

Hemostatic Effect of Intrauterine Instillation of Tranexamic Acid in Hysteroscopic Myomectomy: a double blind RCT

A Thesis

Submitted for partial fulfillment of master degree
in Obstetrics and Gynecology

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2019**



Acknowledgement

First and foremost, I feel always indebted to *Allah*, The Kindest and the Most Merciful.

I wish to express my deep thanks and profound gratitude to Prof. Dr. Ahmed Khairy Makled, Professor of Obstetrics and Gynecology, Faculty of Medicine-Ain Shams University, for his scientific help, valuable guidance, and kind supervision. He gave me much of his precious time, experience and valuable advices to complete this work in the best way.

Special thanks for Pro. Dr. Amgad Al-Said Abou-Gamrah, Professor of Obstetrics and Gynecology, Faculty of Medicine-Ain Shams University, for dedicating so much of his precious time and efforts and for honest and constant guidance to complete this work.

I would like to express my deep appreciation and profound respect to Dr. Radwa Rasheedy Ali, Lecturer of Obstetrics and Gynecology, Faculty of Medicine-Ain Shams University, for her valuable instructions, co-operation, guidance, unlimited help, and efforts to complete this work.

I could never forget to offer my special thanks to all members of my Family, especially my Parents and my Husband, for pushing me forward in every step of my life.



 Hajer Giuma Z. Soliman

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List of Abbreviations

<i>Abbr.</i>	<i>Full-term</i>
AAGL	: American Association of Gynecologic Laparoscopists
ACOG	: American College of Obstetricians and Gynecologists
AUB	: Abnormal uterine bleeding
BSGE	: The british society for gynecological endoscopy
CEE	: Conjugated equine estrogen
EACA	: Epsilone-aminocaproic acid
ECDU	: The Early Cancer Detection Unit
ECM	: Extracellular matrix
ESGE	: The European society for gynecological endoscopy
ESH	: The European society of hysteroscopy
ESU	: The electrosurgical unit
FDA	: Food and Drug Administration
FIGO	:International federation of gynecology and obstetrics.
GnRH.	: Gonadotropin releasing hormone
HI-FU	: The high-intensity focused ultrasound
HMB	: Heavy menstrual bleeding
LNG-IUD	: Levonorgestrel-releasing intrauterine device

MRgFUS	:High-frequency magnetic resonance-guided focused ultrasound surgery
MRI	: Magnetic resonance imaging
PAECs	: Progesterone receptor modulator-associated endometrial changes
PID	: Pelvic inflammatory disease
PPH	: Postpartum hemorrhage
QoL	: Quality of life
RPL	: Recurrent pregnancy loss
SHBG	: Sex hormone binding globulin
SPRMs	: Selective Progesterone Receptor Modulators
TGF- B	: Transforming growth factor b
TXA	: Tranexamic acid
UAE	: Uterine artery embolization
UPA	: Ulipristal Acetate

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Introduction

Uterine fibroids are the most frequent benign solid tumors that can be discovered in the female genital tract (**Okolo, 2008**). The age with highest prevalence (which can reach 70% to 80%) is that of 50 (**American Association of Gynecologic Laparoscopists, 2012**).

Myomas are benign, monoclonal tumors of the smooth muscle cells of the myometrium, which are made up of significant quantities of extracellular matrix which include collagen, fibronectin, and proteoglycan. Collagen type I and type III are plentiful, however, the formation of collagen fibrils is abnormal and lack order, similar to collagen in keloid (**Parker, 2007**).

Often myomas are asymptomatic, however they have been linked to a considerable amount of clinical issues, such as abnormal uterine bleeding (AUB), in particular heavy menstrual bleeding (HMB), infertility, consistent pregnancy loss, and problems that are connected to an enlarged uterus compressing nearby structures (**American Association of Gynecologic Laparoscopists, 2012**).

Abnormal uterine bleeding (AUB) is shown in publications to be the most common cause of hysteroscopic myomectomy. In fact, submucous fibroids have been put forward as the main type causing AUB either due to cavity

distortion and/or augmentation of the bleeding surface of the endometrium (**Sardo et al., 2008**).

The classification of submucous leiomyomas is helpful when considering different therapeutic options (**American Association of gynecologic Laparoscopists, 2012**). The European society of hysteroscopy (ESH) classified submucous myomas according to the extent of myometrial involvement into: Type 0 in which the myoma is completely within the endometrial cavity, type I in which the myoma extends less than 50 percent into the myometrium, and type II in which the myoma extends 50 percent or more within the myometrium (**Wamsteker et al., 1993**).

Regarding to the submucous myoma, resection by operative hysteroscopy is more beneficial than other traditional surgical routes, as there is less myometrial trauma, reduction in hospitalization time, the recovery period is shorter, and there is less risk, if indeed any at all, of formation of postoperative adhesions (**Muzii et al., 2010**).

Success of hysteroscopic myomectomy depends on good visualization throughout the procedure, via the correct distending pressure and control of blood loss. A number of strategies have been put forward to obtain this, including the utilization of danazol and GnRH analogues preoperatively, these medications lead to reduction of intraoperative bleeding, however, they do not have any control over the post-operative bleeding (**Sayyah-Melli et al., 2013**).

Tranexamic acid is an antifibrinolytic which is derived from synthetic Lysine amino acid. It reversibly binds to plasminogen and stops its interaction with fibrin; thus causing an inhibition of the fibrin clots dissolution (**McCormack, 2012**).

There are specific clinical conditions in which localized excessive fibrinolysis within the organs may lead to hemorrhage. This is seen most often in the uterus causing menorrhagia; stomach and duodenum, which can cause gastrointestinal bleeding; and in prostate gland causing hematuria (**Prentice, 1980**).

The reason for localized hemorrhage in these organs is that the relevant tissues are rich in plasminogen activator (tissue activator), which is released excessively in response to trauma. The equilibrium between coagulation and fibrinolysis within these tissues is disturbed with local production of free plasmin causing digestion of hemostatic plugs (**Prentice, 1980**).

Fortunately, the penetration of fibrinolytic inhibitors such as Tranexamic acid is good, so the systemic administration of these agents can inhibit plasmin produced at sites of organ damage. However it is notable that the thrombotic complication of antifibrinolytic agents are not often seen when the drugs are locally administrated (**Prentice, 1980**).

Oral tranexamic acid is commonly utilized in gynecological practice to treat menorrhagia. There are a

number of other indications and forms of administration that are discussed in the literature. A Cochrane review showed that when tranexamic acid was intravenously infused, patients who did not have bleeding diathesis were able to decrease their needs for perioperative blood transfusions by 1 unit (**Sarris et al., 2007**).

A cochrane review, which focused on assessing the effects of the topical administration of tranexamic acid in the control of bleeding. And included 29 trials involving 2612 participants, tranexamic acid reduced blood loss by 29% (**Ker et al., 2013**).

Aim of the Work

The purpose of this study was to investigate whether the intrauterine instillation of Tranexamic acid (TXA) into the distention medium during hysteroscopic myomectomy can reduce blood loss and provide better surgical hemostasis.

Uterine Fibroid

Uterine fibroids (also known as leiomyomas or myomas) are the most common form of benign uterine tumors **(Drayer and Catherino, 2015)**. They are monoclonal tumors of the uterine smooth muscle, composed of large amounts of extracellular matrix (ECM) containing collagen, fibronectin and proteoglycans **(Parker, 2007)**. Leiomyomas occur in 50–60% of women, rising to 80% by the age of 50, and in 20%–50% of cases can cause abnormal uterine bleeding (AUB), anemia, bulk symptoms (urinary symptoms, constipation and tenesmus) and fertility issues **(Singh et al., 2018)**.

Risk factors:-

Race:

Race constitutes an important risk factor for leiomyoma development. The incidence of uterine fibroids reaches 60% by the age of 35 among African-American women, increasing up to >80% by the age of 50, while Caucasian women showing a rate of 40% by the age of 35, increasing to 70% by the age of 50 **(Baird et al., 2003)**. Differences in gene expression in uterine fibroids between these two groups may influence these growth rates **(Davis et al., 2013)**.

Nevertheless, it is clear that African-American women have a greater chance of being affected by uterine fibroids, particularly at an earlier age **(Wise et al., 2016)**.

Age:

Peddada and his colleges (2008) followed the size of 262 leiomyomas from 72 women for up to 12 months using magnetic resonance imaging (MRI). The average growth rate was 9% over 6 months, but growth rates differed between races when age was taken into account. White women under 35 years of age had faster-growing tumors than white women over 45, who exhibited a comparatively slow growth rate.

On the other hand, women of African origin did not show any decrease in myoma growth rates with age. Moreover, delaying the first pregnancy until the third decade of life also places women at higher risk of uterine fibroids (**Petraglia et al., 2013**).

Early menarche:

Early menarche is associated with an increases risk of developing fibroids and is also considered a risk factor for other hormonally mediated diseases, such as endometrial and breast cancers (**Khan et al., 2014**).

Parity:

Pregnancy has been found to have a protective effect on the development of uterine fibroids, but the mechanism remains unclear. It has been suggested that during postpartum uterine remodeling, small lesions may be subject to selective apoptosis. Furthermore fibroid tissue may be highly susceptible to ischemia during both uterine remodeling and parturition (**Laughlin et al., 2010**).

Caffeine and alcohol:

An association has been reported between alcohol and caffeine intake and an increased risk of developing uterine fibroids in a study concerning the health of women of african origin (**Wise et al., 2016**).

Genetic factors:

Some specific genetic alterations are linked to fibroid growth. **Mehine et al. (2013)**, performed whole genome sequencing and gene expression profiling of 38 uterine leiomyomas and the corresponding myometrium. The common occurrence of chromothripsis in uterine fibroids suggests that it also plays a role in their genesis and progression (**Mehine et al., 2013**).

Other factors:

General health status may also be predictive of leiomyoma growth, with factors such as obesity and high blood pressure and diet rich in red meat appears to increase the risk of developing leiomyomas, while smoking decreases the risk (**Islam et al., 2013**).

Classifications:

Numerous classifications of myomas can be found in the literature (**Stamatellos and Bontis, 2007**). All of them take into account the degree of intramural extension and/or uterine cavity distortion.