Research protocol:

Project summary

Background and Objectives: Total knee arthroplasty (TKA) is sometimes associated with significant perioperative bleeding. The aim of this study was to determine the efficacy of tranexamic acid (TXA) in reducing perioperative blood loss in patients undergoing primary TKA. The secondary objectives are to assess the efficacy of TXA in reducing the need for blood transfusion in these patients and to determine its effect on verticalization and ambulation after TKA.

Patients and Methods: The study will include patients who will be randomly assigned to two groups, each containing 50 patients. The study group will receive tranexamic acid TXA intravenously at two time points, immediately after the induction with doses of 15 mg/ kg, and 10 mg/kg 15 minutes before the release of the pneumatic tourniquet. The control group will receive an equivalent volume of 0.9% saline solution via the same route. .

Time frame: investigators expect to recrute partcipants (patients) in time frame up to 24 months.
Expected outcomes: TXA is an effective drug for reducing the incidence of perioperative bleeding, decreasing transfusion rates, and indirectly improving postoperative functional recovery in patients undergoing primary TKA.

General information

RESEARCH PROTOCOL TITLE: The Effect of Intravenous Tranexamic Acid on Perioperative Blood Loss, Transfusion Requirements, Verticalization, and Ambulation in Total Knee Arthroplasty

Date:_____

Clinical Centre of Vojvodina. Hajduk Veljkova street no 1. Novi Sad, Serbia, zip code: 21 000.

www.kcv.rs. telephone no +381214843484

Prime investigator: Gordana Jovanovic M.D., Ph.D, Clinical Centre of Vojvodina. Hajduk Veljkova street no 1, Novi Sad, Serbia, zip code: 21 000, gordana.jovanovic@mf.uns.ac.rs, telephone no :+381642919537

Rationale & background information

This study's strength lies in its meticulously design double blind randomized trial, which examines the effects of tranexamic acid on transfusion requirements and the functional recovery of patients, in addition to its effectiveness in reducing perioperative bleeding following primary unilateral total knee replacement. This is a broad view on the subject not done in many efficacy studies of tranexamic acid. In light of the accelerated recovery after surgery (ERAS) idea, practicing physicians can benefit greatly from this research.

Study goals and objectives

Hypothesis

The nul hypothesis is that there is no difference among two groups in perioperative blood loss, need for transfusion, and postoperative verticalisation and ambulation after tranexamic acid (TXA) application in total knee replacement. Our Hypothesis is that there is statistically significant difference between two groups in perioperative blood loss, need for transfusion, and postoperative verticalisation and ambulation.

Objectives: Primary objective: This trial was designed to determine the efficacy of TXA in reducing perioperative blood loss in patients undergoing primary TKA. **Secondary objectives**: to determine the efficacy of TXA in reducing the need for blood transfusion in patients undergoing primary TKA, and to assess its effect on verticalization and ambulation after TKA.

Study design

The research was conducted as a single centered, controlled, prospective, randomized, double-blind study at the Clinic for Orthopedic Surgery and Traumatology of the University Clinical Center of Vojvodina in Novi Sad

Patients

Inclusion Criteria

Adult female and male patients who underwent primary, unilateral TKA due to degenerative knee diseases, with ASA status 1-3, who provided written informed consent to participate in the study.

Exclusion Criteria

Patients with a known allergy to TXA, coagulation disorders, previous history of any type of thromboembolic event, or those who received fresh frozen plasma, other blood products, or drugs affecting the coagulation system 24 hours before surgery were excluded from the study. Additionally, patients with severe heart disease (New York Heart Association Classification-NYHA III and IV), creatinine values above115 μmol/l for men and 100 μmol/l for women, elevated liver enzymes, or congenital thrombophilia were also excluded.

Sample size calculation

Sample size calculated with significance level $\alpha = 0.005$, and P (power) of 90% (0.9) is 43 in each group.

Anesthesia and surgery

All patients received spinal anesthesia with isobaric bupivacaine 0.5% (Marcain spinal 0.5%, Astra Zeneca) at a dose of 15mg (3ml). Standard intraoperative monitoring was conducted, including continuous monitoring of heart function by electrocardiogram (D II lead), non-invasive blood pressure measurement, and pulse oximetry (Infinity Delta XL, Drager) . The night before the surgery, all participants received subcutaneous low molecular weight heparin nadroparin calcium (Fraxiparine 2850 IU/0.3mL, GlaxoSmithKline), dosed according to body weight.

All TKA's were performed by the same surgical team, using a pneumatic tourniquet inflated at 200-250 mmHg.

Method of Drug Administration:

The study group received TXA (Tranexamic acid Medochemie® 500mg/5 mL) at two time points (T1 and T2), with doses of 15 mg/ kg and 10 mg/kg, respectively. The drug was administered as a continuous intravenous (i.v.) infusion over 15 minutes. The first time point (T1) was immediately after the induction of anesthesia, while the second time point (T2) was 15 minutes before the release of the pneumatic tourniquet.

The control group received the same volume of 0.9% saline solution via the same route (i.v.).

The attending anesthesiologist and anesthesia assistant were blinded to IV infusion content. Patients were allocated using a random selection method.

Blood Loss Measurement

During the research, blood loss was measured as intraoperative and postoperative blood loss. The intraoperative loss was estimated by visually examining graduated suction canisters, expressed in milliliters, and gauze/sponges loss was determined using the gravimetric method.

The postoperative blood loss was measured after 6, 12, and 24 hours, including drain loss measured in milliliters and total postoperative loss from 0-24 hours.

The hemoglobin level at which allogeneic blood transfusion was initiated in this study was 9 g/dl.

Verticalization and Ambulation

Following surgery, each patient underwent the same early rehabilitation regimen led by a physiotherapist. Every patient received the same multimodal analgesia, including weak opioid and nonsteroidal anti-inflammatory drugs (NSAID's) intravenously.

Safety considerations

The study is underpowered to determine safety of tranexamic acid, but all significant side effects or complications will be recorded, from induction of anesthesia up to discharge from the hospital.

For each individual patient Wells score for DVT (deep venous thrombosis), Wels score for PTE (pulmonary thromboembolism) and revised Geneva score for PTE will be calculated.

Follow-up

Follow –up period is up to discharge from the hospital, done by study investigators

Data management and statistical analysis

Following the randomization procedure, the study data protocol (in paper form) will be completed. The study's data protocol includes the following: general information (age, sex, admission and discharge dates), ASA status, BMI, preoperative diagnoses, concomitant diseases, length of the procedure, pneumatic tourniquet pressure, preoperative laboratory data (CBC,urea,

creatinin, trombocytes, aptt, PT), intraoperative bleeding in mililiters (gravimetric + aspirator), postoperative bleeding (6, 12, 24 hours), quantity of blood units, timing of blood application, use of kristaloids and colloids, postoperative laboratory data (CBC,urea, creatinin, trombocytes, aptt, PT), and postoperative recovery variables, including first meal and first time to sit, stand, and walk.

All individual study protocols will be entered in excel table for further statistical analysis. In excel table all names will be deindentified by number (code). Data analysis will be performed SPSS 26 for Windows.

Standard methods of statistical research, including descriptive statistics and frequency distribution, were used in the analysis. Numerical data were presented through mean arithmetic values and standard deviation, while comparisons of the examined groups were performed using the t-test and the Mann-Whitney U test. Pearson's $\chi 2$ test was used to test the difference in frequency (distribution) of the observed parameters. Binary logistic regression analysis was used to analyze factors related to the use of transfusion. The significance level was set at a *p*-value less than 0.05 .

Expected outcomes of the study

Expected outcome is that TXA is an effective drug for reducing the incidence of perioperative bleeding, decreasing transfusion rates, and indirectly improving postoperative functional recovery in patients undergoing primary TKA.

Dissemination of results and publication policy

Publication policy: A peer-reviewed journal is where the study is intended to be published.

Duration of the project

Study design and ethical approvement: up to 12 months

Recruiting the patients and gathering the research data :up to 24 months

Data analysis: up to 6 months

Problems anticipated

Investigators do not expect any major problems in the conducting the study.

Project management

author	email address	telephone no	ORCID ID
Gordana Jovanovic	gordana.jovanovic@mf.uns.ac.rs	+381642919537	0000-0003-4899-4748
Teodora Tubic	teodora.tubic@mf.uns.ac.rs	+381641114434	0000-0001-8094-4607
Mirka Lukic-Sarkanovic	mirka.lukic-sarkanovic@mf.uns.ac.rs	+381600148289	0000-0001-8977-1423
Filip Lazetic	lazetic90@gmai.com	+381631028087	none
Dajana Lendak	dajana.lendak@mf.uns.ac.rs	+381638181042	0000-0003-4323-1776
Arsen Uvelin	arsen.uvelin@mf.uns.ac.rs	+381642750276	0000-0002-5930-0089

Author Contributions

Author GJ-designing the research study, performing the research, writing final manuscript

Author MLS- performing conceptualization and writing the original drafts

Author FL -performing the research

Author TT -performing conceptualization and writing the original drafts.

Author AU- writing original drafts, writing final manuscript

Author DL- gathering and analyzing the data.

Ethics

The study was approved by the Ethics Committee of the Clinical Center of Vojvodina in Novi Sad (Serbia). Document no 00-01/97 . The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants signed written informed consent.

Informed consent forms

ПРИЛОГ 2

Пристанак информисаног испитаника

Предложено ми је да учествујем у клиничком испитивању које се спроводи на Клиници за ортопедску хирургију и трауматологију, Клиничког центра Војводине у Новом Саду, чији је циљ боље разумевање деловања транексамичне киселине на периоперативно крварење код уградње тоталне протезе колена. Дато ми је до знања да се могу добровољно укључити у истраживање или да не морам пристати на њега, а да при том не сносим последице. Информисан/а сам да је тајност података који ће се користити у испитивању загарантована. Прочитао/ла сам и у потпуности разумео/ла предочену информацију и дајем свој добровољни пристанак за учешће у клиничком испитивању.

ПОТПИС ИСПИТАНИКА ПОТПИС ИСПИТИВАЧА

У Новом Саду ,

Датум:

INFORMED CONSENT

I was invited to take part in a clinical trial at the Clinic for Orthopedic Surgery and Traumatology, Clinical Center of Vojvodina in Novi Sad. The purpose of the trial is to gain more insight into how tranexamic acid affects bleeding during surgery when a total knee prosthesis is being installed. I have been informed that I can voluntarily participate in the research, or that I do not have to agree to it, without suffering any consequences. I have been informed that the confidentiality of the data in the research is guaranteed.

I have read and fully understood the presented information and I give my voluntary consent to participate in the clinical trial

SIGNATURE OF THE EXAMINER SIGNATURE OF THE PARTICIPANT

In Novi Sad,

Date

ПРИЛОГ 3

Информација за пацијента

Поштовани,

Позивамо Вас да учествујете у нашој студији, која ће се спроводити У Клиничком Центру Војводине на Клиници за ортопедску хирургију и трауматологију у Новом Саду.

Ви се подвргавате хируршкој интервенцији замене тоталне протезе колена, која представља дефинитивни вид лечења вашег обољења. Напредком хируршке технике и анестезиологије ова интервенција је успешна и безбедна. Међутим, оно што прати сваку хируршку интервенцију је крварење које се код различитих интервенција дешава у различитом обиму. Трендови у модерној медицини и хирургији иду у правцу смањивња крварења и што мање употребе крви и крвних препарата који су добијени од добровољних давалаца (туђе крви). Наша студија ће се бавити управо таквом тематиком. Током хируршке интервенције био би примењен лек –транексамична киселина који спада у групу фибринолитика, а то су лекови који деловањем на систем згрушавања крви

смањују крварење током и после операције. Овај лек је у употреби већ око 50 година и у ове сврхе већ успешно користи при операцијама на отвореном срцу и другим хирургијама. Сврха нашег истраживања је да утврдимо каква су дејства овог лека у ортопедској хирургији. За ово истраживање нису потребна никаква додатна испитивања сем стандардне припреме за оперативни захват. Била би примењена стандардна анестезија примерена овом хируршком захвату. Подаци добијени од вас уз Ваш пристанак би били употребљени за касније истраживање.

Ваше право је да од Вашег анестезиолога затражите све додатне информације које вас занимају, пре него што донесете одлуку о укључивању у ово истраживање. Од укључивања у ово истраживање нећете имати никакве материјалне користи ни надокнаде, сем потенцијално бољег квалитета лечења.

Уколико не желите да учествујете у овом истраживању, то неће имати никакав утицај на Ваше лечење и однос Вашег лекара према Вама.

Име и презиме и сви Ваши подаци су поверљиви и остају лекарска тајна. Ако се се одлучите да приступите овом истраживању молимо Вас да потпишете понуђени образац.

Са поштовањем ,

др Гордана Јовановић

INFORMATION FOR THE PATIENT

With respect,

Please accept our invitation to take part in our study, which will be carried out in Novi Sad at the Clinic for Orthopedic Surgery and Traumatology's Clinical Center of Vojvodina.

You are undergoing a surgical intervention to replace a total knee prosthesis, which is the definitive form of treatment for your disease. With the advancement of surgical technique and anesthesiology, this intervention is successful and safe. However, what accompanies any surgical intervention is bleeding, which occurs to a different extent in different interventions.

Reducing bleeding and utilizing blood and blood products from voluntary donors (other people's blood) as little as possible, are the current trends in surgery and medicine. Our research will focus on this subject. Tranexamic acid, the class of medications known as fibrinolytics—drugs that lessen bleeding during and after surgery by influencing the blood clotting system—would be given during the surgical procedure.

This drug has been in use for about 50 years and is already successfully used for these purposes in open heart surgery and other surgeries. Finding out how this medication affects orthopedic surgery is the aim of our study. Other than the routine testing before surgery, no further tests are

needed for this investigation. The standard anesthetic would be used, suitable for this type of surgery. With your permission, data collected from you will be utilized in future studies.

Before choosing to take part in this study, you have the right to ask your anesthesiologist for any more information that you interested in. Your participation in this study will not result in any financial gain or remuneration, although you might receive higher overall quality of care.

Name and surname and all your data are confidential and remain a medical secret. If you decide to participate in this research, please sign the provided informed consent form.

With respect ,

Gordana Jovanović M.D., PhD

Research protocol: part 2

Budget

The research is financed by investigators and Clinical Center of Vojvodina.

Other support for the project: NONE

Collaboration with other scientists or research institutions: NONE

Links to other projects: NONE

Financing and insurance

The research is financed by investigators and Clinical Center of Vojvodina.