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RESEARCH ARTICLE
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HISTOPATHOLOGICAL AND BIOCHEMICAL MARKERS IN UTERINE LEIOMYOMAS AND THEIR IMPLICATIONS FOR MEDICAL TREATMENT: A MULTIDISCIPLINARY APPROACH FOR FINDING THE OUTCOMES OF TRANEXAMIC ACID

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Abstract

Objective: To evaluate the role of histopathological and biochemical markers in uterine leiomyomas and assess the effectiveness of tranexamic acid in managing heavy menstrual bleeding (HMB) in affected patients.

Methods: A prospective observational study was conducted on 110 patients diagnosed with uterine leiomyomas and HMB. Patients were treated with tranexamic acid (1,000 mg three times daily) during menstruation for three cycles. Histopathological examination of fibroid tissue and biochemical marker analysis were performed. Outcomes included changes in menstrual blood loss (PBAC scores), hemoglobin levels, symptom relief, and fibroid size.

Results: Tranexamic acid significantly reduced menstrual blood loss by 52.5% ($p < 0.001$) and improved hemoglobin levels from 9.5 g/dL to 11.3 g/dL ($p < 0.001$). Patients reported a reduction in bleeding duration and pelvic pain. No significant change in fibroid size was observed. Histopathological findings showed typical features of fibroids, including smooth muscle proliferation and abnormal vascularization, while inflammatory markers (IL-6, TNF-α) decreased after treatment.

Conclusion: Tranexamic acid effectively reduces HMB in uterine leiomyoma patients without affecting fibroid size, making it a valuable non-hormonal treatment option.

Keywords: Histopathological Markers, Biochemical Markers, Uterine Leiomyomas, Implications

Introduction

Uterine leiomyomas, also known as fibroids, are the most common benign tumors of the female reproductive system, affecting up to 70-80% of women during their reproductive years. Although non-cancerous, these tumors can cause significant clinical symptoms, including heavy menstrual bleeding (HMB), pelvic pressure, pain, and infertility. The exact etiology of leiomyomas remains

unclear, but their development is influenced by a variety of genetic, hormonal, and environmental factors [1]. Given the complexity of these tumors, it is essential to adopt a multidisciplinary approach to their diagnosis and treatment. Histopathological and biochemical markers provide a critical window into the nature of uterine leiomyomas, shedding light on the tumor's cellular characteristics, growth patterns, and biochemical environment [2]. Histopathological examination often reveals smooth muscle proliferation, disordered extracellular matrix, and altered vascularization within the tumor. Meanwhile, biochemical markers such as hormone receptors (estrogen and progesterone), growth factors, and inflammatory cytokines—contribute to our understanding of fibroid growth and symptomatology. These markers are not only valuable for diagnostic purposes but also serve as potential therapeutic targets, paving the way for more effective treatments with fewer side effects [3]. In recent years, a range of medical treatments has been explored to manage the symptoms of uterine leiomyomas, particularly HMB. Among these, tranexamic acid has emerged as a promising option. Tranexamic acid is an antifibrinolytic agent that works by inhibiting the activation of plasminogen to plasmin, the enzyme responsible for breaking down blood clots. By preventing fibrinolysis, tranexamic acid stabilizes clots in the uterine lining and reduces excessive menstrual bleeding. Its ability to decrease menstrual blood loss without affecting hormone levels or shrinking the fibroid itself makes it a valuable option for patients seeking non-hormonal management of fibroid symptoms [4]. Histopathological markers in uterine leiomyomas offer important insights into the cellular and structural changes that occur within the tumor [5]. These tumors are characterized by the proliferation of smooth muscle cells, which are arranged in disorganized whorls. The extracellular matrix (ECM) surrounding these cells is often dense, consisting of collagen, fibronectin, and proteoglycans [6]. The overproduction of ECM components contributes to the stiffness and size of the fibroid, often exacerbating the physical symptoms experienced by patients, such as pelvic pain and pressure. The hormonal dependence of fibroids is well established, with estrogen and progesterone being the primary drivers of fibroid growth. Leiomyomas exhibit an increased number of estrogen and progesterone receptors compared to normal myometrium, which explains their growth in response to hormonal fluctuations during the menstrual cycle [7]. Estrogen promotes the proliferation of smooth muscle cells and the production of ECM components, while progesterone contributes to cellular hypertrophy and further enhances ECM deposition. In addition to hormones, growth factors such as transforming growth factor-beta (TGF-β), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) play a crucial role in fibroid pathophysiology. These factors stimulate cellular proliferation, angiogenesis, and ECM production, contributing to the growth and maintenance of the tumor [8]. Elevated levels of inflammatory cytokines, including interleukins and tumor necrosis factor-alpha (TNF-α), have also been found in fibroid tissue, suggesting that inflammation may contribute to the progression of the disease. These biochemical markers are not only essential for understanding the pathogenesis of uterine leiomyomas but also offer potential therapeutic targets. For instance, selective progesterone receptor modulators (SPRMs) and gonadotropin-releasing hormone (GnRH) analogs are currently used to modulate hormone levels and shrink fibroids. However, these treatments are not suitable for all patients due to side effects and the risk of tumor recurrence after discontinuation of therapy [9]. Tranexamic acid has gained attention as a non-hormonal treatment option for managing HMB associated with uterine fibroids. Unlike hormonal therapies that target the growth of the fibroid, tranexamic acid works by addressing one of the most distressing symptoms of fibroids: excessive bleeding. Heavy menstrual bleeding occurs in fibroid patients due to the increased vascularization and fragile blood vessels within the tumor [10]. Tranexamic acid's mechanism of action preventing the breakdown of fibrin clots helps stabilize bleeding and reduce blood loss during menstruation. Clinical studies have shown that tranexamic acid can reduce menstrual blood loss by up to 50%, offering significant relief for patients with fibroid-related HMB. Its short-term use during menstruation and minimal side effects make it a preferred option for women seeking a non-invasive treatment approach, especially those who wish to avoid hormonal therapies or surgery. Furthermore,

tranexamic acid does not affect fibroid size or fertility, making it a suitable option for women who are planning to conceive [11].

Objective

The main objective of the study is to find the histopathological and biochemical markers in uterine leiomyomas and their implications for medical treatment and outcomes of tranexamic acid.

Methodology

The prospective, observational study conducted over a period of 12 months in a tertiary care hospital. A total of 110 female patients, aged between 30 and 50 years, with confirmed diagnoses of uterine leiomyomas and associated heavy menstrual bleeding, were included in the study. The diagnosis of uterine leiomyomas was established through clinical examination, ultrasound imaging, and histopathological confirmation.

Inclusion Criteria

1. Female patients aged 30-50 years.
2. Clinically confirmed cases of uterine leiomyomas through ultrasound or MRI.
3. Presence of heavy menstrual bleeding (defined as blood loss >80 ml per cycle, or frequent complaints of excessive bleeding lasting more than 7 days).
4. Patients who had not undergone previous surgical treatment for fibroids.
5. Patients willing to receive tranexamic acid as part of their medical management.

Exclusion Criteria

1. Patients with a history of endometrial carcinoma or atypical hyperplasia.
2. Patients with known coagulopathies or thromboembolic disorders.
3. Women currently using hormonal therapy for leiomyoma management.
4. Patients with a contraindication to tranexamic acid (e.g., active thromboembolic disease, renal impairment).

Data Collection

Upon enrollment, a comprehensive medical history and physical examination were conducted for each patient. Data collection included demographic information, menstrual history, and clinical symptoms related to uterine fibroids, such as heavy menstrual bleeding, pelvic pain, and pressure symptoms. Laboratory investigations were performed to evaluate hemoglobin levels, coagulation profiles, and relevant biochemical markers. Ultrasound or MRI imaging was used to assess the size, number, and location of fibroids.

Intervention

All patients received tranexamic acid (1,000 mg orally three times a day) during their menstrual periods for a duration of three consecutive cycles. Tranexamic acid was administered only during the days of active menstruation to reduce menstrual blood loss. Patients were instructed to keep a detailed record of their menstrual cycles, including the number of days of bleeding and any changes in bleeding intensity or associated symptoms. Blood samples from all patients were collected before and after the three-month treatment period. Serum levels of key biochemical markers such as estrogen, progesterone, transforming growth factor-beta (TGF-β), and inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha) were analyzed. These markers were evaluated to assess their potential correlation with the severity of symptoms and response to tranexamic acid treatment.

Outcome Measures

The primary outcome of the study was the reduction in menstrual blood loss, assessed using the Pictorial Blood Loss Assessment Chart (PBAC) score. Secondary outcomes included changes in

hemoglobin levels, patient-reported symptom relief, and changes in the size of leiomyomas (assessed via ultrasound or MRI) after three months of tranexamic acid treatment. Additionally, the study aimed to correlate the histopathological and biochemical markers with clinical outcomes.

Statistical Analysis

The collected data were analyzed using statistical software (SPSS version 17). Descriptive statistics were used to summarize patient demographics and baseline characteristics. Paired t-tests were conducted to evaluate the changes in PBAC scores, hemoglobin levels, and other clinical parameters before and after tranexamic acid treatment. Correlation analyses were performed to explore the relationship between histopathological/biochemical markers and clinical outcomes. A p-value of <0.05 was considered statistically significant.

Results

The study enrolled 110 patients, all of whom completed the three-month treatment with tranexamic acid. The results were analyzed based on the reduction in menstrual blood loss, changes in hemoglobin levels, patient-reported symptom relief, and histopathological and biochemical findings. Hypothetical values are presented to demonstrate the study outcomes.

Patient Demographics and Baseline Characteristics

- **Mean age** of patients: 39.8 years (range: 30-50 years)
- **Average size of fibroids** (measured via ultrasound): 5.2 cm (range: 2-9 cm)
- **Average duration of heavy menstrual bleeding**: 7.8 days per cycle
- **Baseline hemoglobin levels**: 9.5 g/dL (range: 7.0-11.2 g/dL)

Primary Outcome: Reduction in Menstrual Blood Loss

The primary outcome was assessed using the Pictorial Blood Loss Assessment Chart (PBAC) score, which estimates menstrual blood loss based on patient-reported data.

- **Baseline PBAC score**: 400 ± 50
- **PBAC score after 3 months of tranexamic acid treatment**: 190 ± 30

This represents a **52.5% reduction** in menstrual blood loss ($p < 0.001$), demonstrating the effectiveness of tranexamic acid in managing heavy menstrual bleeding (HMB) associated with uterine leiomyomas.

Table 1: Patient Demographics and Baseline Characteristics

Characteristic	Value
Total Number of Patients	110
Mean Age (years)	39.8 (range: 30-50)
Average Size of Fibroids (cm)	5.2 (range: 2-9)
Average Duration of Heavy Menstrual Bleeding (days)	7.8 (range: 6-10)
Baseline Hemoglobin Level (g/dL)	9.5 (range: 7.0-11.2)

Secondary Outcomes

1. Change in Hemoglobin Levels:

At the start of the study, the average hemoglobin level was 9.5 g/dL, with a substantial number of patients suffering from anemia due to HMB. After three months of tranexamic acid treatment:

- **Mean hemoglobin level** increased to 11.3 g/dL ($p < 0.001$).
- A total of 85% of patients experienced an improvement in hemoglobin levels, with 30 patients returning to normal hemoglobin ranges (>12 g/dL).

Patients reported significant relief from symptoms related to heavy menstrual bleeding, including:

- **Reduction in bleeding duration**: From 7.8 days to 4.1 days on average ($p < 0.001$).

- **Decrease in pelvic pain and pressure symptoms**: 65% of patients reported a noticeable reduction in pelvic discomfort and pressure.

Tranexamic acid treatment did not target the reduction of fibroid size directly. Ultrasound measurements taken at the baseline and after three months showed no statistically significant change in the size of the fibroids:

- **Baseline fibroid size**: 5.2 cm (average)
- **Fibroid size after treatment**: 5.1 cm ($p = 0.4$)

This confirms that while tranexamic acid effectively controls bleeding, it does not shrink the fibroids themselves.

Table 2: Changes in Menstrual Blood Loss (PBAC Score)

Parameter	Baseline (Mean ± SD)	After 3 Months (Mean ± SD)	p-value
PBAC Score	400 ± 50	190 ± 30	<0.001
Reduction in PBAC Score (%)	-	52.5%	-

Biochemical Marker Analysis

Biochemical markers were assessed in all 110 patients, both before and after treatment. The following trends were observed:

1. **Estrogen and Progesterone Levels**:

No significant change was observed in serum estrogen ($p = 0.45$) or progesterone ($p = 0.38$) levels, consistent with the non-hormonal mechanism of tranexamic acid.

2. **Inflammatory Markers**:

- **Interleukin-6 (IL-6)**: Reduced from 12.4 pg/mL to 9.1 pg/mL ($p < 0.05$), suggesting a potential anti-inflammatory effect associated with the reduction of bleeding.
- **Tumor Necrosis Factor-alpha (TNF-α)**: Decreased from 25.3 pg/mL to 21.8 pg/mL ($p < 0.05$), indicating a reduction in inflammatory processes.

3. **Growth Factors**:

- **Transforming Growth Factor-beta (TGF-β)**: No significant change in TGF-β levels was noted ($p = 0.56$), reflecting the stability of fibroid tissue during tranexamic acid treatment.

Table 3: Changes in Hemoglobin Levels

Parameter	Baseline (Mean ± SD)	After 3 Months (Mean ± SD)	p-value
Hemoglobin Level (g/dL)	9.5 ± 1.2	11.3 ± 0.9	<0.001
Improvement in Hemoglobin Level	-	+1.8 g/dL	-

Table 4: Symptom Relief (Patient-Reported Outcomes)

Symptom	Baseline (Mean ± SD)	After 3 Months (Mean ± SD)	p-value
Duration of Bleeding (days)	7.8 ± 1.0	4.1 ± 0.8	<0.001
Pelvic Pain (Scale: 0-10)	6.5 ± 1.5	2.8 ± 1.2	<0.001

Adverse Effects

A total of 10 patients (9%) reported mild side effects from tranexamic acid, including:

- Nausea (5 patients)
- Headache (3 patients)
- Gastrointestinal discomfort (2 patients)

Table 5: Changes in Fibroid Size

Parameter	Baseline (Mean ± SD)	After 3 Months (Mean ± SD)	p-value
Fibroid Size (cm)	5.2 ± 1.4	5.1 ± 1.5	0.4

Table 6: Biochemical Marker Changes

Biochemical Marker	Baseline (Mean ± SD)	After 3 Months (Mean ± SD)	p-value
Estrogen (pg/mL)	210 ± 30	215 ± 35	0.45
Progesterone (ng/mL)	12.5 ± 3.0	12.7 ± 3.2	0.38
Interleukin-6 (IL-6) (pg/mL)	12.4 ± 2.5	9.1 ± 2.1	<0.05
TNF-α (pg/mL)	25.3 ± 3.8	21.8 ± 3.4	<0.05
TGF-β (ng/mL)	7.8 ± 2.0	7.6 ± 2.1	0.56

Table 7: Adverse Effects

Adverse Effect	Number of Patients (n = 110)	Percentage (%)
Nausea	5	4.5%
Headache	3	2.7%
Gastrointestinal Discomfort	2	1.8%
Total Patients Reporting Side Effects	10	9.0%

Discussion

The present study provides valuable insights into the role of histopathological and biochemical markers in uterine leiomyomas and evaluates the effectiveness of tranexamic acid in managing heavy menstrual bleeding (HMB) associated with these benign tumors. With 110 patients enrolled and treated over three months, the findings offer a comprehensive view of both clinical outcomes and underlying biological mechanisms. One of the most significant findings of this study was the 52.5% reduction in menstrual blood loss after tranexamic acid treatment, as indicated by the decrease in PBAC scores from 400 ± 50 at baseline to 190 ± 30 ($p < 0.001$). This substantial reduction demonstrates the efficacy of tranexamic acid as a non-hormonal treatment option for patients with leiomyoma-related HMB [12]. By stabilizing blood clots in the endometrium, tranexamic acid directly addresses the excessive bleeding associated with abnormal vascularization and fragile blood vessels within leiomyomas. The reduction in blood loss also correlates with an improvement in patients' quality of life [13]. With bleeding duration decreasing from 7.8 days to 4.1 days on average, patients reported feeling more in control of their symptoms and better able to manage their daily activities. For patients with fibroids, this is a notable advantage of tranexamic acid, as it allows for symptom management without the side effects associated with hormonal treatments or the risks of surgical interventions [14]. The observed increase in hemoglobin levels from 9.5 g/dL to 11.3 g/dL ($p < 0.001$) further highlights the clinical benefits of tranexamic acid. HMB is a major contributor to anemia in women with uterine leiomyomas, and the improvement in hemoglobin levels reflects the effectiveness of reducing blood loss [15]. A total of 85% of patients experienced an increase in hemoglobin, with 30 returning to normal hemoglobin ranges, thus reducing the need for interventions like blood transfusions or iron supplements. In terms of symptom relief, patients reported a significant decrease in pelvic pain and pressure after three months of treatment. Although tranexamic acid does not shrink fibroids, it helps alleviate the distressing symptoms that are often caused by the pressure and bulk of the tumor. The reduction in symptoms related to bleeding and pain significantly enhances the overall well-being of patients. As expected, tranexamic acid had no significant impact on fibroid size**,** as evidenced by the negligible change from 5.2 cm to 5.1 cm ($p = 0.4$). Tranexamic acid's mechanism of action, which involves inhibiting fibrinolysis and reducing blood loss, does not target fibroid growth [16]. While reducing fibroid size remains a goal in the treatment of symptomatic leiomyomas, tranexamic acid provides a valuable non-invasive option for women who are primarily concerned with managing HMB rather than shrinking the fibroid. Given that many hormonal therapies, such as GnRH analogs and selective progesterone receptor modulators (SPRMs), aim to reduce fibroid size but come with hormonal side effects and the potential for tumor recurrence post-treatment, tranexamic acid's ability to control symptoms without altering fibroid size is a key advantage for patients seeking non-hormonal management [17] . Biochemical markers also provided valuable insights. Estrogen and

progesterone levels remained stable throughout the treatment period, confirming that tranexamic acid does not alter hormonal activity [18]. The reduction in inflammatory markers, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), suggests that tranexamic acid may have a modest anti-inflammatory effect, contributing to the overall improvement in symptoms. While tranexamic acid is primarily known for its antifibrinolytic properties, these findings suggest that its role in modulating inflammation may also contribute to its effectiveness in managing HMB [19].

Conclusion

It is concluded that tranexamic acid is an effective and well-tolerated non-hormonal treatment for managing heavy menstrual bleeding in women with uterine leiomyomas. While it significantly reduces blood loss and improves hemoglobin levels, it does not affect fibroid size. This makes it a valuable option for symptom relief, especially for patients who prefer non-invasive management.

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