Oral Tranexamic Acid Versus Diosmin for Treatment of Menorrhagia in Women using Copper IUD: Randomized controlled trial

Thesis

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By

Rahma Aly Mohammed

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Al-Galaa Teaching Hospital

Under Supervision of

Prof. Hassan Tawfek Khairy

Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Assist. Prof. Sherif Hanafi Hussain

Assistant professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Ahmed Ali Moustafa Al Anwar

Lecturer of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

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List of abbreviations & Acronyms

AUB	**:**	Abnormal uterine bleeding
COCs	**:**	Combined oral contraceptive pills
CRASH2	**:**	Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage
DUB	**:**	dysfunctional uterine bleeding
EMB	**:**	Endometrial biopsy
FDA	**:**	Food and Drug Administration
FDPs	**:**	Fibrinogen degradation products
FSH	**:**	follicle stimulating hormone
GI	**:**	Gastrointestinal
Hb	**:**	Hemoglobin
hCG	**:**	Human Chorionic Gonadotropin
HMB	**:**	Heavy Menstrual Bleeding
ICC	**:**	Intraclass Correlation Coefficient [
IUCD	**:**	Intrauterine contraceptive device
IUD	**:**	Intra intrauterine device
JOGC	**:**	Journal of obstetric and gynaecology
LH	**:**	Luteinizing Hormone
LNG-IUS	**:**	Levonorgestrel-releasing intrauterine device
MBL	**:**	Menstrual Blood Loss
MPA	**:**	Medroxyprogesterone acetate
NSAIDs	**:**	Non steroidal anti-inflammatory drugs

OCP	**:**	Oral contraceptive pills
PBAC	**:**	Pictorial blood assessment chart
PGE2	**:**	Prostaglandin E2
PGs	**:**	Prostaglandins
PID	**:**	Pelvic Inflammatory Disease
PIDs	**:**	Pelvic Inflammatory Diseases
PM	**:**	Pharmacy Medicines
PMS	**:**	Premenstrual Syndrome
PoM	**:**	Prescription only Medicines
SD	**:**	Standard deviation
SPSS	**:**	Statistical Program for Social Science
STD	**:**	Sexual transmited diseases
TXA	**:**	Tranexamic acid
TxA2	**:**	Thromboxane A2

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Introduction

Menorrhagia is a problem that involves a large group of women. 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 IUD ***(Berek et al., 2012).***

Among the contraceptive methods, IUD is a safe one with failure rate of below 1% ***(Madden et al., 2010; Berek et al., 2012).*** More than 100 million women around the world use this device ***(Black et al., 2004).*** The most common complications of using IUD include increased bleeding and cramps ***(Ferraz do Lago et al., 2003).*** Also, bleeding may be to the extent that leads to iron deficiency anemia ***(Cunningham et al., 2010)***.

Each year, an estimated 40 million women have an IUD inserted. From 5% to 15% of women discontinue IUD use within one year because of bleeding ***(Speroff and Darney, 1996).*** In a large trial sponsored by the World Health Organization, the cumulative net probability of removal of a Copper T380A IUD for bleeding over 12 years of use was 36 per 100 women ***(WHO, 2012).***

Tranexamic acid is a synthetic derivative of the amino acid lysine. 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 not different from the spontaneous incidence of thrombosis in women ***(James et al., 2009; Tengborn et al., 2015)***.

Diosmin is a naturally occurring flavonoid glycoside, it's available in many trade name, the one used in this study is oral (Daflon ®500, Servier Egypt, 6th October, Egypt) tablets. Diosmin protects the microcirculation by fighting the microcirculation-damaging process; it combats venous inflammation by decreasing leukocyte activation, and as a consequence, by inhibiting the release of inflammatory mediators, principally free radicals and prostaglandins. Thus, diosmin normalizes capillary permeability and strengthens capillary resistance ***(Manthey, 2000)***.

Flavonoids are a group of polyphenolic compounds, diverse in chemical structure and characteristics, found

ubiquitously in plants. Until now, more than 9000 different flavonoid compounds were described in plants, where they play important biological roles by affecting several developmental processes. There has been increasing interest in the research of flavonoids from dietary sources, due to growing evidence of the versatile health benefits of flavonoids including anti-inflammatory, antioxidant, antiproliferative and anticancer activity, freeradical scavenging capacity, antihypertensive effects, coronary heart disease prevention and anti-human immunodeficiency virus functions ***(Xiao et al., 2011).***

Research has shown that the endometrium of women with heavy menstrual bleeding contains higher levels of prostaglandin E2 and prostaglandin F2α. NSAIDs inhibit the enzyme cyclooxygenase, thereby reducing prostaglandin levels. A Cochrane review in2013 showed that NSAIDs (mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin, and acetylsalicylic acid)are more effective than placebo at reducing menstrual blood loss in women with regular menstrual cycles, but they were less effective than tranexamic acid, danazol (not approved in the United States), and the levonorgestrel-releasing intrauterine device (LNG-IUS) ***(Lethaby et al., 2013).***

Research hypothesis:

In women having IUCD and suffer from menorrhagia, tranexamic acid therapy may reduce mensterual blood equally as diosmin.

Research question:

In women having IUCD and suffer from menorrhagia, does tranexamic acid reduce blood loss equally as diosmin.

This Study Aims:

To compare the efficacy of tranexamic acid and diosmin in reducing menstrual blood loss in women having IUCD and suffer from menorrhagia.

Patients and Methods

In this randomized controlled study hundred women will be included. They will be selected from the women attended to outpatient clinic of Obstetrics and Gynecology, Ain Shams University family planning Clinic complaining from an increased menstrual flow secondary to a current copper IUCD use.

All cases in this study should include the following criteria:

Inclusion Criteria:

- Women complaining from an menorrhagia secondary to a current copper IUD use.
- Age: 20-40years.
- Menorrhagia , will be defined as a PBAC-Score greater than 100.
- No systemic causes of abnormal uterine bleeding as hypertension and hemorrhagic blood diseases.
- No other local causes of abnormal uterine bleeding as, (fibroid, adenomyosis, polyps).
- No drugs decreasing blood coagulation.
- Well fitted IUD not misplaced.

Exclusion criteria:

- Age <20y and >40y.
- 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).
- Taking drugs decrease blood coagulation.
- Misplaced IUD.

They will be divided into 2 groups; each group will be 50 patients:

- ***1st group***: used tranexamic acid oral tablets (Kapron®)500 mg two tablets every six hour with the onset of the first day of menstrual cycle till the end of bleeding.
- ***2nd group***: used diosmin oral tablets (Daflon®) 500 mg t.d.s (three times daily) with the onset of the first day of menstrual cycle till the end of bleeding.

All women will be subjected to the following after taking their written consent: detailed clinical history with special consideration to age, parity, duration of IUCD use, duration of menorrhagia and history of other contraceptive methods before insertion of IUCD.

Menstrual history before participation in the study will be taken 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.

Clinical examination will be done including 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.

Transvaginal ultrasound will be done to exclude other local causes of abnormal uterine bleeding or misplaced IUD.

CBC before the onset of the study will be done to the patients who agree to participate in the study to exclude anemia.

Patients of all groups will be asked to follow the respective protocol of treatment of their allocated group for the following three cycles.

All the patients will be asked to fill out menstrual diaries provided to them and to come to follow-up three