important impact on your conclusions about what to offer or tell your patient?	No	No	Kamal, et el (2020): The meta-analysis revealed there is no difference in mortality in non-variceal UGIB patients with tranexamic acid use compared to placebo. Twum-Barimah, et al (2019): The meta-analysis revealed tranexamic acid reduced non-variceal UGIB patients' risk of mortality compared to placebo. However, the result of all RCTs included in this meta-analysis reveals no significant difference in risk of mortality in non-variceal UGIB patients with tranexamic acid use compared to placebo.

*based on OCEBM 2011 guidelines for level of evidence

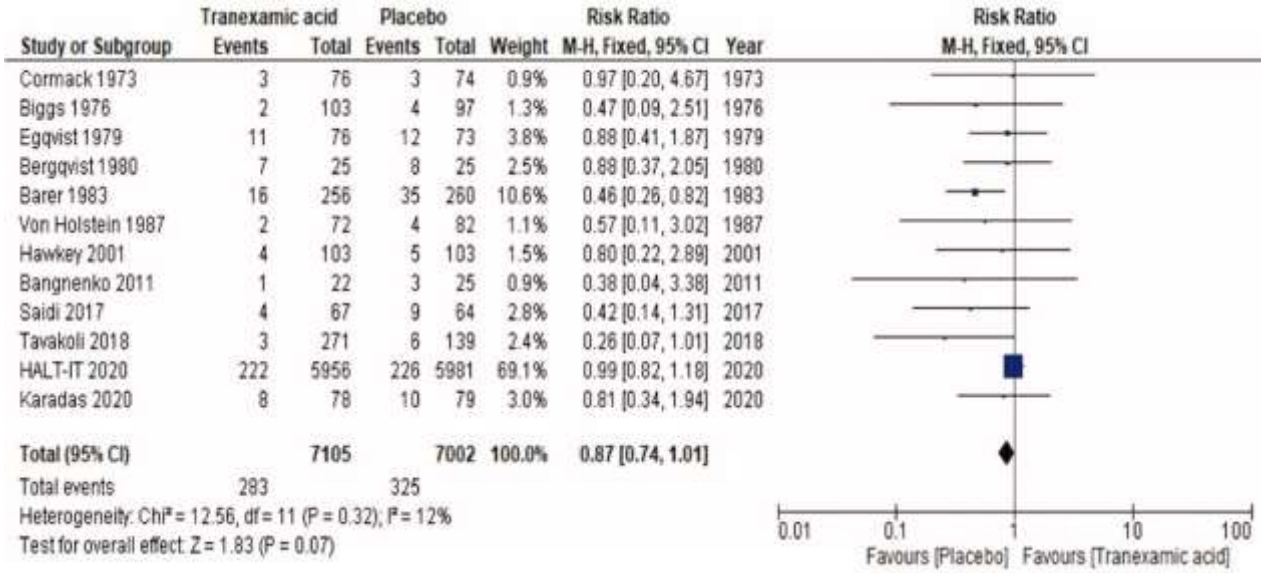

Figure 3.2. Forest plot of RCTs of tranexamic acid versus placebo in UGIB patients (Kamal, et al: 2020).[9]

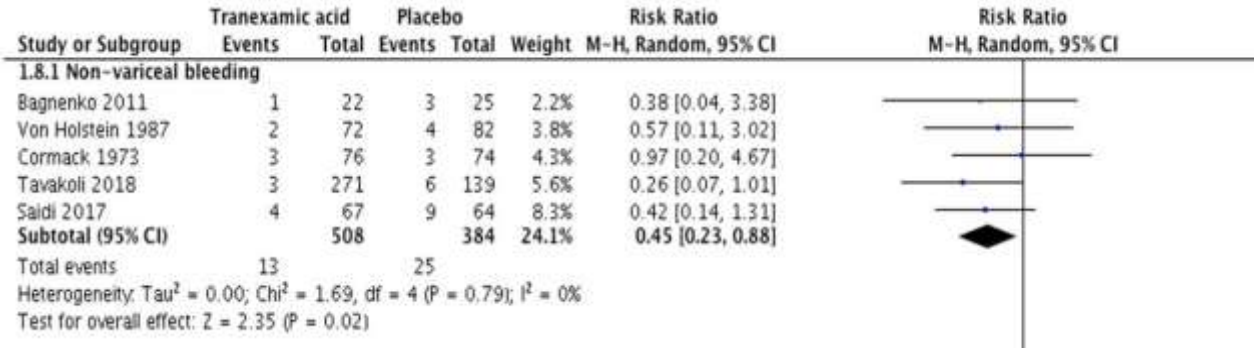

Figure 3.3. Forest plot of RCTs of tranexamic acid versus placebo in only non-variceal UGIB patients Subgroup (Twum-Barimah, et al: 2019).[10]

Table 3.3. PICO Criteria Relevance of Included Study

No.	Author	Similarity in population	Similarity in intervention	Similarity in comparator	Similarity in outcome
1.	Kamal, et al (2020)	+/-	+	+	+
2.	Twum-Barimah, et al (2019)	+/-	+	+	+

+ : high similarity
+/- : uncertain similarity

PICO CRITERIA RELEVANCE

We evaluated individual similarity of population, intervention, and outcome criteria between the non-variceal UGIB subgroup of the meta-analysis and our patient's case. We have found the studies to have mostly similar characteristics of these criteria to our case (**Table 3.3**). Both studies involved tranexamic acid which is readily available in Indonesia which aids in making the results of this report applicable to our patient's case. Furthermore, both studies compared tranexamic acid to placebo as control which would help in revealing our patient's case would be if he were to only receive standard therapy. Outcomes measured in the studies for the non-variceal UGIB subgroup were mortality—outcome measures which may be easily applied to prognosticate our patient's outcome with the use of tranexamic acid. These similarities reflect optimal comparability to allow application of the reports' results to our case. However, it is important to note some differences in population parameters. Although both studies included patients with non-variceal UGIB, both of the meta-analysis include studies mostly done in USA and Europe, with no country from South East Asia, which may have differences in ethnicity or healthcare systems, impacting results. Moreover, neither of the studies perform subgroup analysis of non-variceal UGIB on the adverse event following tranexamic acid use. This may affect comparability of their populations to our case.

DISCUSSION

The Impact of Tranexamic Acid Use in Non-variceal UGIB Patients

Tranexamic acid a synthetic derivative of the amino acid lysine which has the function of inhibiting plasminogen activation to become plasmin.[11] Tranexamic acid does this by competitively blocking plasminogen binding with formed plasmin and fibrin, preventing the interaction of plasmin with lysine residues of the fibrin polymer, disrupting the process of fibrinolysis.[11] Due to its high affinity to the lysine binding site of plasminogen, tranexamic acid is expected to reduce the incidence of bleeding or recurrent bleeding from cases of upper gastrointestinal bleeding.

The meta-analysis by Twum-Barimah, et al. (2019) revealed the impact of tranexamic acid, towards UGIB by observing parameters of mortality.[10] In the subgroup analysis of non-variceal UGIB patients which included 829 patients across 5 RCTs, Twum-Barimah, et al. reported a significant reduction in rates of mortality in patients treated with tranexamic acid compared to placebo with (RR 0.45; 95% CI: 0.23-0.88, p = 0.02; I^2 = 0%).[10] However, when we look at the RCTs individually, none of them significant differences of mortality between intervention and control group, which means the RCTs does not have adequate evidence to support the beneficial impact of tranexamic acid use in non-variceal UGIB patient compared to placebo.[10] In addition, the meta-analysis also analyzes the occurrence of thromboembolic events (1,041 patients across 6 RCTs) and thrombophlebitis (354 patients across 2 RCTs) following the administration of tranexamic acid in UGIB patient, not specific to non-variceal UGIB.[10] Tranexamic acid was found to have similar occurrence of thromboembolic events (RR 0.89; 95% CI: 0.17 – 4.59, p = 0.89, I^2 = 55%), and thrombophlebitis (RR 2.02; 95% CI: 0.44 – 9.26, p = 0.37, I^2 = 0%), when compared to placebo.[10] These results demonstrate how tranexamic acid administration does not increase the risk of thromboembolic event nor thrombophlebitis in UGIB patients.

On the contrary, the meta-analysis by Kamal, et al. (2020), revealed how the use of tranexamic acid does not have significant difference, in terms of mortality (RR 0.84; 95% CI: 0.63 – 1.11; I^2 = 2%), when compared to placebo in non-variceal UGIB patients.[9] In addition, the meta-analysis also analyzes the occurrence of vein thromboembolic events in patients receiving high-dose tranexamic acid in UGIB patient, not specific to non-variceal UGIB.[9] Tranexamic acid was found to increase the risk of vein thromboembolic events when administered in high dose (RR 2.21; 95% CI: 1.32 – 3.69; I^2 = 0%) compared to low-dose administration.[9] However, based on the quality of evidence assessment using GRADE framework, the studies included in the subgroup analysis were assessed as having a very low quality of evidence, meaning that we cannot say for certain how the impact of tranexamic acid on UGIB patients is.[9] However, even though the

quality of evidence is very low, it is safer to avoid the usage of tranexamic acid on UGIB altogether to avoid any unwanted risk, just like what Kamal, et al. recommend to do, since the current guidelines from the National Institute for Health and Care Excellence and the American Collage of Gastroenterology do not recommend the use of tranexamic acid on UGIB as well.[12,13]

Tranexamic acid may be not effective in managing upper gastrointestinal bleeding due to gastric acid interfering with hemostasis.[14,15] Gastric acid may disrupt the hemostasis process, slowing the formation of clot, and reduces the quality of formed clot.[14,15] This study suggests that acid-dependent factors in the gastric juice, such as gastric protease, are responsible for impairing clot formation. Although tranexamic acid is able prevent fibrinolysis by inhibiting plasmin-mediated pathway, it may not be as effective in preventing fibrinolysis due to non-specific protease activity in patients with upper gastrointestinal bleeding.

Strength and Limitation

Strengths of our evidence-based case report include its comprehensive systematic literature search which covered 4 databases (CDSR, Embase, PubMed, and Scopus) in addition to hand-searching, thus ensuring that all relevant literature have been included in our report. Furthermore, studies we have included in this case report are of high quality and provided robust evidence based on their high LoE of 1 meta-analysis of blinded RCTs which are the best study designs for interventional research. The quality of these studies has been evaluated using the OCEBM tools for critical appraisal, each demonstrating fulfillment of most appraisal elements. In total, we have included a total of more than 829 patients with non-variceal UGIB, pooled from the meta-analyses which allows strong evidence to be gathered.

Despite our efforts to maximize the quality of our analysis, our report also possesses limitations, such as only included two studies to collect evidence from. Furthermore, these studies only perform subgroup analysis of non-variceal UGIB on the mortality parameter, while for other parameters, such as thromboembolic event, both variceal and non-variceal UGIB are analyzed. In addition, neither studies reported the average age nor gender proportion of the patients, making it more difficult to compare similarity with our patient's case. As a result, the conclusions made from this evidence-based case report should be taken with these limitations in consideration.

CONCLUSION AND RECOMMENDATION

Conclusion

The use of tranexamic acid in the management of patients with non-variceal UGIB still has conflicting results. Although one meta-analysis suggests tranexamic acid reduces the mortality rate of non-variceal UGIB patients compared to placebo, none of included RCTs concurs. Another meta-analysis suggests, when compared to placebo, the use of tranexamic acid does not have any beneficial impact on non-variceal UGIB patients, while high dose use is associated with increased risk of thromboembolic events.

Recommendation

Tranexamic acid is not recommended to be used in managing bleeding in patients with non-variceal UGIB due to inadequate evidence supporting its beneficial impact. Future researchers should focus on analyzing different set of population to find more appropriate use of tranexamic acid. More RCTs is needed to find more suitable and safer therapeutic choice for non-variceal UGIB, in addition to available guidelines, in order to achieve reduction in mortality of non-variceal UGIB.

REFERENCES

1. Indonesian Society of Gastroenterology. National consensus on management of non-variceal upper gastrointestinal tract bleeding in Indonesia. Acta Med Indones. 2014 Apr;46(2):163–71.
2. Antunes C, Copelin II EL. Upper gastrointestinal bleeding. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470300/
3. Malik TF, Gnanapandithan K, Singh K. Peptic ulcer disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK534792/
4. Sharma A, Nagalli S. Chronic liver disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554597/
5. Khan MA, Howden CW. The role of proton pump inhibitors in the management of upper gastrointestinal disorders. Gastroenterol Hepatol (N Y). 2018 Mar;14(3):169–75.
6. Cai J, Ribkoff J, Olson S, Raghunathan V, Al-Samkari H, DeLoughery TG, et al. The many roles of tranexamic acid: An overview of the clinical indications for TXA in medical and surgical patients. Eur J Haematol. 2020 Feb;104(2):79–87.
7. Oxford University Centre for Evidence-Based Medicine. Critical appraisal tools [Internet]. Centre for Evidence-Based Medicine; 2022. Available from: https://www.cebm.ox.ac.uk/files/ebm-tools/systematic-review.pdf

8. Oxford University Centre for Evidence-Based Medicine. Oxford centre for evidence-based medicine 2011 levels of evidence [Internet]. Centre for Evidence-Based Medicine; 2022. Available from: https://www.cebm.ox.ac.uk/files/levels-of-evidence/cebm-levels-of-evidence-2-1.pdf
9. Kamal F, Khan MA, Lee-Smith W, Sharma S, Imam Z, Jowhar D, et al. Efficacy and safety of tranexamic acid in acute upper gastrointestinal bleeding: meta-analysis of randomised controlled trials. Scandinavian Journal of Gastroenterology. 2020 Dec 1;55(12):1390–7.
10. Twum-Barimah E, Abdelgadir I, Gordon M, Akobeng AK. Systematic review with meta-analysis: the efficacy of tranexamic acid in upper gastrointestinal bleeding. Alimentary Pharmacology & Therapeutics. 2020;51(11):1004–13.
11. Laine L. Gastrointestinal bleeding. In: Harrison's principles of internal medicine. 19th ed. New York: McGraw-Hill; 2015. p. 276–9.
12. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012 Mar;107(3):345–60; quiz 361.
13. Acute upper gastrointestinal bleeding in over 16s: management [Internet]. London: National Institute for Health and Care Excellence (NICE); 2016 [cited 2023 Jul 15]. (National Institute for Health and Care Excellence: Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK554919/
14. Green FW, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. Gastroenterology. 1978 Jan;74(1):38–43.
15. Ghassemi KA, Kovacs TOG, Jensen DM. Gastric acid inhibition in the treatment of peptic ulcer hemorrhage. Curr Gastroenterol Rep. 2009 Dec;11(6):462–9.