ORIGINAL ARTICLE

Efficacy of Tranexamic acid in treatment of heavy menstrual bleeding

Afshan Batool, Sanha Sarwar, Majida Zafar, Ishtiaq Anwar

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Abstract

Objective: To determine efficacy of tranexamic acid in heavy menstrual bleedings

Study design: Randomized controlled trial

Place & duration of study: Study was conducted at Department of Obstetrics and Gynecology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. Study duration was six months (14th June 2016 to 13th December 2016)

Material and methods: A sample size of 80 patients was calculetd with 1:1 ratio randomization. Simple random sampling was used for recruitment of participants. Patients were randomly divided into two groups; Group A, oral dosage of tranexamic acid 3.9-4 g/day for 4-5 days starting from the first day of the menstrual cycle and Group B (Placebo), folic acid supplementation dose 400µg. patients were followed for 5 days. Efficacy of treatment was measured through mean blood loss (using pre-weighted pads). Chi- square test was applied for observing association between different variables.

Results:Total 80 patients were included with 40 patients in each group. Mean age of patients in Group A (Tranexamic acid) was 25.9±0.7 SD while mean age of patients in Group B (Placebo) was 23.6±0.6 SD. Group A (Tranexamic acid) had <80 ml blood loss in 83% patients while Group B (Placebo) had <80ml blood loss in 30% patients (P=0.000). A significant association was found between mean blood loss in both group & age (p=0.001), hypertension (p=0.00), Diabetes mellitus (p=0.00).

Conclusion:Tranexamic acid is an effective medical therapy for treatment of heavy menstrual bleeding. It is helpful in significant reduction of blood loss and could potentially improve women's quality of life.

Keywords: Heavy menstral bleeding, tranexamic acid, folic acid, placebo

Mother and Child health center, Pakistan Institute of Medical Sciences, Islamabad
A Batool
M Zafar

Allama Iqbal Memorial Hospital, Silakot
S Sarwar

Eye Donors Organization, Wah Cantt
I Anwar

Correspondence:
Dr Ishtiaq Anwar
Research Officer, Eye Donors Organization, Wah Cantt, EDO Eye Hospital, Gadwal, 26 Area, Wah Cantt.
Cell: + 92-301-5038267
Email: Sulehrionline99@hotmail.com

Introduction:

Heavy menstrual bleeding is significantly associated with women's quality of life. Prevalence of heavy menstrual bleeding in Europe is 27%.[1] However, prevalence of heavy menstrual bleeding in Pakistan's semi urban areas is 16.2% while 16.4% in urban areas.[2] Heavy menstrual bleeding is defined as "blood loss > 80 ml per menstrual cycle or excessive menstrual bleeding that can affect a women's physical, emotional and social quality of life". Heavy menstrual bleeding etiology is variable and could be divided as local, systematic and idiopathic. Patho-physiology of heavy menstrual bleeding includes ovulatory & anovulatory cycles. Ovulatory cycles includes regular menstrual bleeding (21-32 days) while anovulatory cycles includes prolonged bleeding (≥35 days).[3]

A number of medical and surgical treatment options are available for HMB. These options include oral progestins, non-steroids anti inflammatory drugs (NSAIDs), Oral contraceptives, anti-fibrinolytic drugs levonorgestrel-releasing

intrauterine system (LNG-IUS), endometrial ablation and hysterectomy. Medical alternatives are considered as first line treatment options for HMB worldwide, so that complication due to surgical interventions could be avoided.[4]

Tranexamic acid is an antifibrinolytic drug that is found to be very effective for heavy menstrual bleeding. According to pharmacokinetics, tranexamic acid block lysine binding sites reversibly on plasminogen and helps in prevention of lysine residues interaction with plasmin leading towards fibrin degradation. Most of studies reported intravenous administration while some of them also reported oral administration of tranexamic acid. These studies reported maximum plasma tranexamic level after 2 to 3 hours after 2g of administration. Contradiction of tranexamic acid includes patients with color vision defects, thrombo-embolism, renal impairment, urinary tract bleeding active intravascular clotting and cardiovascular disease.[b]

Naoulu et al reported that 34-54% reduction in blood loss was observed in patients treated with tranexamic acid as compared to placebo. They report tranexamic acid as safe, effective intervention that improves quality of life in patients suffering with idiopathic and non functional heavy menstrual bleeding.[6]

Another similar study reported that 3.9g of tranexamic acid daily reduced mean blood loss < 80 ml in 43% patients as compared to placebo ($p<0.05$). Moreover, mean blood loss at least 50 ml per cycle was achieved in 56% patients who were treated with tranexamic acid compare to placebo ($p<0.001$). Mild adverse effects including headache, stomach pain, redness of eye and back or muscle pain was reported.[7] Milsom et al reported that mean blood loss was significantly reduced in tranexamic acid group as compared to NSAIDs (flurbiprofen 200mg/day for 5 days) ($p<0.05$).[8]

Limited data is available on efficacy of tranexamic acid in heavy menstrual bleeding in Pakistan. So the study aims to determine efficacy of tranexamic acid in heavy menstrual bleedings.

Material and methods:

A randomized controlled trail (RCT) with 1:1 ratio was conducted in Department of Obstetrics and Gynaecology, Pakistan Institute of Medical sciences, Islamabad. The study duration was six months (14th June 2016 to 13th Dec 2016). A sample size of 80 patients was achieved through WHO calculator with 95% confidence interval, 5% level of significance and 80% power of study, P1=43% and P2=17%. Simple random sampling (computer generated number) was used for randomly assigning patients into two groups. Patients age 20-45 years, diagnosed with heavy menstrual bleed, women who had at least 6 months of regularly occurring menstrual cycle (21-35 days apart) with menstrual period not > 10 days were included in study while exclusion criteria was based upon or presence of clinically significant disease; anovulatory dysfunctional uterine bleeding, metrorrhagia, menometrorrhagia, polymenorrhea, endometrial polyps, Patients with uncontrolled hypothyroidism, Severe anemia (hemoglobin < 8g/dL), potential pituitary-prolactin secreting or producing tumor (prolactin ≥30 μg/L), women with a history of bilateral oophorectomy or hysterectomy, hypersensitive patients towards tranexamic acid, female genital tract infections and patients with systemic illness other than diabetes & hypertension (thyroid, kidney, cardiovascular disease). Ethical approval was taken from ethical review board of PIMS. Consenting women were randomized to either Group-A, oral dosage of tranexamic acid 3.9-4 g/day for 4-5 days starting from the first day of the menstrual cycle or Group B (Placebo), folic acid supplementation dose 400μg. Patients were followed for 5 days. Blood loss was quantified with frequency of standard pre- weighted pads utilized by patient. (1 pad=10 ml blood absorption). Efficacy was measured as frequency of pads utilized in 5 days. Data was analyzed using SPSS 22.0. Qualitative variables efficacy, hypertension, DM was measured as frequency and percentages. Quantitative variables age was measured as mean and standard deviation. Effect modifiers like age, hypertension and diabetes mellitus was controlled by stratification. Post-stratification chi-square

Table-1: Comparison of blood loss (No. of pads Utilized) Tranexamic acid versus placebo group

Blood loss (No. of pads utilized)	Groups		Total	Chi-square value	P-value
	Group A (Tranexamic acid)	Group B (Placebo)			
≤ 7 Pad(<80 ml blood loss)	33(83%)	12(30%)	45(56%)	23.478	0.00
>7 pads (≥80 ml blood loss)	7(17%)	28(70%)	35(44%)		
Total	40(50%)	40(50%)	80(100%)		

Table-2: Association between interventional groups & age, hypertension, DM

Age groups	Groups		Total	Chi-square value	P-value
	Group A (Tranexamic acid)	Group B (Placebo)			
20-30 years	33(82%)	35(88%)	68(85%)	10.898	0.690
31-45 years	7(18%)	5(12%)	12(15%)		
Hypertension					
Yes	15(38%)	15(38%)	30(38%)	5.675	0.234
No	25(62%)	25(62%)	50(62%)		
Diabetes Mellitus					
Yes	10(25%)	10(25%)	20(25%)	6.734	0.145
No	30(75%)	30(75%)	60(75%)		
Total	40(50%)	40(50%)	80(100%)		

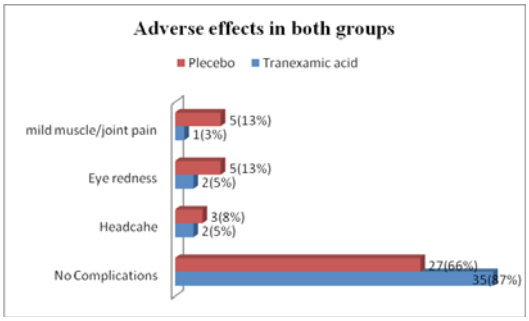

Fig. 1: Adverse effects of both interventional groups

was applied. P value ≤0.05 was considered significant.

Results:

Total 80 patients were included with 40 patients in each group. Mean age of patients in group-A (tranexamic acid) was 25.9±0.7 SD while mean age of patients in group-B (Placebo) was 23.6±0.6 SD. There were 30(38%) patients who had hypertension while 50(62%) patients did not have hypertension during course of study. Among all the patients 80(100%), 20(25%) patients had diabetes mellitus while 60(75%) patients did not have diabetes.

Comparison of blood loss in both Groups is shown in table 1

Among all the patients who had blood loss <80 ml 45(56%), 38 (84%)were in age group 20-30 years while 7(16%) were in age group 30-45 years. similarly among all those patients who had ≥80 ml blood loss 35(44%), 30(86%) were in age group 20-30 years age group while 5(14%) were in age group 30-45 years. a significant association was found between age groups and blood loss (χ2=20.734, df=1, p=0.001). Among all the patients who had blood loss <80 ml 45(56%), 20(44%) patients had hypertension while 25(55%) patients did not have hypertension. Similarly among all those who had ≥80 ml blood loss 35(44%), 10(29%) patients had hypertension while 25(71%) patients did not have hypertension. (χ2=35.982, df=1, p=0.000). Among all the patients who had blood loss <80 ml 45(56%), 5(11%) patients had diabetes while 40(89%) patients did not have diabetes. Similarly, among all those who had ≥80 ml blood loss 35(44%), 15(43%) patients had diabetes while 20(56%) patients did not have diabetes(χ2=35.982, df=1, p=0.000).

Discussion:

Heavy menstrual bleeding is accounts an important indicator of morbidity in women's life. Present study reported that a significant difference in mean blood loss was found between two groups. Patients treated with tranexamic acid, 83% of them had <80 ml blood loss as compared to placebo (p=0.00). Preston et al reported that 45% reduction in mean blood loss(175 to 97 ml) was observed in tranexamic acid group. However, an increase in blood loss was reported with norethisterone by 20% (173 to 208 ml).[9]

Naoulou & Tsai reported that women with idiopathic menorrhagia had significant reduction in mean blood loss from 34% to 54% by using tranexamic acid as treatment option. They also reported that an improved quality of life parameters were observed in patients treated with tranexamic acid.[10] Bonner & Sheppard reported

that significant greater reduction in mean blood loss by 54% was found in tranexamic acid group as compared to ethamyslate and mefenamic acid.[11]

Present study reported that, among all the patients who had blood loss <80 ml 45(56%), 20(44%) patients had hypertension while 25(55%) patients did not have hypertension. (χ2=35.982, df=1, p=0.000). Dunne et al reported that blood pressure usually remain normal at starting phases of menstruation while an adjusted high diastolic blood pressure is found in later stages.[12] Lee et al. reported that a significant high blood pressure is associated with menstrual irregularity.[13]

Present study reported that among all the patients who had blood loss <80 ml 45(56%), 38 (84%) were in age group 20-30 years while 7(16%) were in age group 30-45 years (χ2=20.734, df=1, p=0.001). Winkler reported that heavy menstrual bleeding was found in relatively elder age group as compared to younger age group.[14,15]

Study was conducted at single centre and its small sample size limits the generlizability of study.

Conclusion:

Tranexamic acid is an effective medical therapy for treatment of heavy menstrual bleeding. It is helpful in significant reduction of blood loss and could potentially improve women's quality of life.

Conflict of interest: None

Funding source: None

Role and contribution of authors:

Dr Afshan Batool, collected the data, references and wrote the initial writeup

Dr Sanha Sarwar, collected the references, and helped in introduction writing.

Dr Majida Zafar, collected the data and helped in discussion writing.

Dr Ishtiaq Anwar, critically review the article and made the final changes.

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