Original Research Article

Targeted treatments for dysfunctional uterine bleeding based on endometrial thickness

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ABSTRACT

Background: Dysfunctional uterine bleeding is a common presentation to both general practitioner and gynaecologists which can have a significant effect on a woman's quality of life. The aim of this study is to assess the effectiveness of treating dysfunctional uterine bleeding according to endometrial thickness.
Methods: This study was a hospital based prospective study undertaken in gynecology outpatient clinic of Central Women's Hospital, Mandalay, Myanmar for one-year period (2016). A total of 60 patients were recruited and divided into 3 groups based on endometrial thickness and offered targeted hormonal treatments. At the end of the one-month treatment, patients were asked to return for a follow-up visit and from their menstrual diaries, the number of bleeding days and bleeding scores were assessed and calculated.
Results: Among sixty women with dysfunctional uterine bleeding, 55% of patients had endometrial thickness less than 6 mm, 25% had endometrial thickness 6-11 mm, with 20% of patients having endometrial thickness more than 11 mm. After one month of study period, treatment was found to be effective in 86.6% of the patients according to bleeding days and in 70% of the patients according to bleeding score.
Conclusions: In women presenting with dysfunctional uterine bleeding, increased endometrial thickness was found to be associated with increased BMI. In the treatment of dysfunctional uterine bleeding, when the endometrial thickness of the patient was assessed and hormonal treatment was given according to the endometrial thickness, treatment was proven to be effective.

Keywords: Dysfunctional uterine bleeding, Endometrial thickness, Hormonal treatments

INTRODUCTION

Menstrual problems are a common reason for presentation to both general practitioners and gynaecologists. Dysfunctional uterine bleeding (DUB) is defined as abnormal bleeding not caused by pelvic pathology, systemic disorders, medications, or pregnancy.[1] It is a common gynaecological problem and proper diagnosis is necessary in order to institute appropriate therapy. The diagnosis of DUB is made after all other causes of abnormal uterine bleeding are ruled out. The current medical options for initial management of DUB are based on clinical presentation and severity and include tranexamic acids, non-steroidal anti-inflammatory drugs (NSAIDs), high dose estrogens, combined oral contraceptives (COCs) or progestogens. A systematic review by the Guideline Development Group showed that tranexamic acids, NSAIDs and COCs were considered equivalent in terms of effectiveness in long-term management of heavy menstrual bleeding.[2] However, there is insufficient data regarding their dose, duration and effectiveness in cases of acute uterine bleeding and effective bleeding control might often take several months changing from one treatment regimen to another, leading to frustration in care-givers and anxiety on patients' behalf.[3]

Impact of dysfunctional uterine bleeding involves physical, psychological and social factors, with women becoming susceptible to iron deficiency anemia needing hospitalization and blood transfusion leading to absence from work. Irregular and unpredictable nature of their menstruation also disturbs their daily activities, making them self-conscious and suffers from mood changes, significantly reducing their quality of life. Therefore, effective and prompt bleeding control is essential in the treatment of DUB to prevent further complications and to improve quality of life.

To improve the management of acute uterine bleeding in DUB, Muneyyirci-Delale et al, tried to tailor the treatments of DUB to endometrial thickness instead of solely on clinical presentation.[3] They reasoned that thin endometrium is a result of denuded endometrium secondary to prolonged bleeding and estrogen might stimulate uniform endometrial growth and promptly stop shedding whereas bleeding caused by endometrial hyperplasia could be effectively stopped with progestogens by reversing the hyperplasia process.

The aim of this study is to evaluate the effectiveness of treating DUB with targeted hormonal regimens based on endometrial thickness instead of solely on clinical presentation. The goal is to tailor the treatments of DUB to endometrial thickness cut-off values as detected by TVS to improve the management of this condition.

METHODS

This study was a hospital based prospective study carried out in gynaecology outpatient clinic of Central Women's Hospital, Mandalay. The study period was one-year duration- from 1st January, 2016 to 31st December, 2016. All patients who consulted at gynecology outpatient clinic at CWH with dysfunctional uterine bleeding were considered as possible candidates for this study.

Detailed history of the bleeding pattern, specifically the onset, duration, frequency and amount were noted. Other associated symptoms that can indicate pelvic pathology or systemic disorders were explored and medical conditions that are considered contraindications for hormonal treatments which are used in the study were excluded.

On physical examination, the patient's general condition was first evaluated to ensure that she was hemodynamically stable. Proper abdominal and pelvic examinations were then continued. As routine laboratory tests, full blood count and urine hCG were performed in each patient to detect anaemia and exclude pregnancy. Among these patients, those without underlying anatomic or systemic pathology were diagnosed as DUB and were included in this study. They were explained about the detail procedure and informed written consent was taken.

First, the patients underwent TVS so that endometrial thickness (ET) could be assessed. Endometrial thickness measurements were done by researcher supervised by senior consultant radiologist. Initial TVS examination was performed to assess the size and position of the uterus and to look for any pathology and both ovaries were examined. The uterus was scanned from the fundus to the internal os in the longitudinal and transverse planes and the presence of focal endometrial thickening, if present, was noted. Endometrial thickness was measured at sagittal position from one endomyometrial junction to another endomyometrial junction at the widest area.

Then, the patients were offered targeted hormonal treatments based on endometrial thickness. The patients were divided into 3 groups. Group 1 included patients with endometrial thickness of less than 6 mm and they were treated with combination of Ethinyl estradiol 0.03 mg and desogestrel 0.15 mg (Combined contraceptive pills), one pill daily for 21 days. Group 2 included patients with endometrial thickness of 6-11 mm who were treated with conjugated estrogen 1.25 mg per oral twice daily for one week then 1.25 mg per oral once daily for next week followed by 0.625 mg per oral once daily for the third week. Norethisterone acetate 5mg BD was also given for the last week (sequential hormonal therapy). Group 3 included patients with endometrial thickness of more than 11 mm who were treated with Norethisterone acetate 5 mg three times daily for 21 days.

Patients were given menstrual diaries to grade bleeding each day for one month beginning at the onset of treatment. The menstrual blood loss was quantified by the use of a pictorial blood assessment chart (PBAC). The number of bleeding days and bleeding scores before targeted treatments were recorded. After 28 days of treatment, patients were asked to return for a follow-up visit and number of bleeding days was assessed from their menstrual diaries and a bleeding score was calculated by adding all grades on calendar for the entire month using PBAC scoring system.

Statistical analysis

Data was collected by using proforma. For all patients, information regarding age, parity, height, weight, BMI, age of menarche, number of days per cycle, endometrial thickness, targeted hormonal treatments they received according to their endometrial thickness, number of bleeding days and bleeding scores after targeted treatments were recorded.

After cleaning and compilation, data analysis was done using SPSS 21 computer software. Comparison of the patients' general characteristics for all three groups was made using chi-square test with p value of 0.05 and confidence interval set at 95%.

Effectiveness of targeted treatments was defined as stoppage of bleeding within 7 days of initiating the

treatment (significant reduction in bleeding days), or bleeding for more than 7 days after targeted treatments but PBAC < 50 (significant reduction in bleeding score) at the end of treatment.

RESULTS

In this study, more than half of women presenting to gynaecology outpatient clinic with the complaint of dysfunctional uterine bleeding were at the age of 31-45 year as shown in Table 1. Mean age of patients with dysfunctional uterine bleeding was 37.06 years.

Table 1: Distribution of patients by age group.

Age group	Number of patients	Percentage
Under 30 years	17	28.3
31-45 years	31	51.7
> 45 years	12	20.0
Total	**60**	**100.0**

Table 2: Distribution of patients by parity.

Parity	Number of patients	Percentage
Nullip	13	21.7
One child	10	16.7
Multip	37	61.7
Total	**60**	**100.0**

As demonstrated in Table 2, majority of patients (61.7%) were multiparous women. Among 60 women, 13 women (21.7%) were nullipara, 10 women (16.7) were primipara and 37 women (61.7%) were multipara.

Table 3: Distribution of patients by endometrial thickness.

Endometrial thickness	Number of patients	Percentage
< 6 mm	33	55.0
6-11 mm	15	25.0
> 11 mm	12	20.0
Total	**60**	**100.0**

As shown in Table 3, more than half (55%) of patients had thin endometrium < 6 mm, while the other half were divided between patients having endometrial thickness 6-11 mm (25%) and patients with endometrial thickness > 11 mm (20%). So, 6.5±2.3 mm was mean endometrial thickness for study population.

Table 4 denotes association between BMI of patients and their endometrial thickness.

In patients with thin endometrium (ET < 6 mm), 6.1% of them were underweight, 36% of them were normal BMI and 42.4% of them were overweight with 15.2% of them being obese. On the other hand, 100% of patients with BMI < 18.5 had thin endometrium, ET < 6 mm.

Table 4: Correlation between BMI and endometrial thickness.

BMI	ET < 6 mm (Group 1)		ET 6-11 mm (Group 2)		ET > 11 mm (Group 3)		Total	
	No.	%	No.	%	No.	%	No.	%
< 18.5 underweight	2	6.1	0	0	0	0	2	3.3
18.5-24.9 normal BM	12	36.4	5	33.3	4	33.3	21	35
25.0-29.9 overweight	14	42.4	5	33.3	0	0	19	31.7
≥ 30.0 obese	5	15.2	5	33.3	8	66.7	18	30
Total patients	**33**	**100**	**15**	**100**	**12**	**100**	**60**	**100**

Table 5: Distribution of patients by number of bleeding days after targeted treatment.

Number of bleeding days	ET < 6 mm (Group 1)		ET 6-11 mm (Group 2)		ET > 11 mm (Group 3)		Total	
	No.	%	No.	%	No.	%	No.	%
≤ 7 days	27	81.8	15	100	10	83.3	52	86.7
8-14 days	5	15.2	0	0	2	16.7	7	11.7
15-21 days	1	3	0	0	0	0	1	1.7
22-28 days	-	-	-	-	-	-	-	-
Total patients	33	100	15	100	12	100	60	100

p value 0.456.

In patients with endometrial thickness 6-11 mm, patients of normal BMI, overweight patients and obese patients were all equally included with 33.3% each but no patients with BMI <18.5 were noted.

In patients with increased endometrial thickness > 11 mm, obese patients predominate with two-third of the proportion being obese. In DUB patients with thick endometrium >11 mm, 66.7% of them were found to be

obese, while the rest 33.3% of them being of normal BMI. p value yield 0.024 and remarked as significant association between increased BMI (≥30.0) with increased endometrial thickness (ET >11 mm).Table 5 revealed the association between different endometrial thickness groups and their bleeding days after one month of treatment.

In Group 1, 81.8% of them had their bleeding days reduced to ≤7 days, 15.2% had bleeding days up to 2 weeks, while only 3% of them had bleeding days up to 3 weeks.

In Group 2, all 15 cases had stopped bleeding within 7 days period. In Group 3, 83.3% of the patients had stopped bleeding within 7 days and 16.7% of them continued bleeding into the 2nd week.Table 6 demonstrated the bleeding scores of the different treatment groups after one month of targeted treatments.

Table 6: Distribution of patients by bleeding score after targeted treatment.

Bleeding score	ET < 6 mm (Group 1)		ET 6-11 mm (Group 2)		ET > 11 mm (Group 3)		Total	
	No.	%	No.	%	No.	%	No.	%
0-50 (mild)	28	84.8	6	40	8	66.7	42	70
> 50-100 (moderate)	4	12.1	9	60	4	33.3	17	28.3
> 100 (severe)	1	3	0	0	0	0	1	1.7
Total patients	33	100	15	100	12	100	60	100

p value, 0.015.

Table 7: Correlation of bleeding days before treatment and after treatment.

Bleeding days before treatment	Bleeding days after treatment							
	≤ 7 days		8-14 days		15-21 days		Total	
	No.	%	No.	%	No.	%	No.	%
≤ 7 days	24	100	0	0	0	0	24	40
8-14 days	15	88.2	2	11.8	0	0	17	28.3
15-21 days	8	72.7	3	27.3	0	0	11	18.3
22-28 days	5	62.5	2	25	1	12.5	8	13.3
Total patients	52	86.6	7	11.7	1	1.67	60	100

Table 8: Correlation of bleeding score before treatment and after treatment.

Bleeding score before treatment	Bleeding score after treatment							
	0-50 (mild)		> 50-100 (moderate)		> 100 (severe)		Total	
	No.	%	No.	%	No.	%	No.	%
0 - 50 (mild)	5	100	0	0	0	0	5	8.3
>50 - 100 (moderate)	32	71.1	13	28.9	0	0	45	75
>100 (severe)	5	50	4	40	1	10	10	16.7
Total patients	42	70	17	28.3	1	1.7	60	100

In Group 1, 84.8% of patients had only mild bleeding scores after the treatment while 12.1% of them had moderate bleeding scores with only 3% of them had severe bleeding score after the treatment period.

In Group 2, 40% of them had only mild bleeding after treatment while 60% of them had moderate bleeding with none of the patients suffered from severe bleeding.

In Group 3, 66.7% of the patients had only mild bleeding pattern with 33.3% of the patients having moderate bleeding scores after the treatment, and this group seemed to show the highest response rates to the hormonal treatments.

As demonstrated in Table 7, when reviewing the effectiveness of targeted treatment according to bleeding days, among patients with bleeding days within 1-week duration (≤ 7 days), all of them were within that bleeding day duration after treatment, but with much reduced bleeding score. In 17 patients who had bleeding days between 8-14 days duration, 15 of them (88.2%) had their bleeding days reduced to under 7 days duration, with only 2 cases remained with prolonged bleeding days. In patients with prolonged bleeding over 2-3 weeks duration, 60-70% of them had their bleeding days reduced to target duration (≤ 7 days) bleeding days after targeted treatments.

To sum up, in accordance with our operational definition of treatment effectiveness (stoppage of bleeding within 7 days of initiating the treatment), 52 out of 60 patients in our study had their bleeding days reduced to ≤ 7 days after targeted treatments, proving the treatment 86.6% effective.

When reviewing the effectiveness of targeted treatment according to bleeding score shown in Table 8, all the 5 patients who had mild bleeding score before treatment were found to have mild bleeding score after treatment. In 45 patients with moderate bleeding score, 32 of them (71.1%) were found to have only mild bleeding score after targeted treatment. In patients with severe bleeding score, 5 out of 10 patients had only mild bleeding score after targeted treatment showing remarkable effectiveness of treatment and as 4 out of 10 patients with severe bleeding score were found to have only moderate bleeding score after treatment, with only 1 patient continue to have severe bleeding score after treatment.

In conclusion, among the 60 of DUB patients in the study, 42 of them (70%) had mild bleeding score < 50 after targeted treatments, in whom according to our operational definitions, treatment was found to be effective.

DISCUSSION

In Myanmar, dysfunctional uterine bleeding is a common gynecological problem and proper diagnosis is necessary in order to institute appropriate therapy. Current treatment regimens for DUB include using COCs, progestogens, tranexamic acids and NSAIDs in a random combination based on clinical assessment and effective bleeding control is not always achieved immediately which leads to further bleeding episodes and significant health consequences.

The aim of this study is to evaluate the effectiveness of treating DUB with targeted hormonal regimens based on endometrial thickness instead of solely on clinical presentation and to improve the management of this condition.

Age is an important factor in the study of DUB because bleeding may occur at any age between menarche and menopause but DUB in perimenopausal age always requires close analysis in order to differentiate it from the most serious bleeding caused by uterine malignancy.[5]

According to study by Mattox, more than 50% of dysfunctional bleeding occurs in pre-menopausal women, about 20% occurs during adolescence, and the remaining 30% is distributed among other women in the reproductive period.[6] In another study, 49.2% of DUB cases were over 40 years of age (perimenopausal age) and 47.1% were of age between 21-40 years and 3.7% were under 20 years.[7]

In this study, mean age of patients presenting to gynecology outpatient clinic with the complaint of DUB was 37.06 years. 28.3% of patients were under 30 years, 51.7% of patients were between 31-45 and 20% of patients were over 45 years. So, the demographic factor in this study was differed from the previous studies with the majority of DUB patients being reproductive age groups rather than being perimenopausal.

In the study of Myat T, most of abnormal uterine bleeding occurred in multiparity group (P2 to P4) which accounts 61.64% and 31.51% of patients (n = 23) were in the grand multiple group.[8] Only 2.74% of patients were in the nulliparity group.

In this study, majority of patients (61.7%) were multiparous women. Among 60 women, 13 women (21.7%) were nullipara, 10 women (16.7%) were primipara and 37 women (61.7%) were multipara. According to above studies, dysfunctional uterine bleeding was more common in multiparous women.

According to Muneyyirci-Delale et al, mechanisms of uterine bleeding differed in DUB according to different thickness of endometrium.[3] In thin endometrium, continued bleeding is due to the denuded endometrium with blood vessels mounts producing small trickles of bleeding with patients complaining of continuous spotting menstruation. In increased endometrial thickness, bleeding is due to the shedding of the thickened endometrium. In DUB patients with normal endometrial thickness, bleeding is due to the imbalance of the endometrial products like prostaglandin and endothelin, which are involved in hemostasis.

In the study of Muneyyirci-Delale et al, 16.32% of patients had thin endometrium <6 mm, 32.65% of patients had endometrial thickness 6-11 mm, and 51.02% of patients had endometrial thickness >11 mm.[3]

In this study, more than half (55%) of patients had thin endometrium < 6 mm, while the other half were divided between patients having endometrial thickness 6-11 mm (25%) and patients with endometrial thickness > 11 mm (20%). Mean endometrial thickness for study population was 6.5±2.3 mm.

In this study population, dysfunctional uterine bleeding patients tended to have thin endometrium < 6 mm, while in the study population of Muneyyirci-Delale et al, patients with increased endometrial thickness > 11 mm were more prevalent.[3] In the study of Muneyyirci-Delale et al, mean BMI was 34 with significant positive correlation with endometrial thickness.[3] This finding supports obesity and increased BMI as a risk factor for anovulatory bleeding and endometrial thickness.

In this study, in patients with increased endometrial thickness >11 mm, obese patients predominate with two-third of the proportion being obese. In DUB patients with

ET >11 mm, 66.7% of them were found to be obese, while the rest 33.3% being of normal BMI. p value yield 0.024 and remarked as significant association between increased BMI (≥30.0) with increased endometrial thickness (ET >11 mm).

In the study of Muneyyirci-Delale et al, bleeding days were reduced to 8±3 days in Group 1, 9±2 days in Group 2 and 3±7 days in Group 3.[3] In this study, after hormonal treatment, 81.8% of patients in Group 1, 100% of patients in Group 2 and 83.3% of patients in Group 3 had stopped bleeding within 7 days.

In the study of Muneyyirci-Delale et al, mean bleeding score was reduced to 11.5 in Group 1, 15.8 in Group 2 and 4.9 in Group 3 with all patients having mild bleeding scores after hormonal treatment.[3] In this study, 84.8% of patients in Group 1, 40% of patients in Group 2 and 66.7% of patients in Group 3 had mild bleeding scores < 50 at the end of treatment.

CONCLUSION

Impact of dysfunctional uterine bleeding involves physical, psychological and social factors, with reducing the quality of life in many patients. Effective and prompt bleeding control is essential in the treatment of DUB to prevent further complications and to improve quality of life. This study was carried out to evaluate the effectiveness of treating DUB with targeted hormonal regimens based on endometrial thickness cut-off values as detected by TVS instead of solely on clinical presentation.

In this study, a total of 60 patients were recruited and divided into 3 groups based on endometrial thickness and offered targeted hormonal treatments. At the end of the one-month treatment, patients were asked to return for a follow-up visit and from their menstrual diaries, the number of bleeding days and bleeding scores were assessed and calculated. Among patients presenting to gynaecology outpatient clinic with the complaint of dysfunctional uterine bleeding, more than half were at the age group of 31-45 year. Majority of patients were multiparous women. More than half of patients had thin endometrium (<6 mm) and the mean endometrial thickness for study population was 6.5±2.3 mm. There was a significant association between increased BMI (≥30.0) with increased endometrial thickness (ET >11 mm).

When reviewing the effectiveness of targeted treatments, 52 out of 60 patients (86.6%) had their bleeding days reduced to ≤7 days proving the targeted treatments to be effective. When PBAC bleeding score of <50 (mild bleeding score) was used as an indicator of treatment effectiveness, in 42 out of 60 patients (70%), treatment was found to be effective. This study revealed that in case of treating patients with dysfunctional uterine bleeding, tailoring the hormonal treatments to the endometrial thickness was proven to be effective. However further studies with larger sample size would be necessary to establish stronger body of evidence and to incorporate these findings into standard treatment guidelines.

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