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Comparing the Effect of Mefenamic Acid and Vitex Agnus on Intrauterine Device Induced Bleeding

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ABSTRACT

Introduction: Increased bleeding is the most common cause of intrauterine device (IUD) removal. The use of alternative therapies to treat bleeding has increased due to the complications of medications. But most alternative therapies are not accepted by women. Therefore, conducting studies to find the right treatment with fewer complications and being acceptable is necessary. This study aimed to compare the effect of mefenamic acid and vitex agnus castus on IUD induced bleeding.

Methods: This was a double blinded randomized controlled clinical trial. It was conducted on 84 women with random allocation in to two groups of 42 treated with mefenamic acid and vitex agnus capsules taking three times a day during menstruation for four months. Data were collected by demographic questionnaire and Higham 5 stage chart (1 month before the treatment and 4 months during the treatment)., Paired t-test, independent t-test, chi-square test, analysis of variance (ANOVA) with repeated measurements, and SPSS software were used to determine the results.

Results: Mefenamic acid and vitex agnus significantly decreased bleeding. This decrease in month 4 was 52% in the mefenamic acid group and 47.6% in the vitex agnus group. The mean bleeding score changes was statistically significant between the two groups in the first three months and before the intervention. In the mefenamic acid group, the decreased bleeding was significantly more than the vitex agnus group. However, during the 4th month, the mean change was not statistically significant.

Conclusion: Mefenamic acid and vitex agnus were both effective on IUD induced bleeding; however, mefenamic acid was more effective.

Introduction

Intrauterine device (IUD) is a key part of modern contraception. More than 130 million women worldwide use it due to its length of effect, high impact in contraception, and its low cost compared to other methods.[1,2] IUD effectiveness during 10 years of use is about 99.2-99.4% which is comparable to tubal ligation (TL).[3-5]

With the exception of progesterone IUD, 50-100% of all types of IUDs increase menstruation blood compared to its pre-placement.[6,7] Among 160 million women who use IUD worldwide[8] about 48% suffering from excessive bleeding, which is often associated with discomfort or pain in the lower abdomen.[9] IUD induced bleeding appears in various ways such as increased bleeding in menstrual cycles of more than 80 ml, and increased duration of bleeding during menstrual period.[7] The reason of bleeding in women using IUD is multifactorial. Increased local fibrinolytic activity is the main cause of menstruation blood. Another reason for the increased bleeding is increased prostaglandin which IUD may cause.[10] IUD induced bleeding may

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be annoying and makes women reluctant to use this method.[11] Therefore, instead of using IUD, they ask for early sterilization, or choose less effective and inappropriate methods that puts them in the risk of unwanted pregnancy.[7,12,13] For the treatment of functional uterine bleeding, if IUD is used, several medical procedures exist including anti-fibrinolytic therapies such as tranexamic acid, nonsteroidal anti-inflammatory drugs, combined contraceptive pills, progesterone, and danazol.[14-17] Since the majority of medical treatments used to control bleeding are associated with several complications, many non-pharmaceutical procedures that are used in most countries have grown recently among which herbal therapy is another one.[16-18]

Herbal therapies and homeopathic treatments are natural alternatives and can be used to regulate the menstrual cycle. Compared to other medications, herbal remedies have fewer complications for the immune system. Many plants through balancing the body's hormone levels can reduce uterine severe bleeding. In addition, herbal medicines can reduce menstrual pain and cramping caused by severe bleeding. Some of the plants functions are anti-inflammatory which acts to remove water and help in relaxation.[18]

One of the plants to reduce bleeding is vitex agnus castus. This plant grows in warm regions of the world. This is a local plant of the Mediterranean, Central Asia, Italy, and Germany,[19,20] and is also local in Iran and has a long history of herbal therapy and traditional medicine in many parts of the world.[19] Vitex agnus castus has long been used in traditional medicine; it belongs to the mint family and is a shrub with purple needle leaves.[21] It is used for the treatment of infertility, menstrual disorders including premenstrual syndrome, dysmenorrhea, menorrhagia, secondary amenorrhea, uterine inflammation, pre-menopausal disorders, acne, fibrocystic breast disease and hyperprolactinemia.[22,23] Vitex angus increases the production of luteinizing hormone (LH) and mildly inhibits the release of follicle stimulating hormone (FSH) resulting in a diversion of the amount of estrogen to progesterone.[24] In Iran, in 1991 research on botany, agriculture, and pharmacognosy and its production began, and from 1996 a drug called "*vitex agnus*" was produced and supplied to the pharmaceutical market in Iran.[25]

Mercorio et al.[26] conducted a study on 24 women with IUD who were suffering from severe menstrual bleeding. The subjects were separated into two groups of receiving 500 mg mefenamic acid 3 times a day for 5 to 8 days and recipients of desmopressin 500 mcg for 5 days. The subjects were asked to continue their treatment for 3 menstrual periods. After the treatment, menstrual bleeding significantly reduced in both groups and there was no statistically significant difference between the two groups. Bleeding was reduced to 75% in the mefenamic acid recipients and 80% in the group receiving desmopressin. The women in this study were divided into two groups of receiving 500 mg mefenamic acid 3 times a day for 5 days and the placebo group. In this study, menstrual irregularities included severe bleeding, bleeding between menstruations and spotting. Statistical significant differences between groups were observed in reducing bleeding after 1 month of treatment.[27]

In a study on 51 women who had excessive bleeding, 25 women used levonorgestrel IUD and 26 women received oral mefenamic acid. The mean reduction in menstrual blood after 6 menstrual cycles in the group with levonorgestrel IUD was 5 ml and in the group receiving mefenamic acid was 100 ml.[25] Another study on 48 women using depot medroxy progesterone acetate (DMPA) who were suffering from menstruation severe bleeding. In this study, 23 women received mefenamic acid capsule and 25 received placebo as the treatment. In a short period of treatment, statistically significant difference was observed between the two groups in the amount of menstrual

bleeding.[28] A study in the Aromatic Medical Center showed that vitex agnus reduced bleeding.[29] A research on 57 women with severe menstrual bleeding (menorrhagia) who were treated with vitex agnus drops showed that 40 patients after the period of treatment had significantly been improved.[30]

Considering the increased bleeding in half of women using IUD, some clients do not choose this safe and effective method or even if they select it, they would be anxious while using IUD and feel uncomfortable due to its bleeding. The increasing numbers of women using the IUD is an important public health aim and the role of midwives in family planning and population control are important, and consequently improving the quality of family planning and care is the primary principles of midwifery. Studies refer to the vitex agnus treatment effect on the reduction of abnormal uterine bleeding, and they show that vitex agnus has less side effects compared to the mefenamic acid.[24] IUD induced bleeding is one of the common and uncomfortable complications among women using this method. Among the recommended herbal therapies, vitex agnus with similar treatment mechanism has minimal side effects and it is convenient to be used due to its positive affects.[24] Therefore, this study was conducted to evaluate the effectiveness of vitex agnus on IUD induced bleeding, and it is hoped to use the results in improving the quality of family planning services, increase the use of this method and finally improve the maternal health.

Materials and methods

This was a double blinded clinical trial study. The target population were married women in reproductive age (15-40 years old) who referred to Shohadaye Fardis Health Medical Center in 2012 (the reason for choosing this center was because of the high rate of IUD placement which was an average of 30 cases per month). Besides, this study aimed to determine the effectiveness of mefenamic acid and vitex agnus on IUD induced bleeding.

Stata Statistical Software, Release 9.2 (Stata Corporation, College Station, TX, USA) was used to determine the sample size. The number of subjects according to the available data from a study was estimated 42 subjects for each group (Mean1 = 100, Mean2 = 134; SD1 = SD2 = 15; Power = 0.80, α = 0.05, n = 38).[24] Inclusive criteria included lack of medicine sensitivity or allergy, within three months of placing the IUD, IUD induced bleeding, not having constraints for using mefenamic acid (peptic ulcer and allergy to this medicine), willingness to participate in the study, having minimal literacy, being younger than 40, no genital tract infections, and gaining a minimum score of 100 in Higham chart.

Data collection tool consisted of two parts. First part included the individual information (age, education, and occupation) and obstetric history (number of pregnancy, number of abortions, the time of the current IUD insertion, history of breastfeeding, and history of IUD insertion). And the second part included Higham chart which was pictorial blood assessment chart (PBAC). This chart is a non-laboratory simple method for diagnosis of menorrhagia. It is a general scoring system which takes observing pads, tampons, and clot appearing as the basis. This method allows the comparison between the perceived bleeding and real blood loss. It is the best tool available for the assessment of menstrual blood loss with 86% sensitivity and 89% accuracy.[31] Since Higham chart is valid, there was no need for its retest validity. To determine the reliability, test-retest was used with 10 days intervals on 84 subjects (r = 0.91).

After obtaining permission from the Ethics and Research Committee of Tabriz University of Medical Sciences, the researcher referred to the Shohadaye Fardis Health Medical Center and invited women with IUD to participate in the study by telephone calls. People who came to the center were examined by a midwife and if they had the inclusive criteria,

the aim of the study was explained to them and written consent was obtained from them (Chart 1). Then information about Higham chart and the method it works was given to them. And they were asked to complete the chart during their bleeding so that during menstrual period, they should mark the number of pads in the boxes that show the intensity of bleeding. If the blood spots on the pad were light or less than 50%, score 1 could be given, if the blood spots were medium and 50% of a pad was contaminated, score 5 could be given, and if it was completely stained with blood or more than 50% of the pad was contaminated, score 20 could be given. If there was also a small clot score 1 and if there was a large, score 5 could be given,[31,32] and then they would give the form to the researcher. Participants bleeding were assessed by the researcher. Women whose their bleeding scored at 100 and over, were chosen for the study subjects. Score 100 or over indicated abnormal bleeding and should be treated. Score less than 100 indicated normal bleeding for women. In case of any possible complications, the women were asked to write down their problems in the complication form so that the researcher was aware and could make a decision, if necessary.

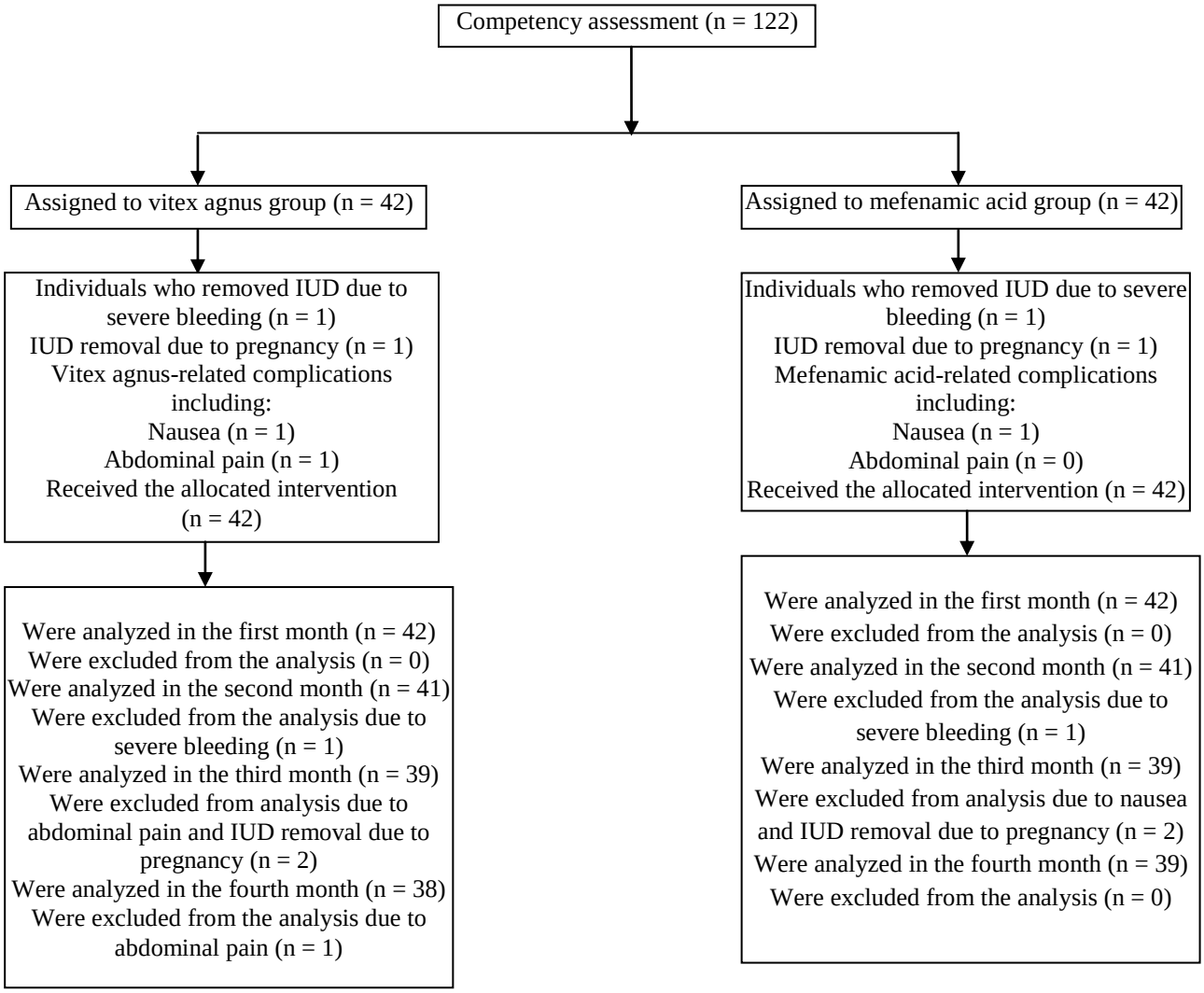

Chart 1. Flowchart of the study subjects

The random allocation of individuals in groups was done by computer random number table with random blocks of 4 and 6. Participants were randomly assigned into two groups, i.e. mefenamic acid and vitex agnus. The researcher and the patients were not aware of the medication allocation in any groups. It was explained to the participants that in order to keep the random assigning of the subjects, the possibility of being assigned to the groups was the same, and even the researcher did not know who would be placed in which group. Each participant was given a sealed envelope (all the envelopes had similar appearance) by the researcher and they were numbered from 1 to 84. The envelopes contained 4 packs of mefenamic acid of 4 packs of vitex agnus. The subjects were asked to take one pack from the envelope and use it 3 times a day from the first day of menstruation until the day 8, and complete the treatment for 4 months. Mefenamic acid capsule was 250 mg product of Poursina Company, and the vitex agnus capsule was similar to the mefenamic acid in color and size which was made in School of Pharmacy of the University of Tabriz. The individuals were also given a package of sanitary pads with the same brand, size, and absorbency. The reason for giving them the same pads was for having the same assessment of the bleeding amount. Then each subject in each month during the menstruation and simultaneous with taking medication completed the Higham chart. All statistical analyses were performed with SPSS for Windows 13.0 (SPSS Inc., Chicago, IL, USA). Data normality was confirmed by Kolmogorov-Smirnov test. According to the normal distribution of the data in order to compare the means, independent t-test, paired t-test, analysis of variance (ANOVA) with repeated measures were done and for the demographic characteristics, obstetric information, and chi-square test was used for the amount of medication complications. P-value < 0.05 was set as a significant level.

Results

In this study, there was no statistically significant difference between the two groups regarding subject distribution in age groups, education, and occupation ($p > 0.050$) (Table 1). There was also no statistically significant difference between the mefenamic acid group and vitex agnus regarding obstetric information according to the t-test (Table 2).

Comparing the mean score of bleeding before and 1, 2, 3, and 4 months after the intervention, there was a statistically significant in mefenamic acid group according to paired t-test. Furthermore,

Table 1. Demographical characteristic of the study subjects in the two groups

Demographical information	Mefenamic acid group (n = 42)	Vitex agnus group (n = 42)	Statistical indicators
Age (years)			
< 20	1 (2.4)	0 (0.0)	
21-25	11 (26.2)	3 (7.1)	t = 1.95
26-30	9 (21.4)	15 (35.7)	df = 81.75
31-35	16 (38.1)	16 (38.1)	p = 0.054
36-40	5 (11.9)	8 (19.0)	
Mean (SD)	29.74 (4.99)	31.81 (4.72)	
Education			
Primary	1 (2.4)	2 (4.8)	$\chi^2 = 0.48$
Secondary	6 (14.3)	7 (16.7)	df = 3
High school	8 (19.0)	8 (19.0)	p = 0.920
Diploma and higher	27 (64.3)	25 (59.5)	
Occupation			$\chi^2 = 0.00$
Housewife	36 (85.7)	36 (85.7)	df = 1
Employee	6 (14.3)	6 (14.3)	p = 1.000

Table 2. Obstetric profile of the participants in the two groups

Obstetric profile	Mefenamic acid group (n = 42)	Vitex agnus group (n = 42)	Statistical indicators
Number of pregnancies			$\chi^2 = 0.20$
1	19 (45.2)	21 (50.0)	df = 2
2	15 (35.7)	14 (33.3)	p = 0.900
3	8 (19.0)	7 (16.7)	
History of abortion			$\chi^2 = 0.10$
Yes	5 (11.9)	6 (14.3)	df = 1
No	37 (87.1)	36 (85.7)	p = 0.740
Current IUD* placement (month)			
Less than 6 months	6 (14.3)	7 (16.7)	t = 1.40
6-12 months	14 (33.3)	18 (42.19)	df = 77.02
Over 12 months	22 (52.4)	17 (40.5)	p = 0.160
Mean (SD)	25.81 (23.11)	19.50 (17.82)	
Breast-feeding			$\chi^2 = 2.02$
Yes	5 (11.9)	10 (23.8)	df = 1
No	37 (88.1)	32 (76.2)	p = 0.150
History of using IUD			$\chi^2 = 0.06$
Yes	9 (21.4)	10 (23.8)	df = 1
No	33 (78.6)	32 (76.2)	p = 0.790

* Intrauterine device

according to table 3, there was a statistically significant in vitex agnus group before and 1, 2, 3, and 4 months after the intervention based on paired t-test. During the 4 months of intervention in the mefenamic acid group, 3 subjects were excluded from the study due to drug complication (nausea), heavy bleeding and IUD removal due to fertility. And in the vitex agnus group, 4 subjects were excluded because of the same reasons i.e. drug complication (nausea and abdominal pain), and the other two reasons. According to the chi-square test, there was no statistically significant difference between the two groups (p = 0.500).

The results also showed that changes in the mean scores of bleeding between the two groups during the first, second, and third months were statistically significant with statistical t-test. Decrease in the mefenamic acid group was significantly greater than the vitex agnus group. While in the fourth month, changes in the mean scores of bleeding between the two groups were not statistically significant (p = 0.110) (Table 4). Results of ANOVA with repeated measures in the 5 cycles between the two groups were statistically significant (p < 0.001) (Table 4).

Discussion

The results indicated that both mefenamic acid and vitex agnus significantly reduced the menstrual bleeding in patients suffering from severe IUD induced bleeding. In month 4 compared to the pre-intervention phase in the group receiving mefenamic acid capsule, bleeding was reduced to 52% and in the group treated with vitex agnus reduced to 47.61%. Zamani quoted from Hayner et al. showed that treatment with mefenamic acid significantly reduced menstrual bleeding (2-78%).[24] In Irvine study, two hormonal combined oral contraceptive pill (OCP) and danazol, and two non-steroidal analgesic compounds (mefenamic acid and naproxen) were compared in the treatment of menorrhagia. Menstrual bleeding reduction of 20-32% with mefenamic acid, 12% with naproxen, 43% with OCP, and 49% with danazol were observed.[33] In a study by Kouides, a comparison of mefenamic acid and tranexamic acid in the treatment of menorrhagia showed that they reduced the

Table 3. Mean bleeding scores before and after the intervention during 4 months in the two groups

	Mefenamic acid group		Vitex agnus group		Statistical indicators
	n	Mean (SD)	n	Mean (SD)	
Mean bleeding score before the intervention	42	181.50 (55.38)	42	171.14 (54.01)	$t^{*} = -0.86$ df = 81.94 p = 0.380
Mean bleeding score 1 month after the intervention	42	158.76 (43.74)	42	165.71 (53.24)	$t^{*} = 3.16$ df = 82 p = 0.002
Mean bleeding score 2 months after the intervention	41	121.61 (40.32)	41	144.76 (37.96)	$t^{*} = 4.08$ df = 80 p < 0.001
Mean bleeding score 3 months after the intervention	39	100.28 (37.13)	39	106.59 (29.85)	$t^{*} = 2.02$ df = 76 p = 0.040
Mean bleeding score 4 months after the intervention	39	87.26 (30.47)	38	89.66 (22.00)	$t^{*} = 1.57$ df = 72.46 p = 0.110
Statistical indicators before and 1 month after the intervention	p < 0.001; df = 41; $^{\dagger}t = 4.43$		p = 0.006; df = 41; $t^{\dagger} = 2.80$		
Statistical indicators before and 2 months after the intervention	p < 0.001; df = 40; $^{\dagger}t = 7.05$		p < 0.001; df = 40; $t^{\dagger} = 5.46$		
Statistical indicators before and 3 months after the intervention	p < 0.001; df = 38; $^{\dagger}t = 9.76$		p < 0.001; df = 38t; $^{\dagger} = 9.79$		
Statistical indicators before and 4 months after the intervention	p < 0.001; df = 38; $^{\dagger}t = 11.23$		p < 0.001; df = 37; $t^{\dagger} = 11.26$		

* t-test, † Paired t-test

Table 4. Mean changes of bleeding scores based on follow-up in the two groups of mefenamic acid and vitex agnus group

	Mefenamic acid group		Vitex agnus group		MD† (95%CI)	Statistical indicators
	n	Mean (SD)	n	Mean (SD)		
Mean changes 1 month after and before the intervention	42	-22.64 (33.10)	42	-5.42 (12.25)	17.21 (6.28, 37.04)	$t^{*} = 3.16$ df = 82 p = 0.002
Mean changes 2 months after and before the intervention	41	-58.97 (53.55)	41	-21.29 (24.94)	37.68 (32.04, 19.56)	$t^{*} = 4.08$ df = 80 p < 0.001
Mean changes3 months after and before the intervention	39	-79.41 (50.78)	39	-58.92 (37.58)	20.48 (40.63, 0.33)	$t^{*} = 2.02$ df = 80 p = 0.040
Mean changes 4 months after and before the intervention	39	-92.43 (51.40)	38	-75.65 (41.41)	16.77 (-40.95, 4.37)	$t^{*} = 1.57$ df = 72.46 p = 0.110
ANOVA with repeated measures testing within subjects	F = 78.30 df = 1.88 p < 0.001		F = 90.15 df = 1.95 p < 0.001			

*t-test, †Mean difference (confidence Interval)

bleeding to 20% with mefenamic acid and 54% with tranexamic acid.[34] Reid and Virtanen-Kari reported a reduction of 100 ml in menstrual bleeding of women suffering from menorrhagia by mefenamic acid. Furthermore, the complication caused by mefenamic acid was 5% which was in accordance with the present study.[35] In a study by Najam et al., the effects of mefenamic acid and tranexamic acid were

compared and showed that mefenamic acid reduced bleeding to 59.3%.[36] In an observational study by Dogan et al., 15 drops of vitex agnus were used in 126 women 3 times a day for several cycles. 33 women with polymenorrhea responded to the treatment and 58 women were treated with menorrhagia.[37] In a clinical study, vitex agnus treatment resulted in a significant improvement of 40 patients from 57 patients suffering from menorrhagia.[21] In the present study, mefenamic acid caused 2% and vitex agnus caused 5% complications in the study subjects. The results from Zamani et al. showed that using vitex agnus and mefenamic acid in patients with menorrhagia for 4 months reduced menstrual bleeding to 65% and 80%, respectively and also increased hemoglobin level.[24] Moreover, mefenamic acid caused 73% and vitex agnus caused 5% complications in the patients ($P > 0.050$). Regarding the complication caused by vitex agnus (5%), this result was in accordance with the present study; however, it was inconsistent regarding the mefenamic acid complication which was 2% in the present study. This difference might be due to lack of proper training in using this medication.

The effectiveness mechanism of vitex agnus is not fully understood.[38] Vitex agnus increases the production of LH and mildly inhibits the release of FSH, resulting in a diversion of the estrogen amount to progesterone that in fact is the same as the effect of luteinizing.[12,38,39] Progesterone prevents the formation of multinucleate leukocytes in the stroma, therefore it will not be formed in case of progesterone inflammatory reaction in the stroma.[12] In addition, another effect was the direct connection to the estrogen receptor.[23,40]

Conclusion

Mefenamic acid and vitex agnus are both effective on IUD induced bleeding, but mefenamic acid was more effective. Since midwives are allowed to use traditional medicine and complementary medicine according to the latest approved regulations by the Iranian Ministry of Health, and the results of the present study indicated the effectiveness of herbal treatment on reducing IUD induced bleeding, herbal treatment as a new and simple option for the midwives of our country is recommended to reduce bleeding in eligible patients of the family planning program. However, further studies are needed on the safety and quality of medicinal plants. Since there are few studies on the effectiveness of vitex agnus on severe menstrual bleeding, further studies are recommended accordingly. The limitations of the study included the time limitation which prolonged monitoring, and this limitation was controlled by the random sample selection.

Ethical issues

None to be declared.

Conflict of interest

The authors declare no conflict of interest in this study.

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References

1. Thonneau P, Goulard H, Goyaux N. Risk factors for intrauterine device failure: a review. Contraception 2001; 64(1): 33-7.
2. Gharekhani P, Behjatnia B, Paydar M. The main protests and cure of diseases. Tehran: Esharat publication; 1993.
3. O'Brien PA, Kulier R, Helmerhorst FM, Usher-Patel M, d'Arcangues C. Copper-containing, framed intrauterine devices for contraception: a systematic review of randomized controlled trials. Contraception 2008; 77(5): 318-27.

4. Ali MM, Cleland J. Oral contraceptive discontinuation and its aftermath in 19 developing countries. Contraception 2010; 81(1): 22-9.

5. Livingstone M, Fraser IS. Mechanisms of abnormal uterine bleeding. Human reproduction update 2002; 8(1): 60-7.

6. Glasier A. Implantable contraceptives for women: effectiveness, discontinuation rates, return of fertility, and outcome of pregnancies. Contraception 2002; 65 (1): 29-37.

7. Reza Soltani P, Parsay S. Maternal and Child Health. Tehran: sanjesh; 2008. 419-21.

8. Mohllajee AP, Curtis KM, Peterson HB. Does insertion and use of an intrauterine device increase the risk of pelvic inflammatory disease among women with sexually transmitted infection? A systematic review. Contraception 2006; 73(2): 145-53.

9. Stanford JB, Mikolajczyk RT. Mechanisms of action of intrauterine devices: update and estimation of postfertilization effects. American journal of obstetrics and gynecology 2002; 187(6): 1699-708.

10. Jindabanjerd K, Taneepanichskul S. The use of levonorgestrel-IUD in the treatment of uterine myoma in Thai women. J Med Assoc Thai 2006; 89(4): S147-S51.

11. Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. Cochrane Database Syst Rev 2006; 4(3): 1-3.

12. Cunningham F, Leveno K, Bloom S, Hauth J, Rouse D, Spong C. Williams Obstetrics. 23th ed. NewYork: McGraw Hill Professional; 2009.

13. Khosravi A, Najafi F, Rahba MR, Esmaeil Motlagh M, Kabir MJ. Health indicators in Iran. Tehran: Ministry of Health, Medical Education Publication; 2009.

14. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev 2000; 4.

15. Lethaby A, Irvine G, Cameron I. Cyclical progestogens for heavy menstrual bleeding. CochraneDatabase Syst Rev 2008; (1): CD001016.

16. Beaumont H, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding. Cochrane Database Syst Rev 2007; (3): CD001017.

17. Samsam Shariat H. Herbs and natural remedies. Tehran: Ruzbehan Publication; 1992.

18. Pavlovich N. Herbal Remedies for Women's Wellness. Integrated Women's Health: Holistic Approaches for Comprehensive Care Gaithersburg. New York: Aspen Publishers; 2000: 180-224 .

19. Schnaubelt K. Essential oil therapy according to traditional Chinese medical concepts. International Journal of Aromatherapy 2005; 15(2): 98-105.

20. World Health Organization. WHO monographs on selected medicinal plants. Geneva: World health organization [Internet]. 2007 [cited 2012 Jun 11]. Available from: http://apps.who.int/ medicinedocs/ documents/s14213e/s14213e.pdf

21. Van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus (Chaste-Tree/Berry) in the treatment of menopause-related complaints. The Journal of Alternative and Complementary Medicine 2009; 15(8): 853-62.

22. Valnet J. Phytothérapie: traitement des maladies par las plantes. 5th ed. Paris: Maloine; 1983.(French)

23. Webster DE, He Y, Chen ShN, Pauli GF, Farnsworth N R, Wang Z J. Opioidergic mechanisms underlying the actions of Vitex agnus-castus L. Biochemical Pharmacology 2011; 81: 170-77.

24. Zamani M, Mansour Ghanaei M, Farimany M, Nasrollahie SH. Efficacy of Mefenamic Acid andVitex in Reduction of Menstrual Blood Loss and Hb Changes in Patients with a Complaint of Menorrhagia. Iran J Obstet Gynecol Infertil 2007; 10(1): 79-86.

25. Shahhosseini Z, Amin Gh, Salehi Sormaghi MH, Danesh MM, Abedian K. Double blind study of anty primery dismenorrhea effects of Vitagnus drop. Journal of Mazandaran University of Medical Sciences 2006; 15(50): 15-22. (Persian)

26. Mercorio F, De Simone R, Di Carlo C, Bifulco G, Tessitore G, Sardo ADS, et al. Effectiveness and mechanism of action of desmopressin in the treatment of copper intrauterine device-related menorrhagia: a pilot study. Human Reproduction 2003; 18(11): 2319-22.

27. Phaliwong P, Taneepanichskul S. The effect of mefenamic acid on controlling irregular uterine bleeding second to Implanon use. J Med Assoc Thai 2004; 87 (Suppl 3): S64–8.

28. Tantiwattanakul P, Taneepanichskul S. Effect of mefenamic acid on controlling irregular uterine bleeding in DMPA users. Contraception 2004; 70(4): 277-9.

29. Brown DJ. Herbal research review: Vitex agnus castus clinical monograph. Quarterly Review of Natural Medicine Summer 1994; 111–21.

30. Dugoua JJ, Seely D, Perri D, Koren G, Mills E. Safety and effecacy of chastetree (Vitex agnus-castus) during pregnancy and lactation. Can J Clin Pharmacol 2008; 15(1). e74-e9.

31. Biri A, Bozkurt N, Korucuoğlu Ü, Yılmaz E, Tıraş B, Güner H. Use of pictorial chart for managing menorrhagia among Turkish women. J Turkish-German Gynecol Assoc 2008; 9(1): 35-7.

32. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. BJOG: An International Journal of Obstetrics & Gynaecology 2000; 107(3): 320-2.

33. Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkilä A, Walker J J, Cameron I T. Randomised comparative trial of the levonorgestrel intrauterine

system and norethisterone for treatment of idiopathic menorrhagia. BJOG: An International Journal of Obstetrics & Gynaecology 1998; 105: 592–8.

34. Kouides PA. Obstetric and gynaecological aspects of von Willebrand disease. Best Pract Res Clin Haematol 2001; 14(2): 281–299.

35. Reid PC, Virtanen-Kari S. Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: a multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment charts. BJOG: An International Journal of Obstetrics & Gynaecology 2005; 112(8): 1121-5.

36. Najam R, Agarwal D, Tyagi R, Singh S. Comparison of traneximic acid with a combination of traneximic acid and mefenamic acid in reducing menstrual blood loss in ovulatory dysfunctional uterine bleeding (DUB). Journal of Clinical and Diagnostic Research 2010; 4(5): 3020-5.

37. Dogan Y, Ay G, Kozuharova E. A study on the anatomical characteristics of Vitex agnus-castus (Verbenaceae). Phytologia Balcanica 2008; 14(1): 97-101.

38. Webster DE, He Y, Chen SN, Pauli GF, Farnsworth NR, Wang ZJ. Opioidergic mechanisms underlying the actions of Vitex agnus-castus L. Biochem pharmacol 2011; 81(1): 170-7.

39. Farrell E.Dysfunctional uterine bleeding. Australian family physician 2004 ; 33(11): 906-8

40. Valent J. Phytothérapie: traitement des maladies par les plantes. Emami A, Nekouei N, Shams Ardakani MR, Mehreghan I, translator. Tehran: Rahe Kamal Publication; 2002.

