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Efficacy of Unani formulations in the management of dysfunctional uterine bleeding-A randomized controlled trial

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Abstract

Back ground & objectives: Dysfunctional uterine bleeding (DUB) is a common debilitating problem amongst women in all age groups and accounts for 20% of gynecology office visits. The aim of the study was to evaluate the efficacy of Unani formulations in the management of dysfunctional uterine bleeding.

Methods: A standard controlled randomized single blind study was carried out at National Institute of Unani Medicine Hospital, Bangalore. Patients (n=40) of reproductive age group with dysfunctional uterine bleeding were randomly allocated to test (n=20) and control (n=20) groups. In test group, Unani formulations (*safoof habis* and *majoon muqawwi rehm sada*), each in a dose of 6 gm twice daily during an active bleeding phase and interval respectively; while in control group, standard drug (norethisterone acetate-5mg) three times daily during an active bleeding phase followed by 5mg once daily for 21 days. The above interventions were administered orally for three consecutive cycles. Primary outcome measures were to assess the effect of test drugs on menstrual regulation and pictorial blood assessment chart (PBAC) score. Secondary outcome measures were changes in endometrial thickness and hormonal profile. Results were analyzed using appropriate test.

Results: Menstrual regulation was achieved in 58.8% patients in test and 63.2% in control groups (P= 1.000); improvement in PBAC score was observed in 100% patients in both the groups (P = 1.000). No significant changes were observed in endometrial thickness and hormonal profile in either group.

Conclusion: The effect of Unani formulations was comparable with that of control drug; hence it can be used as an effective alternative in the management of dysfunctional uterine bleeding.

Keywords: Dysfunctional Uterine Bleeding, Pictorial Blood Assessment Chart, Endometrial Thickness, Unani Formulation, *Safoof Habis, Majoon Muqawwi Rehm Sada.*

Introduction

Dysfunctional uterine bleeding (DUB) is excessively heavy, prolonged or frequent bleeding of uterine origin which is not due to pregnancy or to recognisable pelvic or systemic disease [1]. Its prevalence is reportedly 20% worldwide and is even higher during adolescence and the decade preceding menopause [2]. In classical Unani literature, dysfunctional uterine bleeding was mentioned under the heading of Istihaza in which bleeding is irregular, excessive in amount and for prolonged duration [3, 4]. Istihaza is caused by the weakness of retentive power of uterus (secondary to either *hiddat or riqaat khoon or sue mizaj rehm* or injury /trauma to the uterus) as a result expulsive power of uterus becomes strong*;* which in turn leads to dilatation of uterine vessels resulting in excessive menstrual blood loss [5, 6]. DUB is the major cause of heavy menstrual bleeding and impacts on women's health both medically and socially causing problems such as iron deficiency anaemia, reduced quality of life, chronic illness, social phobia and are associated with increased healthcare costs & financial burdens [7]. The initial management of DUB is medical treatment; and surgical procedures are restricted to those cases in which medical treatment prove ineffective [7, 8]. The medical treatment of DUB includes antifibrinolytics, NSAID'S, COCs, progestins and Gn RH agonists; [9, 10]. but none of these treatments proved its definite efficacy in spite of high price and side effects. Therefore, there is a need for alternate therapy which is to be safe, effective, easily available and free from side effects. In classical Unani literature, various effective formulations are available for the treatment of Istihaza; hence *safoof habis* and *majoon muqawwi rehm sada* has been selected as research drugs for the study, possessing the properties like *habis*, *qabiz* and *muqawwi rehm;* consequently it arrest the excessive menstrual blood loss and strengthen the uterus to prevent further episodes of bleeding [11]. The ingredients of *safoof habis* are *quercus infectoria* oliv (mazu), *tamarix gallica* (mayeen khurd), *uncaria gambier* (kaat safaid), hydrated magnesium silicate (sange jarahat); all these drugs contain tannins which has got strong astringent property that helps in coagulation of blood and reduces the excessive MBL [12, 13]. In addition, *majoon muqawwi rehm sada* which contains *withania somnifera* (asgand) to strengthens the uterus and regularize the menstruation as it is known to contain phytohormones [14]. The study was conducted to test the hypothesis that use of Unani formulations in one group compared with standard drug in other group will be effective in the management of DUB. The study was planned with an objective to evaluate the efficacy of Unani formulations in the management of DUB.

Materials and methods

Study Design: A standard controlled randomized single blind study was carried out in the Dept. of Obstetrics and Gynecology, National Institute of Unani Medicine Hospital, Bangalore from Nov 2011 to April 2013. The study was approved by Institutional ethical committee.

Participants: A total (n=168) patients of DUB were assessed for eligibility, out of which (n=64) denied for participation and (n = 64) excluded for not meeting the inclusion criteria. The patients (n=40) who fulfilled the inclusion criteria were randomly divided in to two groups by computer generated simple randomization table with the help of Random Allocation Software [15].

Selection Criteria: Patients in reproductive age group with dysfunctional uterine bleeding (infrequent cycles followed by heavy prolonged bleeding with history of above complaints at least for 2-3 cycles) were included in the study and patient with organic pelvic pathology, thyroid dysfunction, coagulation disorders, systemic illness, malignancy, and on hormonal contraceptives were excluded. Written informed consent was obtained from each included patients.

Study Procedure: In each patient on entry into the study, detailed menstrual history (including duration of cycle, duration & amount of flow and history of passing clots) were recorded in case record form designed for the study; complete physical examination was performed to look for anaemia and pelvic examination was done to exclude the pelvic pathology. Blood loss was assessed by Pictorial blood assessment chart scoring system [16]. All patients were instructed to maintain a menstrual calendar and not to use any medication during the trial. Assessment of *mizaj* of every patient was done as per the parameters mentioned in classical Unani literature [17]. In each patient, biochemical investigations like SGOT, SGPT, alkaline phosphatase, blood urea, Sr. creatinine along with Sr. estrogen, Sr. progesterone were carried out in fasting on 2nd day of menstrual cycle to assess the safety & efficacy of drugs and ultrasound pelvis was done to look for changes in endometrial thickness before and after the trial.

Intervention: The test drugs was purchased from the local crude drug market of Bangalore and submitted for identification and preparation to the Dept of Ilmul Saidla, NIUM.

Test group: Unani formulations; *Safoof habis* -6 gm in two divided doses during an active bleeding phase and *majoon muqawwi rehm sada* -6gm twice daily was administered orally during an interval. *Qurs kushta Faulad* one tablet twice daily was given as haematinics for 3 months.

Control group: Norethisterone acetate-5mg three times daily during an active bleeding phase followed by 5 mg once daily was administered orally for 21 days. (Manufactured by Cipla limited) and Ferrous sulphate one tablet twice daily was given for 3 months.

Duration of protocol therapy: 3 Cycles.

Blinding and Compliance: Blinding of patients in either group was maintained as medicine was dispensed in similar pack to one patient at a time. For maintaining patient compliance, drugs were given to patients for 1 month only, informed them to revisit and receive the remainder of the treatment in subsequent follow ups.

Assessment cum Follow up: Patients were followed for three consecutive cycles during treatment and one cycle after treatment. During this period, menstrual cycle pattern, degree of anaemia and changes in PBAC score were assessed. Patients were also enquired for any adverse effect of drug during the study. Repeat biochemical test, hormonal assay and ultrasound pelvis were carried out after completion of treatment.

Outcome Measures: Primary outcome measures were restoration of normal menstruation and changes in Pictorial blood assessment chart score; secondary outcome measures (changes in endometrial thickness and hormonal profile) were assessed for effectiveness of either therapy.

Sample Size Estimation: It was determined on the basis of previous studies conducted on DUB with reduction of menstrual blood loss by 75%, provided 80% to power with a significance level of 5% and dropout rate of 10% each, effective sample size of 84 was calculated. But due to practical feasibility and availability of the patients in the hospital, the sample size of 40 was kept which were distributed equally in two groups [18].

Statistical Analysis: Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Significance is assessed at 5% level of significance. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

Results

From 40 patients enrolled into the study, 36 accomplished the study and the same was subjected to statistical analysis. One patient was drop out during 3rd cycle of treatment in test group. Two patients in test and one in control group were lost to follow up.

Table 1: Comparative evaluation of baseline characteristics in two groups

Baseline Characteristics	Test Group (n=20)	Control Group (n=20)	P value
Age in years			
13-20	8(40.0%)	8(40.0%)	0.384
21-30	8(40.0%)	11(55.0%)	
31-40	4(20.0%)	1(5.0%)	
Marital status			
Unmarried	15(75.0%)	15(75.0%)	1.000
Married	5(25.0%)	5(25.0%)	
Socio economic status			
Upper Lower	5(25.0%)	5(25.0%)	0.834

Lower Middle	3(15.0%)	5(25.0%)	
Upper Middle	11(55.0%)	10(50.0%)	
Upper	1(5.0%)	0(0%)	
Age of Menarche (yrs)			
11-12	7(35.0%)	5(25.0%)	0.780
13-14	12(60.0%)	14(70.0%)	
15-16	1(5.0%)	1(5.0%)	
MIZAJ			
Safravi	3(15.0%)	1(5.0%)	0.783
Saudavi	2(10.0%)	2(10.0%)	
Damvi	6(30.0%)	8(40.0%)	
Balghami	9(45.0%)	9(45.0%)	

Table 2: Comparative evaluation of subjective parameters in two groups

Parameters	BT	1st cycle	2nd cycle	3rd cycle	AT	P value
Duration of cycle (Days)						
Test Group	37.50±18.74	41.80±18.43	31.55±8.99	30.30±5.34	38.00±15.73	<0.001**
Control Group	37.75±22.97	56.10±31.42	31.00±4.62	32.45±6.06	36.47±10.16	<0.001**
Duration of flow (Days)						
Test Group	9.25±4.25	6.05±1.61	5.30±1.56	4.40±1.39	4.18±1.07	<0.001**
Control Group	7.90±3.74	5.65±1.42	5.05±1.39	4.5±1.05	4.68±1.20	<0.001**
Amount of flow(pads/cycle)						
Test Group	26.10±15.62	15.55±10.22	10.70±6.55	5.75±2.27	5.12±1.96	<0.001**
Control Group	19.85±8.95	11.70±3.42	9.50±3.75	7.60±2.60	7.42±2.95	<0.001**

Objective Parameters

Table 3: Comparative evaluation of PBAC score in two groups

PBAC	BT	1st cycle	2nd cycle	3rd cycle	AT	P value
Test Group	528.4±295.44	327.45±230.59	191.4±131.81	94.3±50.19	88.47±43.33	<0.001**
Control Group	365.15±171.29	231.25±60.06	183.2±84.24	145.45±58.11	139.74±64.88	<0.001**
P value	0.039*	0.079+	0.816	0.006**	0.009**	-

** Strongly significant

Table 4: Comparative evaluation of objective parameters in two groups

Objective Parameters	BT	AT	P value
Hb%			
Test Group	11.10±0.92	11.32±1.27	0.856
Control Group	10.76±1.1	12.81±0.94	<0.001**
P value	0.302	<0.001**	-
Pelvic scan (ET mm)			
Test Group	8.36±2.37	7.27±2.22	0.212
Control Group	8.73±2.69	7.08±1.65	0.011*
P value	0.647	0.769	-
Sr.E2 pg/ml			
Test Group	73.60±69.19	63.66±34.84	0.473
Control Group	51.01±21.91	42.60±18.35	0.281
P value	0.172	0.027*	-
Sr.Prog. ng/ml			
Test Group	0.91±2.08	1.13±2.85	0.903
Control Group	0.28±0.17	0.32±0.20	0.046*
P value	0.185	0.224	-

*Moderately significant

Table 5: Comparison of outcome measures in two groups

Outcome Measures	Test Group (n=17)	Control Group (n=19)	P value
Primary			
MR	10(58.8%)	12(63.2%)	1.000
PBAC	17(100%)	19(100%)	1.000
Secondary			
Hr.Pr.	9(52.9%)	11(57.9%)	1.000
ET	9(52.9%)	8(42.1%)	0.739

MR- Menstrual regulation, PBAC- Pictorial blood assessment chart. Hr.Pr. - Hormonal profile, ET. - Endometrial thickness.

Discussion

Both groups were homogenous in baseline characteristics (P>0.05).In present study, high incidence of DUB was noted in 21-30 years of age i.e. 47.5%; Mehrotra *et al* reported (48%), Kanaka durg amba *et al* reported 44%, Wagh and Swamy reported 39% and Dawn reported 37.9% in age group of 21-30 years; all these studies are in accordance with the present study. Maximum patients were unmarried i.e. 30(75%) which correlates with the study conducted by Dr Sudakshina chakrabarti [19]. Most of the patients belongs to upper middle class family i.e. 52.5%. Majority of patients were of *balghami mizaj* i.e. 90% which correlates well with the theories proposed by Unani physicians in the causes of Istihaza; *sue mizaj barid* due to dominance of *khilt balgham*, causes *riqat khoon* which dilates the uterine vessels and ultimately weakens the retentive power of uterus resulting in excessive menstrual blood loss [3, 20]. (Table 1).

Subjective parameters

Abnormal bleeding per vaginum was assessed by duration of cycle, duration of flow and amount of flow. The mean duration of cycle at baseline was similar in both groups (P= 0.970) which reduced from 1st cycle to post treatment follow up in either group with P<0.001 considered strongly significant. The improvement in duration of cycle in test group is attributed to medicinal properties of test drugs particularly *asgand* as it was administered during the interval period like hormonal pills. *Asgand* is widely used for curing menstrual disorders in females and is also known as an adaptogenic [21, 22]. The mean duration of flow (DOF) and amount of flow (AOF) was similar in both groups at baseline; after treatment strongly significant difference was observed in each group (P< 0.001). Significant improvement in DOF and AOF is attributed to medicinal properties of *safoof habis* which was administered during an active bleeding phase. The ingredients of *safoof habis* contains tannin, gallic acid, ellagic acid, catechin and flavonoids which act as potential styptic and powerful astringent hence arrest the excessive MBL [13]. Better improvement in anaemia was observed in control group than test group. (Table 2)

Objective parameters

Significant reduction in PBAC score was achieved in either group at each follow up with P< 0.001. Significant improvement in PBAC score in test group is attributed to medicinal properties of *safoof habis* like haemostatic, astringent, dessicant [23]. which causes stasis, condensation of tissue fluids, promotes absorption of body fluids and thus reduces the bleeding [24]. Hence it shows that test drug was clinically as significant as control drug. Changes in Hb% were significant in control group (p< 0.001) than test group (P=0.856). No significant change in endometrial thickness was observed on inter group comparison. (Table 3) Hence, an attempt has been made for the first time to assess the endometrial thickness based on ultrasound in medical treatment of DUB. Further while evaluating the patients during the study, one of the retrospective finding noted was that 10 patients in test and 13 in control groups had PCOD on pelvic scan at baseline, while post treatment repeat scan was normal in 5 and 6 patients in test and control groups respectively; which indicates that DUB is frequently associated with PCOD [8]. This effect is attributed to medicinal properties of *asgand* which consists of steroidal lactones and alkaloids that serve as an important hormone precursor and even it acts as gonodotropic due to its phytoestrogens [25]. Change in serum estradiol was not significant within the groups and moderately significant on inter group comparison with P=0.027. No significant change in serum progesterone was observed on inter group comparison. (Table 4) No previous studies on hormonal profile are available for correlation but it is in accordance with the report that no abnormalities in steroid hormonal profile occur in ovulatory DUB [26].

Outcome Measures

Primary outcome measures were menstrual regulation and changes in PBAC score. In test group, 10(58.8%) and in control group 12(63.2%) patients achieved menstrual regulation after treatment with P = 1.000. This effect is attributed to *majoon muqawwi rehm sada* consist of *asgand* only which act as uterine tonic, antioxidant and adaptogenic [27]. And thus beneficial in menstrual disorder [21]. *Asgand* is known to contain phytohormones (steroidal lactones, saponins, flavonoids) and also alkaloids, tannins, proteins etc which together regulates the menstruation by maintaining hormonal balance [13, 25]. Support the integrity of uterine tissue, blood vessels and capillaries [28]. Improvement in PBAC score was achieved in 17(100%) patients in test group and 19(100%) in control group with p = 1.000. The ingredients of *safoof habis* contain tannins which has got strong astringent property that increases coagulation of blood, reduces uterine blood flow by causing vasoconstriction, thus arrest the bleeding [13, 29]. This result correlates well with the theories proposed by Unani physicians regarding the use of haemostatic and astringent drugs in patients of DUB [30]. Secondary outcome measures were endometrial thickness and hormonal profile which showed no significant changes in both groups. (Table 5) Moreover, no adverse effect of test drugs was observed as safety parameters were normal during the study. Finally, it can be concluded that the effect of Unani formulations (*safoof habis and majoon muqawwi sada*) was comparable with that of control drug although the difference was not significant statistically. Limitation of the study were small sample size, short follow up, hormonal profile was not done at appropriate time due to practical feasibility; endometrial thickness was not classified in two groups to know the better effect of test drugs.

Future trial can be carry out on large sample size for a longer duration to assess the efficacy & safety of test drugs; to assess improvement in anaemia and Hb% without iron supplementation and test drugs can be tried in anovulatory DUB.

Conclusion

Safoof habis was found to be effective in reducing excessive MBL due to its medicinal properties like haemostatic and astringent and its ingredients contain tannins which has got strong astringent property that helps in coagulation of blood, causes vasoconstriction and reduces uterine blood flow thus arrest the excessive menstrual blood loss; hence beneficial in dysfunctional uterine bleeding. On the basis of this result, it can be inferred that the effect of test drugs was comparable with that of control drug; therefore it can be safely used as an alternative therapy for DUB.

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Conflict of interest: none declared

References

1. Lessard C, Framarin A. endometrial ablation techniques in the treatment of dysfunctional uterine bleeding. Agence d evaluation des technologies et des modes d intervention en santé 2003; 550(2):2-10.
2. Hickey M, Higham J, Fraser IS. Progestogens versus estrogens and progestogen for irregular uterine bleeding associated with anovulation. International journal of biological sciences. 2007; (4):1-7.
3. Ibn Sina, Al Qanoon Fil Tib. (Urdu trans. by Kantoori GH). New Delhi: Idarae Kitabus Shifa; 2000; 332(334-36):1089-92.
4. Khan A, Al Akseer. (Urdu trans. by Kabeeruddin) New Delhi: Ejaz Publishing House; 2003; 2(1364):1370-72.
5. Tabri AR. Firdausul Hikmat. New Delhi: Idarae Kitabus Shifa; 2010; 61:254-59.
6. Arzani A. Tibbe Akbar. Deoband: Faisal Publication; 1903, 594-597.
7. Farrell E. Dysfunctional uterine bleeding. Clinical practice Australian Family Physician November 2004; 33(11):906-08.
8. Delale OM, Gupta A, Abraham C, Chandrareddy A, BowersJr CH, Cutler JB. Management of dysfunctional uterine bleeding based on endometrial thickness. International Journal of Women's Health 2010; 2:297-302.
9. Thomas CM. Treatment options for dysfunctional uterine bleeding. Lippincott Williams & Wilkins 2011; 36(8):15-20.
10. Saraiya UB, Rao KA, Chatterjee A. Principles and Practice of Obstetrics and Gynecology for postrgraduate.New Delhi: Jaypee Brothers; 2003:383-88:520.
11. Khan Ajmal. Bayaz Ajmal. 1st ed. New Delhi: Ejaz Publication; 2010, 135.
12. Evans WC, Evans D. Trease and Evans Pharmacognosy. 15th ed. New Delhi: Elsevier; 2005; (224-227):474.
13. Nadkarni KM. The Indian plants and drugs. New Delhi: Shrishti Book Distributors; 2005; (329-330):392,406-415.
14. Gajalakshmi S, Mythili S, Sathiavelu A. Pharmacological activities of *Withania somnifera* - a review. International Journal of Universal Pharmacy and Life sciences. 2011; 1(3):18-33.
15. Saghaei M. Random allocation software for parallel group randomized trials. BMC Medical Research Methodology 2004; 4(26):1-6.
16. Aydan B, Nuray B, Umit K, Ercan Y, Bulent T, Haldun G. Use of pictorial chart for managing menorrhagia among Turkish women. J Turkish- German Gynecol Asso 2008; 9(1):35-37.
17. Nafeesi ABU, Kulliyate Nafeesi. (Urdu trans. by Kabeeruddin M). New Delhi: Idarae Kitabus Shifa; 2000, 265.
18. Shravage J, Mekhala D, Bellad MB. Ganachari Ms, Dhumale HA. Ormeloxifene versus medroxyprogesterone acetae in the treatment of dysfunctional uterine bleeding A double blind randomized controlled trial. Journal of South Asian Federation of Obstetrics and Gynaecology. 2011; 3(1):21-24.
19. Chakrabarthi S. Study of thyroid dysfunction (Hypothyroidism) in patients with provisional diagnosis of dysfunctional uterine bleeding. Dissertation. J.J.M. Medical College. Dept of obstetrics and gynaecology, Davangere, Karnataka; 2006, 61-71.
20. Jurjani I, Zakheerae Khawarzam Shahi. (Urdu trans. by Khan AH). New Delhi: Idarae Kitabus Shifa; 2010; 4:591-98.
21. Singh N, Verma P, Pandey BR, Gilca M. Role of *Withania somnifera* in Prevention and Treatment of Cancer An Overview. International Journal of Pharmaceutical Sciences and Drug Research. 2011; 3(4):274-79.
22. Nasreen S, Radha R. Assessment of quality of *Withania somnifera Dunal*- pharmacognostical and phyto physicochemical profile. International Journal of Pharmacy and Pharmaceutical Sciences. 2011; 3(2):153-55.
23. Ghani N. Khazainul Advia. New Delhi: Idarae Kitabul Shifa; 2010: 230-31,847,1021-22,1208-09,1210-11,1215,1364-65
24. Dayanisiriwardena SA, Karunathilaka LP, Karunarthane YA, Kodithuwakku ND. Comparative clinical study on the efficacy of *Amaranthus viridis Linn* (Tanaduliyaka) and *Symplocos racemousa Roxb* (Lodhra) on Asrugdara with special reference to menorrhagia. Journal of Ayurveda. 2009; 30(4):421-24.
25. Ahlawat P, Khajuria A, Bhagwat DP, kalia B. Therapeutic benefits of *Withania somnifera* An Exhaustive Review. International. Journal of Pharmaceutical and Chemical Sciences. 2012; 1(2):491-96.
26. Corbacioglu A. The Management of dysfunctional uterine bleeding. Focus on metabolism, growth and Reproduction 2001; 72:447-70.
27. Anonymous. Standardisation of single drugs of Unani medicine. Part III. New Delhi: CCRUM; 1997, 9-14.
28. Mayo JL. A Healthy Menstrual Cycle. Clinical Nutrition Insights 1997; 5(9):1-8.
29. Kassim MJ, Hussin MH, Achmad A, Dahon NH, Suan TK, Hamdan HS. Determination of total phenol, condensed tannin and flavonoid contents and antioxidant activity of *Uncaria gambir* extracts. Majalah Farmasi Indonesia 2011; 22(1):50-59.
30. Ibn Rushd. Kitab ul Kulliyat.2nd ed. New Delhi: CCRUM; 1987, 159.