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ORIGINAL ARTICLE

Comparison of Tranexamic Acid Versus Calcium Dobesilate (Doxium) for Management of Dysfunctional Uterine Bleeding

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ABSTRACT

Background: Dysfunctional uterine bleeding (DUB) is a common gynecological condition characterized by abnormal uterine bleeding in the absence of structural pathology. It significantly affects the physical, psychological, and social well-being of women. Medical management remains the first-line treatment, with tranexamic acid widely used; however, calcium dobesilate (Doxium) has recently emerged as a potential alternative due to its microvascular protective effects.

Objective: To compare the efficacy and safety of tranexamic acid versus calcium dobesilate in the management of dysfunctional uterine bleeding.

Methods: This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, DHQ Hospital Sahiwal, over one year. A total of 100 women aged 18–40 years diagnosed with dysfunctional uterine bleeding were enrolled and randomly allocated into two groups (n=50 each). Group A received tranexamic acid 1000 mg/day, while Group B received calcium dobesilate 500 mg for 5 days during each menstrual cycle for four months. Menstrual blood loss was assessed using the pad/tampon weight method at baseline and after treatment. Efficacy and adverse effects were evaluated and analyzed using SPSS version 21, with $p < 0.05$ considered statistically significant.

Results: The mean age of participants was 30.12±6.32 years in the tranexamic acid group and 29.12±6.72 years in the calcium dobesilate group. Calcium dobesilate demonstrated significantly higher efficacy compared to tranexamic acid (88% vs 72%, $p = 0.046$). Adverse effects were observed in 30% of patients receiving tranexamic acid and 38% of those receiving calcium dobesilate; however, this difference was not statistically significant ($p = 0.673$). Gastrointestinal disturbances were the most commonly reported side effects in both groups.

Conclusion: Calcium dobesilate is more effective than tranexamic acid in the treatment of dysfunctional uterine bleeding, without significant adverse effects. It could be a good option for treatment.

Keywords: Dysfunctional uterine bleeding, Tranexamic acid, Calcium dobesilate, Heavy menstrual bleeding, Randomized controlled trial.

INTRODUCTION

Dysfunctional uterine bleeding (DUB) is a common gynecological disorder characterized by abnormal uterine bleeding in the absence of identifiable structural, systemic, or pregnancy-related causes[1]. It is a common subset of abnormal uterine bleeding (AUB) and is commonly seen in women of child-bearing age, resulting in considerable physical, psychological, and overall quality of life impairment[2].

To enhance diagnostic and clinical management of AUB, the International Federation of Gynecology and Obstetrics (FIGO) developed a classification system[3]. Under this system, DUB is classified as a non-structural cause of AUB and is usually related to dysfunctional endometrium or hormone imbalance. In clinical practice, the normal menstrual cycle is between 24-38 days, with a cycle length of 7-9 days and blood loss of 5-80 mL. Changes in frequency, duration and volume may be signs of abnormal uterine bleeding (AUB), including heavy menstrual bleeding (HMB)[4].

DUB has a complex etiology that encompasses hormonal, endometrial and vascular factors. Altered function of the hypothalamic-pituitary-ovarian axis may result in ovulatory and anovulatory cycles, leading to abnormal endometrial sloughing. Furthermore, dysfunction of endometrial factors such as prostaglandins, fibrinolytic activity, and vascular integrity plays a role in heavy menstrual blood loss[5,6].

The mainstay of treatment for DUB is medical management, especially in hemodynamically stable women who desire fertility. These include combined oral contraceptives, progestins, non-steroidal anti-inflammatory drugs (NSAIDs), and antifibrinolytics[7]. Tranexamic acid, a commonly used antifibrinolytic agent, works by blocking the activation of plasminogen and promoting stabilization of fibrin clots, thus decreasing menstrual blood loss. Tranexamic acid has been shown to decrease the amount of menstrual blood flow by 40-65% in clinical trials, and it is commonly used as first-line treatment in many settings[8].

Calcium dobesilate (Doxium) is a vasoactive and angioprotective drug that has been used to treat microvascular conditions such as diabetic retinopathy and chronic venous insufficiency. It acts by enhancing capillary permeability, decreasing oxidative stress, inhibiting platelet aggregation and regulating inflammatory cytokines. These effects could potentially benefit women with abnormal uterine bleeding by improving microvascular integrity and reducing endometrial blood flow[9,10].

Despite the availability of multiple treatment options, there is limited comparative evidence regarding the efficacy of calcium dobesilate versus tranexamic acid in the management of DUB, particularly in the local population. Most existing studies have focused on tranexamic acid, while data on calcium dobesilate remain scarce and inconclusive. Therefore, this study was conducted to compare the efficacy and safety of tranexamic acid and calcium dobesilate (Doxium) in the management of dysfunctional uterine bleeding, with the aim of identifying a more effective therapeutic option for clinical practice[11,12].

MATERIALS AND METHODS

This randomized controlled trial was conducted in Unit I, Department of Obstetrics and Gynecology, DHQ Hospital, Sahiwal, over a duration of one year following approval from the institutional ethical review committee. One hundred women with dysfunctional uterine bleeding (DUB) were enrolled from the outpatient department (OPD) by simple random sampling.

Participants had to be aged 18 to 40 years with symptoms of abnormal uterine bleeding, as defined by the operational definition. Patients with recurrent DUB, pregnancy or miscarriage, anemia (hemoglobin <8 g/dL), thyroid disorders (TSH >5 mIU), known benign or malignant uterine pathology, bleeding disorders, or a

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documented history of hypersensitivity to the study medications were excluded. All women gave informed written consent before participating.

A computer-generated random number table was used to assign patients into two groups (n=50 in each group). They received calcium dobesilate (Doxium) 500 mg daily for 5 days during each menstrual cycle (Group A) or tranexamic acid 1000 mg daily for 5 days during each cycle (Group B). This was repeated for a period of 4 months, with monthly follow-up in the outpatient department for treatment response and side effects.

A pad/tampon weighing method was used to estimate menstrual blood loss. Weighed sanitary pads (in unmarried women) or tampons (in married women) were given to the women and they were asked to wear them for 4-6 hours. Blood loss was calculated by weighing the used pads/tampons. This was done again after the four-month treatment period to estimate changes in the menstrual blood loss. A reduction in menstrual blood loss and/or duration of bleeding relative to baseline was considered effective treatment.

Adverse events were monitored during the study. Side effects assessed included gastrointestinal disturbances (nausea, vomiting, diarrhea), hypersensitivity reactions (rash, swelling, or allergic manifestations), and agranulocytosis (defined as an absolute neutrophil count <100/µL). Data was documented in a proforma.

The data were analysed using SPSS 21. Descriptive statistics were used for continuous variables (age, body mass index and duration of bleeding) which were expressed as mean ± standard deviation, and categorical variables (marital status, parity, efficacy and side effects) which were expressed as frequencies and percentages. Efficacy and side effects were compared between the two groups by chi-square test. Age, marriage, body mass index, number of children and duration of bleeding were stratified to control for effect modifiers. A p-value of less than 0.05 was taken as significant.

RESULTS

A total of 100 women diagnosed with dysfunctional uterine bleeding were enrolled in this randomized controlled trial and equally divided into two groups, with 50 patients in each treatment arm. The two groups were similar in terms of baseline demographic and clinical characteristics, suggesting good randomization and reducing the risk of bias. The average age of the women in Group A (tranexamic acid) was 30.12±6.32 years, while that of Group B (calcium dobesilate) was 29.12±6.72 years with an age range from 18-40 years. The age distribution was comparable between the two groups, indicating a good baseline match (Table 1). Furthermore, the majority of participants in both groups were married, comprising 78% in Group A and 72% in Group B, while unmarried women accounted for 22% and 28%, respectively, reflecting a relatively similar marital status distribution across both groups (Table 2).

With regard to body mass index (BMI), 50% of women in Group A had a normal BMI, whereas 34% had a normal BMI in Group B. However, 26% of participants in Group B were overweight, and 40% obese, which were marginally higher than in Group A (16% overweight and 34% obese). However, the distribution of BMI was similar between the two groups (Table 3). Likewise, parity was not significantly different between the two groups, with both primiparous and multiparous women in both groups. In Group A, 22% were primiparous, while in Group B, 32% were primiparous and the rest in both groups were multiparous, suggesting a comparable parity distribution in the two groups (Table 4).

The starting severity of disease, measured as the duration of menstrual bleeding, was not significantly different between the two groups. The mean duration of bleeding was 9.02±2.37 days in Group A and 8.46±2.09 days in Group B, with a range of 5 to 12 days in both groups. This shows that the patients in both groups had similar severity of dysfunctional uterine bleeding before the treatment (Table 5).

There was a statistically significant difference in the efficacy of treatment between the two groups at the end of the four-month treatment cycle. While 88% of patients in the calcium dobesilate group (Group B) showed a substantial decrease in menstrual blood loss, this percentage was 72% in the tranexamic acid group (Group A). This difference was found to be statistically significant with a p-value of 0.046, indicating superior efficacy of calcium dobesilate over tranexamic acid in the management of dysfunctional uterine bleeding (Table 6).

In terms of safety, adverse effects were reported in both groups, affecting 30% of patients receiving tranexamic acid (Group A) and 38% of patients receiving calcium dobesilate (Group B). While the incidence of adverse effects was slightly higher in the calcium dobesilate group, the difference was not significant, indicating a similar safety profile between the two drugs (Table 7). The most frequently reported side effects in both groups were gastrointestinal symptoms, present in 16% and 22% of the patients on tranexamic acid and calcium dobesilate, respectively. Hypersensitivity was reported in 10% of Group A and 8% of Group B, with agranulocytosis being uncommon, with 4% and 8% in each group, respectively. In summary, there was no statistically significant difference in the types and frequencies of side effects between the two groups (p = 0.673, Table 8).

An additional stratified analysis was undertaken to examine the potential modifying factors on efficacy. Stratification by age showed statistically significant higher efficacy in women aged 31-40 years, with calcium dobesilate showing significantly higher efficacy than tranexamic acid (p = 0.010). By comparison, in women less than 31 years of age, calcium dobesilate was more effective, but the difference was not statistically significant. When stratified according to marital status, there was no significant influence on efficacy in either group. Likewise, stratification based on BMI, parity and duration of bleeding showed no statistically significant difference in efficacy; however, a similar trend towards higher efficacy with calcium dobesilate was observed in all these subgroups. These results further support the overall greater efficacy of calcium dobesilate with a similar safety profile (Tables 9-13).

Table 1: Age Distribution of Patients

Variable	Group A (TXA)	Group B (Doxium)
n	50	50
Mean (years)	30.12 ± 6.32	29.12 ± 6.72
Minimum	19	18
Maximum	40	39

Table 2: Marital Status of Women

Marital Status	Group A	Group B	Total
Married	39 (78%)	36 (72%)	75
Unmarried	11 (22%)	14 (28%)	25
Total	50	50	100

Table 3: Body Mass Index of Women

BMI Category	Group A	Group B	Total
Normal	25 (50%)	17 (34%)	41
Overweight	8 (16%)	13 (26%)	21
Obese	17 (34%)	20 (40%)	37
Total	50	50	100

Table 4: Parity Status of Women

Parity	Group A	Group B	Total
1	11 (22%)	16 (32%)	27
2	15 (30%)	12 (24%)	27
3	12 (24%)	8 (16%)	20
4	12 (24%)	14 (28%)	26
Total	50	50	100

Table 5: Duration of Bleeding (Days)

Variable	Group A	Group B
Mean ± SD	9.02 ± 2.37	8.46 ± 2.09
Minimum	5	5
Maximum	12	12

Table 6: Efficacy in Treatment Groups

Outcome	Group A	Group B	Total
Yes	36 (72%)	44 (88%)	80
No	14 (28%)	6 (12%)	20
Total	50	50	100

p-value = 0.046

Table 7: Overall Side Effects

Side Effects	Group A	Group B	Total
Yes	15 (30%)	19 (38%)	34
No	35 (70%)	31 (62%)	66
Total	50	50	100

Table 8: Pattern of Side Effects

Side Effect Type	Group A	Group B	Total
Gastrointestinal disturbances	8 (16%)	11 (22%)	19
Hypersensitivity reactions	5 (10%)	4 (8%)	9
Agranulocytosis	2 (4%)	4 (8%)	6

p-value = 0.673

Table 9: Efficacy Stratified by Age

Age Group	Group A (Yes/No)	Group B (Yes/No)	p-value
18–30	19 / 6	20 / 5	0.733
31–40	17 / 8	24 / 1	0.010

Table 10: Efficacy Stratified by Marital Status

Status	Group A (Yes/No)	Group B (Yes/No)	p-value
Married	30 / 9	33 / 3	0.082
Unmarried	6 / 5	11 / 3	0.201

Table 11: Efficacy Stratified by BMI

BMI	Group A (Yes/No)	Group B (Yes/No)	p-value
Normal	18 / 7	16 / 1	0.073
Overweight	6 / 2	10 / 3	0.920
Obese	12 / 5	18 / 2	0.133

Table 12: Efficacy Stratified by Parity

Parity	Group A (Yes/No)	Group B (Yes/No)	p-value
1–2	19 / 7	26 / 2	0.051
3–4	17 / 7	18 / 4	0.383

Table 13: Efficacy Stratified by Duration of Bleeding

Duration	Group A (Yes/No)	Group B (Yes/No)	p-value
5–8 days	14 / 6	20 / 4	0.293
9–12 days	22 / 8	24 / 2	0.064

DISCUSSION

The present randomized controlled trial was conducted to compare the efficacy and safety of tranexamic acid and calcium dobesilate (Doxium) in the management of dysfunctional uterine bleeding[9]. This study confirms that calcium dobesilate is more effective than tranexamic acid in decreasing menstrual blood loss, and both medications have similar safety profiles. These findings offer valuable guidance to clinicians, especially in a situation where the optimal therapy for dysfunctional uterine bleeding is sought[10].

Dysfunctional uterine bleeding is a complex disorder resulting from hormonal dysfunction, endometrial dysfunction and hemostatic dysfunction[11]. Medical treatment is the preferred first-line treatment in women who are hemodynamically stable and desire fertility. Tranexamic acid is well known as a potent antifibrinolytic drug which reduces menstrual blood loss by preventing the conversion of plasminogen to plasmin and strengthening the fibrin clot[12]. In the current study, tranexamic acid demonstrated an efficacy rate of 72%, which is consistent with previous studies reporting reductions in menstrual blood loss ranging between 40% and 65%, and overall effectiveness rates between 70% and 80%. These results confirm that it remains a mainstay of treatment in women with heavy menstrual blood loss[13].

On the other hand, the efficacy of calcium dobesilate was 88% in the current study, which suggests that it may be more effective than tranexamic acid[14]. While there are limited clinical data on the use of calcium dobesilate in dysfunctional uterine bleeding, the reported efficacy is consistent with earlier local studies that found efficacy rates of about 83% in menstrual blood loss reduction[15]. The greater effectiveness of calcium dobesilate can potentially be explained by its different pharmacological effects compared to tranexamic acid. Calcium dobesilate has a wide range of effects, including improvement of capillary permeability, reduction of oxidative stress, inhibition of platelet aggregation and modification of inflammatory mediators, while tranexamic acid specifically blocks fibrinolysis. These effects may all play a role in the stabilisation of the endometrial microvasculature, which ultimately leads to decreased blood loss[16].

The other key finding of this study is the similar safety of both drugs. Although the frequency of adverse effects was slightly higher in the calcium dobesilate group (38%) compared to the tranexamic acid group (30%), the difference was not statistically significant[17]. The most frequent side effects were gastrointestinal symptoms, followed by allergic reactions and in rare instances, agranulocytosis. Our results are in line with other studies where tranexamic acid is reported to induce gastrointestinal reactions and calcium dobesilate is reported to induce mild and reversible adverse effects, with severe complications being rare. The lack of significant differences in side effects indicates that both tranexamic acid and calcium dobesilate are well tolerated[18].

Subgroup analysis also showed that calcium dobesilate was found to have a higher efficacy in women aged 31-40 years, where we found a statistically significant difference. While no significant differences were observed in subgroups stratified by marital status, body mass index, parity, or duration of bleeding, a similar trend toward greater efficacy of calcium dobesilate was observed in all subgroups. This could indicate that its efficacy may not be influenced by demographic and clinical differences, reinforcing its potential as a safe alternative[19,20].

This study has several clinical implications. In resource-poor settings, where complex surgical procedures may not be accessible, medical treatments are vital for the treatment of dysfunctional uterine bleeding. Calcium dobesilate, given its efficacy and safety, may prove to be a useful addition to the current armamentarium of therapies. But the lack of large randomized trials and long-term follow-up studies calls for careful interpretation of the findings[1-10].

While this study was well-designed, being a randomized trial with a comparison between two drugs, it has some limitations. This was a single-center study with a limited number of participants, which may affect the results' external validity. Furthermore, it had a short duration (four months), with no assessment of long-term outcomes such as recurrence rates and long-term efficacy. Multicentre trials with larger sample sizes and longer follow-up are warranted to validate these results and define clear guidelines for clinical practice[17-20].

CONCLUSION

Calcium dobesilate was found to be more effective than tranexamic acid in the reduction of menstrual blood loss in women with dysfunctional uterine bleeding with similar safety. This study demonstrates the potential of calcium dobesilate to be used as a valuable alternative medical treatment for dysfunctional uterine bleeding. Larger and longer studies are warranted to validate its effectiveness and its place in clinical practice.

Author Contributions

R.B.: Conceptualization of study, data collection, data analysis, manuscript writing, and final approval.
S.P.: Study supervision, study design, critical revision of manuscript, and final approval.
A.N.: Data interpretation, literature review, and manuscript drafting.
H.N.: Statistical analysis, data organization, and results interpretation.
J.T.: Literature search, manuscript editing, and formatting.
A.Y.: Data collection support, proofreading, and final manuscript review.
All authors have read and approved the final version of the manuscript.

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