# Tranexamic acid versus Mefenamic acid for treatment of heavy menstrual bleeding in IUCD users : A Randomized Controlled Trial

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# *List of abbreviations*

**DNA:** *Deoxy-ribonucleic acid*
**DUB:** *Dysfunctional uterine bleeding*
**EC**: *Emergency contraception*
**$FDP_s$:** *Fibrinogen degradation products*
**FSH**: *Follicular stimulatory hormone*
**Gn- RH**: *Gonadatrophine releasing hormone*
**HCG:** *Human chorionic gonadotropin*
**HCG**: *Human chorionic gonadotropine*
**HIV**: *Human immunodeficiency virus*
**HMB**: *Heavy menstrual bleeding*
**IUCD:** *Intra uterine contraceptive device*
**IUD:** *Intra uterine device*
**IUS**:*Intrauterine system*
**LH**: *Lutenizing hormone*
**LH-RH**: *Lutenizing hormone releasing hormone*
**LNG-IUD:** *Levonorgestrel intra uterine device*
**MBL:** *Menstrual blood loss*
**$NSIAD_s$**: *Non steroidal anti inflammatory drugs*
**PAS** : *Periodic acid- Schiff*
**PCOS**:*Polycystic ovary syndrome*
**$PG_s$:** *Prostaglandins*
**PID:** *Pelvic inflammatory disease*
**STIs**:*Sexually transmitted infections*
**$TXA_2$:** *Thromboxane $A_2$*

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# Introduction

The IUD is the most common method of reversible contraception worldwide. More than 100 million women around the world use IUD device. Among the contraceptive methods, IUD is a safe one with failure rate of below 1%, which is approximately equal to tubal sterilization **(Madden, 2010).**

Potential side effects of intrauterine devices include expulsion, uterus perforation, pelvic inflammatory disease (especially in the first 21 days after insertion), as well as irregular menstrual pattern. A small probability of pregnancy remains after IUD insertion, and when it occurs there is a greater risk of ectopic pregnancy. Substantial pain that needs active management occurs in approximately 17% of nulliparous women and approximately 11% of parous women **( Gemzell, 2013).**

The most common complication of using IUD includes increased bleeding and cramps. Also, bleeding may be to the extent that leads to iron deficiency anemia **(Cunningham,2010).** Therefore, increased amounts of bleeding have a great impact on the lives of many women **(Yen , 2010).**

Menorrhagia is an abnormally heavy and prolonged menstrual period. Menorrhagia can be caused by abnormal blood clotting, disruption of normal hormonal regulation of periods, or disorders of the endometrial lining of the uterus. Abnormal uterine bleeding including menorrhagia and intermenstrual bleeding, is one of the most frequent side effects of intrauterine device (IUD) use, and the most common medical reasons for premature discontinuation of the IUD. Among women 30-49 years of age, 1 out of every 20 women refers with menorrhagia and about 30% of the women report that 10-15% of their menorrhagia was caused by IUDs **(Berek ,2012).**

Medical therapy for menorrhagia should be tailored to the individual. Factors taken into consideration when selecting the appropriate medical treatment include the patient's age, coexisting medical diseases, family history, and desire for fertility. Medication cost and adverse effects are also considered because they may play a direct role in patient compliance. The above mentioned derangement of the haemostatic process, suggests an approach to the treatment of IUD related menorrhagia by means of oral anti-fibrinolytic agent Tranexamic acid and NSAID Mefenamic acid **( Julia, 2013).**

Tranexamic acid is a synthetic derivative of the amino acid lysine. It's available in many trade names; the one used in this study is oral (Kapron® 500) tablets. It exerts its antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules. It inhibits endometrial plasminogen activator and thus prevents fibrinolysis and the breakdown of clot. Side effects are uncommon. While prolonged treatment may heighten the risk of an increased thrombotic tendency, such as deep vein thrombosis, large scale studies reveal that the incidence of thrombosis in women treated by tranexamic acid is no different from the spontaneous incidence of thrombosis in women **(James et al., 2009).**

Mefenamic acid (Ponstan®) is a member of the fenamate group of nonsteroidal anti- inflammatory drugs (NSAIDs). Each capsule contains 500mg of mefenamic acid for oral administration. Mefenamic acid is a competitive inhibitor of COX-1 and COX-2, which are responsible for the first committed step in prostaglandin biosynthesis. Decreasing the activity of these enzymes thus reduces the production of prostaglandins, which are implicated in inflammation and pain processes. Mefenamic acid is recommended to be taken with food to minimise GIT side effects **( Lukes, 2010).**

# Aim of work

This study aims to compare the efficacy of the Tranexamic acid and Mefenamic acid in controlling menorrhagia induced by Cu IUCD.

## Research Hypothesis

In women having menorrhagia with IUCD Tranexamic acid and Mefenamic acid may be equally effective in controlling the symptoms.

## Research Question

In women having menorrhagia with IUCD, is Tranexamic acid effective as Mefenamic acid in treatment of symptoms?

# Patients and methods

## Study Design

Two-arm, single-blind, randomized controlled trial to assess the efficacy of the Tranexamic acid and Mefenamic acid in controlling menorrhagia induced by Cu IUCD :

- The **first** arm (group T) represents patients who will receive Tranexamic acid (52 patients).
- The **second** arm (group M) represents patients who will receive Mefenamic acid (52 patients).

## Study Setting

The study will be carried out in Ain Shams University Maternity Hospital.

## Study Population

Patients will be selected from patients attending to Ain Shams University Maternity Hospital outpatient clinic of Gynecology, complaining of increased menstrual flow secondary to a current copper IUD use. The study aims will be explained and a written informed consent to participate in the study will be obtained.

All subjects will undergo full medical interview and clinical examination to ensure eligibility for enrolment in the study.

## Including criteria

All cases in this study should include the following criteria:

- Age: 20-40 years.
- Subjectively perceived menorrhagia (heavy and prolonged menstrual period).
- Well fitted IUD, not misplaced.

## Exclusion criteria

- Irregular menstrual cycle.
- Presence of systemic causes of abnormal uterine bleeding as hypertension and hemorrhagic blood diseases.
- Presence of other local causes of abnormal uterine bleeding as, (fibroid, adenomyosis, polyps).
- Receiving drugs affecting blood coagulation.
- Preexisting renal disease.
- History of venous or arterial thrombosis.
- Acute active ulceration or chronic inflammation of the GIT.

## Randomization

After enrolment, participants would be given the next available number in a computer-generated randomization plan (Appendix 1).

## Allocation and Concealment

Opaque, serially-numbered, sealed envelopes will enclose the letter corresponding to the group the patient will follow. Envelopes will be opened when the patient is enrolled and she will receive the intervention accordingly.

## Study Interventions

- **Group(T):** patients will be asked to fill out menstrual diaries provided to them for one cycle without treatment, then will use **tranexamic acid (Kapron®)**2*500 mg oral tablets t.d.s(three times daily) on the day before the next menstrual cycle and for 5 days for two cycles.

- **Group (p):** patients will be asked to fill out menstrual diaries provided to them for one cycle without treatment, then will use **Mefenamic acid (Ponstan®)** 500 mg oral tablets t.d.s on the day before the next menstrual cycle and for 5 days for two cycles.

## Study Outcomes

## Primary Outcome Measure

The efficacy of the treatment to minimize menorrhagia in IUCD users will be measured by using **Pictorial Blood Assessment Chart and Scoring System** (Appendix 2).

## Secondary Outcome Measures

Between the two groups, the following parameters will be assessed and compared:

- HB %
- Side effects of the drug
- Patient satisfaction

## Methodology

All women will be subjected to the following :

1. Taking their **consent** to participate in the study.

2. Detailed **clinical history** with special consideration to age, parity, duration of IUCD use, duration of menorrhagia and history of other contraceptive methods prior to IUCD use.

3. **Menstrual history** before participation in the study including duration and amount of menstrual flow, regularity and length of the cycle, intermenstrual bleeding or spotting, contact bleeding and any associated symptoms or complaints. Also history of any drug intake, blood disease or any medical disorders will be considered.

4. **Clinical examination** include general, abdominal and pelvic examination including bimanual examination to detect any abnormal findings and speculum examination to detect the threads of the IUCD and exclude any local cause of bleeding as polyp or erosion.

5. **Transvaginal ultrasound** will be done- after instructing the patients to empty their bladders- to measure uterine size and dimensions, endometrial thickness, exclude other local causes of abnormal uterine bleeding as ( fibroid, adenomyosis, polyps) , ovarian size, texture, presence of follicles and misplaced IUD.

6. **CBC** will be done to know the basal hemoglobin level.

7. patients will be asked to fill out menstrual diaries provided to them for one cycle without treatment, then will use **treatment** on the day before the next menstrual cycle and for 5 days for two cycles. All patients will be asked to fill out menstrual diaries provided to them and to come for **following up** after the initial evaluation until the end of the study. After that, another CBC will be performed.