RESEARCH PROTOCOL

THE ROLE OF TRANEXAMIC ACID FOR THE TREATMENT OF GASTROINTESTINAL BLEEDING: A RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL

INVESTIGATORS:

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I. BACKGROUND

Acute gastrointestinal (GI) bleeding is one of the most common emergency problems and is one of the most important causes of mortality and morbidity worldwide. Acute upper GI bleeding is the cause of the 60,000 patients who come to the hospital each year in the UK and such as 10% causing fatal problems.[1,2] Lower GI bleeding causes 15,000 patients to come to the hospital each year with a fatal case rate of 15%.[3] GI bleeding is common in low- to middle-income countries.

The most common causes of acute upper GI bleeding in developed countries are peptic ulcer (40%) and esophageal varices (11%).2 However, in developing countries, the most common are esophageal varices that reach 45% of all cases including Indonesia. In Indonesia, based on data from Cipto Mangunkusumo Hospital, esophageal varices are the most common cause of upper GI bleeding (33.5%), with 49.3% of which are the third-grade esophageal varices.[4] Although with advanced management for two decades, the mortality rate for GI bleeding remains high.[2,5] Predictor of mortality in patients with upper GI bleeding is re-bleeding, which occurs in about 10% of patients with non-variseal bleeding and 25% in patients with variseal bleeding.[6,7,8]

Tranexamic acid is one of the most frequent treatments given to patients with bleeding cases. A summary of clinical trials study suggests that tranexamic acid can reduce the need for blood transfusions up to 30% in surgical patients.[9] A clinical trial study in patients with trauma showed that the administration of tranexamic acid reduced the risk of dying from bleeding and all-cause mortality compared with placebo.[10]

In cases of GI bleeding, a meta-analysis of clinical trials study showed a decreased risk of death and the need for surgical intervention in patients given tranexamic acid. However, most of the quality was not good and the results were not significant.[11] Tranexamic acid does not become therapeutic options in international guidelines nor in national consensus. Thus, the effectiveness and safety of tranexamic acid using in GI bleeding remains unclear. In Indonesia, the used of tranexamic acid for GI bleeding treatment is limited. Therefore, a clinical trial study of tranexamic acid is required to assess the effectiveness and the safety in gastrointestinal bleeding treatment.

II. OBJECTIVE AND HYPOTHESIS

A. General Objective

To determine the effect of tranexamic acid injection in patients with upper and lower GI bleeding

B. Specific Objective

1. To determine the re-bleeding incidence of patients GI bleeding with tranexamic acid injection compared to placebo.
2. To determine the number of deaths in hospital of patients with GI bleeding with injection tranexamic acid compared to placebo after 30 days of randomization.
3. To determine the need for blood transfusion in of GI bleeding patients with tranexamic acid injection compared to placebo.
4. To determine the average length of stay in intensive care unit of GI bleeding patients with tranexamic acid injection compared to placebo.
5. To determine the need for endoscopic hemostasis of GI bleeding patients with tranexamic acid injection compared to placebo.
6. To determine the quality of life patients with tranexamic acid injection compared to placebo using questionnaire SF-36
7. To determine anxiety level patients with tranexamic acid injection compared to placebo using Hamilton Anxiety Rating Scale

C. Hypothesis

1. Administration of tranexamic acid injection decreased the number of re-bleeding incidence compared to placebo.
2. Administration of tranexamic acid injection decreased the number of deaths in hospital compared to placebo after 30 days of randomization.
3. Administration of tranexamic acid injection decreased the number of need of blood transfusion compared to placebo.
4. Administration of tranexamic acid injection decreased the length of stay in intensive care unit compared to placebo.

5. Administration of tranexamic acid injection decreased the number of need of endoscopic hemostasis compared to placebo.
6. Administration of tranexamic acid injection improved quality of life patients compared to placebo.
7. Administration of tranexamic acid injection decreased level of patients anxiety compared to placebo.

III. METHODS

A. Study Design

This study is a randomized double-blind controlled trial.

B. Time and Place

This study will be conducted in Cipto Mangunkusumo National Central General Hospital, especially in emergency unit, intensive care unit (ICU), *high care unit* (HCU), *intensive cardiac care unit* (ICCU), inpatient ward, and endoscopy centre. It will be lasted from April 2018 – March 2019

C. Study Population

1. Targeted population: Patients with acute upper and lower GI bleeding in Indonesia

2. Sample: Patients with acute upper and lower GI bleeding in Cipto Mangunkusumo National Central General Hospital

3. Inclusion Criteria

- Adults (minimum age : 18 years old)
- Patients with acute lower and upper gastrointestinal bleeding (assessed clinically)
- Patients agreed to participate in the study and signed the informed consent

4. Exclusion Criteria

- Allergy with tranexamic acid
- Patients considered by the clinician cannot be randomized to participate in the study
- Patients with chronic kidney disease stage III - V

5. ***Drop Out*** **Criteria:** Patients who have signed the informed consent but wish to stop participating before completed the study.

6. Estimation Sample Size

Formula:

$$N1 = N2 = \frac{(Z_\alpha\sqrt{2PQ} + Z_\beta\sqrt{P_1Q_1 + P_2Q_2})^2}{(P_1 - P_2)^2}$$

Explaination:

N1=N2= required sample for each control group and intervention group

Z_α is a type I error that is set at 5% so the value of Zα is 1,64

Z_β is a type II error that is set at 20% so the value of Z_β is 0,84

P2 = the proportion of primary output in the control group is 25% (0,25)

P1-P2 = the difference of proportion of minimal exposure considered significant is set at 0,125

P1 = P2-0,125 = 0,125

P = (P1+P2/)2 = 0,1875

Q1 = 1-P1 = 0,875

Q2 = 1-P2 = 0,75

Q = 1-P = 0,8125

From calculation above, the sample size for each group is about 151,7; added with 10% drop out so it will be rounded to 168 samples for each group.

D. Study Procedure

1. Randomization

Patients who have met the inclusion and exclusion criteria will be randomized using a computer for admission to an intervention group or a placebo group. Each patient will be given a patient code or subject code.

2. *Blinding*

The patient code will be given to the pharmacy to adjust the intervention group. Pharmacy will not be given the identity of the patient. Each drug will be given a drug code. Pharmacy will give the drug to nurses or doctors who will provide the intervention. The interventionist, either the doctor or the nurse, will also be disguised about the drug. They only know the drug code to be given on the subject according to the patient code. Patients will not be informed of the treatment between placebo or tranexamic acid injection.

3. Intervention

The tranexamic acid will be administered 4 grams compared to placebo or 0.9% sodium chloride (NaCl). Administration of tranexamic acid is 1 gram loading dose followed by 3 grams maintanance dose for 24 hours. The procedure is given in Table 1.

Table 1. Procedure Intervention

Intervention	Ampul	Dosage	Description
Loading dose	2	1 gram	Given in 100 ml of 0.9% NaCl as much as 100 ml intravenously for 10 minutes.
Maintenance dose	6	3 grams	Given in any isotonic fluid of 1000 ml and with infusion rate of 125 mg / h or 42 cc / h for 24 hours.
Additional information: • Drugs for clinical trial intervention should not be mixed with blood products for transfusion. • Should not be added in liquids containing penicillin or mannitol.			

Other routine medications for the management of GI bleeding will be given as usual. The injection of tranexamic acid or placebo will be the additional medication. Other drugs used for management of GI bleeding will be recorded.

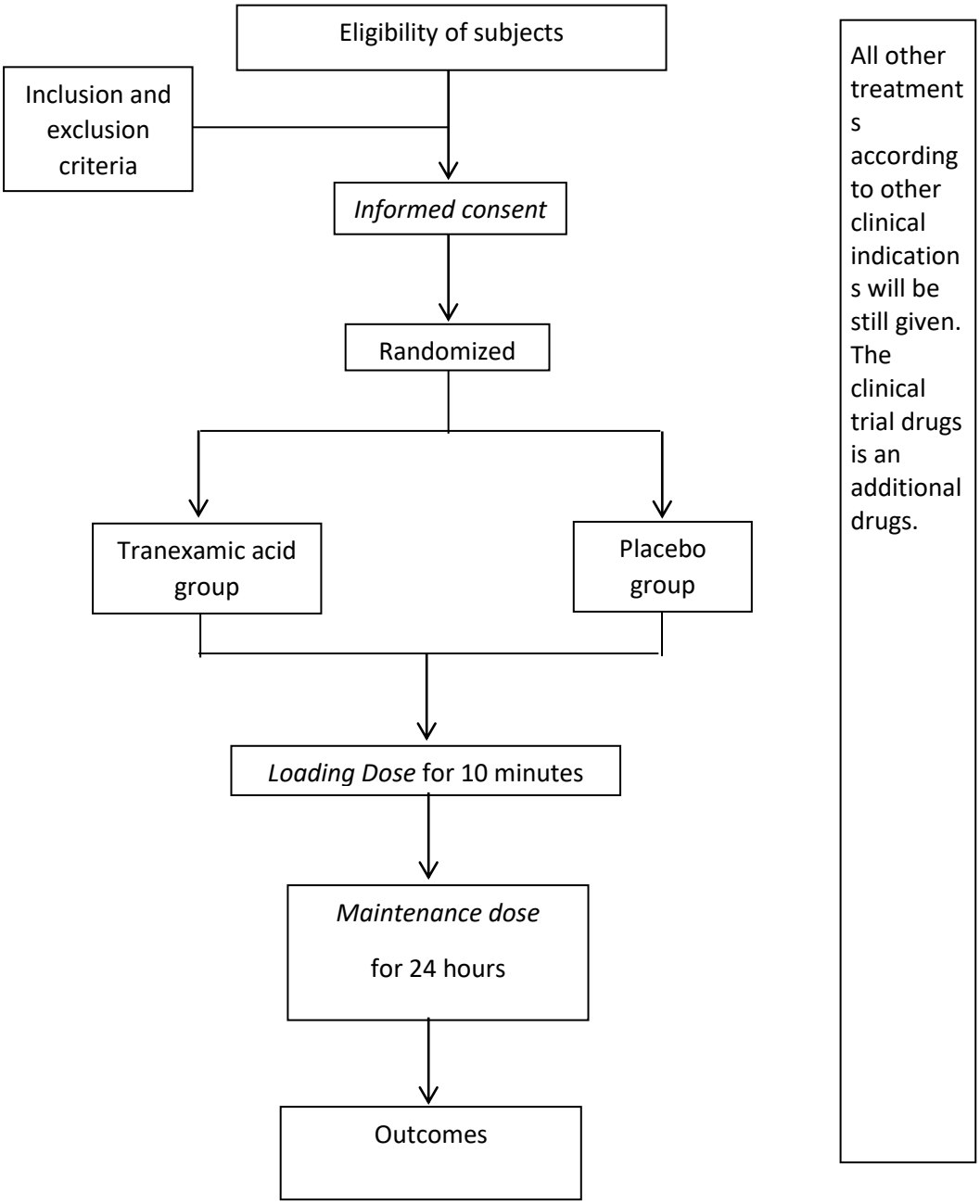
4. Side Effects

All side effects that may arise and related to tranexamic acid injection will be reported. Serious adverse events besides the outcome adverse events of the study will be reported immediately to the principal investigator and will be written within 24 hours.

5. Research Variable

- Independent variable: tranexamic acid injection
- Dependent variable:
  - Rebleeding (primary outcome)
  - Number of death within 30 days post randomisation
  - Need for blood transfusion
  - Length of stay in intensive care unit
  - Need for endoscopic hemostasis
  - Quality of life
  - Level of anxiety

F. Research Flow



E. Ethics

This research will seek the approval Ethics Committee of the Faculty of Medicine, University of Indonesia. (approval as attachment)

IV. STUDY ANALYTICAL PLAN

Analysis method using IBM SPSS Windows program version 22. Output with categorical variables of two groups will be analyzed using chi square test, with alternative Fisher exact test. Output with two groups numerical variables will be analyzed using independent t-test, with alternative Mann-Whitney test. Output with numerical variables of more than two groups will be analyzed using one-way ANOVA, with alternative Kruskal-Wallis test. The significance value of each test is 5%, if $p < 0.05$ means that it is statistically significant and if $p > 0,05$ it means not significant. In the analysis, 95% confidence interval (CI) between each group should not pass zero so it can be said statistically significant. The 95% confidence interval value that passes zero is considered statistically significant.

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Attachment:

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KETERANGAN LOLOS KAJI ETIK

ETHICAL APPROVAL

Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Indonesia dalam upaya melindungi hak asasi dan kesejahteraan subyek penelitian kedokteran, telah mengkaji dengan teliti protokol berikut informasi yang diberikan kepada calon subjek yang berjudul:

The Ethics Committee of the Faculty of Medicine, University of Indonesia, with regards of the Protection of human rights and welfare in medical research, has carefully reviewed the research protocol including the information given to the potential subjects entitled:

"Peran Injeksi Asam Traneksamat pada Tatalaksana Perdarahan Saluran Cerna: Sebuah Uji Klinis Terkontrol Acak Tersamar Ganda".
No. protokol: 18-04-0393

Peneliti Utama : **Dr. dr. Ari Fahrial Syam, SpPD-KGEH, MMB**
Principal Investigator

Nama Institusi : **Ilmu Penyakit Dalam FKUI-RSCM**
Name of the Institution

dan telah menyetujui protokol berikut informasi yang diberikan kepada calon subjek.
and approves the above mentioned protocol including the information given to the potential subjects.

1 6 APR 2018
Ketua
Chairman

Prof. dr. Rita Sita Sitoras, SpM(K), PhD

* *Ethical approval* berlaku satu tahun dari tanggal persetujuan.
** Peneliti berkewajiban:
1. Menjaga kerahasiaan identitas subyek penelitian.
2. Memberitahukan status penelitian apabila
   a. Setelah masa berlakunya keterangan lolos kaji etik, penelitian masih belum selesai, diminta hal ini *ethical approval* status diperpanjang.
   b. Penelitian berhenti di tengah jalan.
3. Melaporkan kejadian serius yang tidak diinginkan (*serious adverse events*).
4. Peneliti tidak boleh melakukan tindakan apapun pada subyek sebelum protokol penelitian mendapat lolos kaji etik dan sebelum memperoleh *informed consent* dari subyek penelitian.
5. Menyampaikan laporan aktivi, bila penelitian sudah selesai.
6. Cantumkan nomor protokol ID pada set up komunikasi dengan KEPK FKUI-RSCM.

Semua prosedur persetujuan dilakukan sesuai dengan standar ICH-GCP.
All procedure of Ethical Approval are performed in accordance with ICH-GCP standard procedure.