Survey Report

Dosage regimen of tranexamic acid in patients with abnormal uterine bleeding

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

Table of Content

1 INTRODUCTION

Abnormal uterine bleeding (AUB) is a notable clinical condition that frequently affects 14–25% of women of reproductive age [1]. Its subset, heavy menstrual bleeding (HMB), is also common. AUB can significantly impact the physical, social, emotional, and material quality of life of affected women [2]. The most frequent cause of AUB in this age group is immaturity of the hypothalamic-pituitary-ovarian (HPO) axis [3]. The HMB is the most common form of AUB [4]. The causes of AUB are classified by FIGO using the PALM-COEIN classification, which is divided into structural causes (PALM) and non-structural causes (COEIN) [5].

Pharmacological treatment to regulate menstrual cycles and reduce monthly bleeding should ideally be the first-line approach provided in primary care before considering referral of women with AUB to secondary care. Among the available treatment options, Tranexamic acid (TXA) is one of the most efficient drugs used in the management of AUB. TXA acts as fibrinolytic inhibitor commonly used in patients with underlying bleeding disorder [6]. TXA, a non-hormonal medication functioning as an antifibrinolytic agent, can effectively reduce menstrual blood loss by half and improve quality of life. Side effects of TXA can include gastrointestinal disturbances, headaches, anemia, fatigue, and in rare cases, thrombosis [7].

TXA is approved for treating heavy menstrual bleeding, defined as more than 80 mL of blood loss per menstrual cycle [8]. A Cochrane Review provided evidence that TXA can reduce blood loss by 40 to 50% per cycle compared to women who received a placebo or other treatments, such as progestogens, non-steroidal anti-inflammatory drugs, herbal remedies, ethamsylate, or a levonorgestrel intrauterine device [9].

This study employs a questionnaire-based survey conducted among physicians across India to gather insights into their perspectives on the dosage regimen of TXA in abnormal bleeding. Physicians' clinical experiences, patient outcomes, and adherence to treatment protocols are critical factors in assessing the effect

of TXA in AUB. By evaluating these perspectives, the study aims to provide valuable data that can inform clinical practice and guide treatment strategies tailored to the Indian hypertensive population.

2 RATIONALE OF THE STUDY

The rationale for this study is to gather comprehensive insights into the clinical use and dosage regimen of TXA in managing AUB among Indian patients. Understanding the prescribing patterns, prevalence, impact, preferred dose, frequency and perceived efficacy among physicians will aid in optimizing therapeutic strategies and improving patient outcomes.

The purpose of this study is to evaluate the perfect frequency in dosage of TXA in Indian patients diagnosed with AUB. This investigation aims to assess its preferred dose in reducing abnormal bleeding, improving patient compliance and determining its long-term safety profile.

3 OBJECTIVES

- Evaluate the frequency and clinical benefits of TXA in Indian patients with AUB.
- Assess physicians' perspectives on the dosage regimen of TXA.
- Determine the preferred dose and long-term safety profile of TXA.

4 METHODS

This cross-sectional, questionnaire-based study involved a sample of Indian physicians who managed patients with AUB. The survey included 11 questions related to physicians' clinical experience, prescribing practices, and perceptions regarding the use of the TXA for Indian patients with AUB.

Physicians were identified and invited to participate through professional networks and medical associations. Before participation, they were provided with detailed information about the study. The 11-question survey was administered electronically, ensuring convenience for the participants. Responses were collected and securely stored to maintain confidentiality. Following data collection, statistical analysis was conducted to summarize findings and identify key trends.

The study was adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was also taken from an Independent Ethics Committee. Participants were assured of their right to withdraw from the study at any time without any consequences. All responses were anonymized to ensure participant confidentiality. As this was questionnaire-based study, no treatment was administered. The focus of the study was on gathering physicians' perspectives and experiences regarding the usage of the TXA.

Data was analyzed using descriptive and inferential statistics. Descriptive statistics such as summarizing demographic information and response frequencies. Inferential statistics, such as chi-square tests or logistic regression, was used to explore associations between physician characteristics and their perceptions and prescribing behaviours.

5 RESULTS

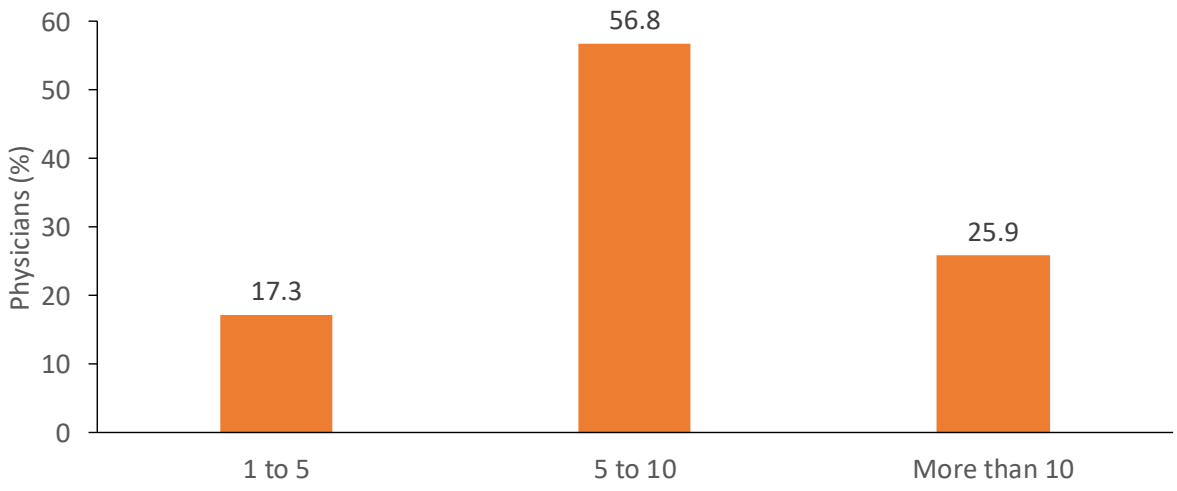
A total of 81 HCPs participated in the survey. Below is the summary of the responses.

[1] In your clinical practice how many patients of AUB you see per week?

A. 1- 5

b. 5- 10

c. More than 10



- A total of 56.8% of physicians attend 5 to 10 patients of AUB per week
- Around 26% of physicians attend more than 10 patients per week
- However, 17% of physicians reported to see around 1 to 5 patients per week

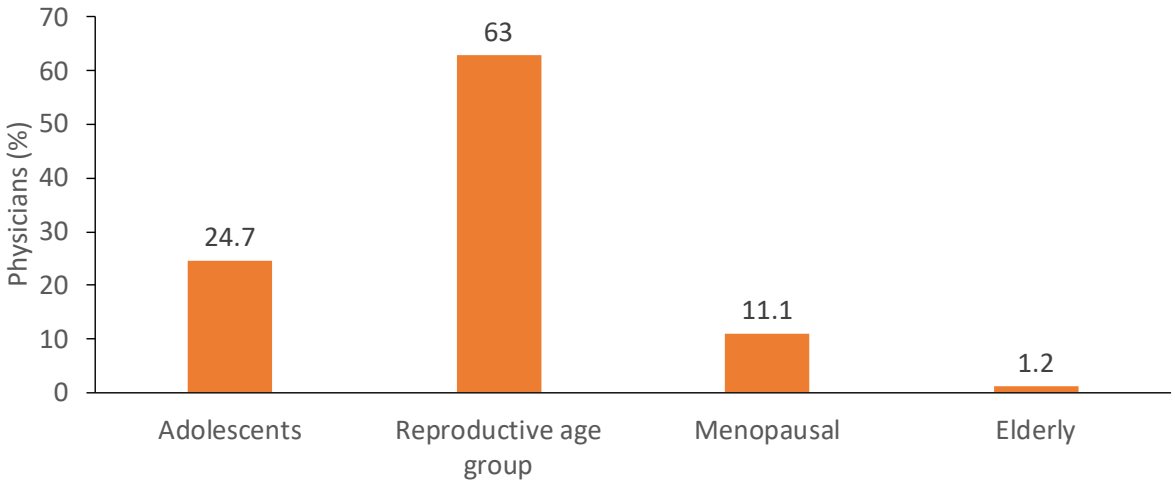
[2] AUB patients generally belong to which age group?

A. Adolescents

b. Reproductive age group

c. Menopausal

d. Elderly



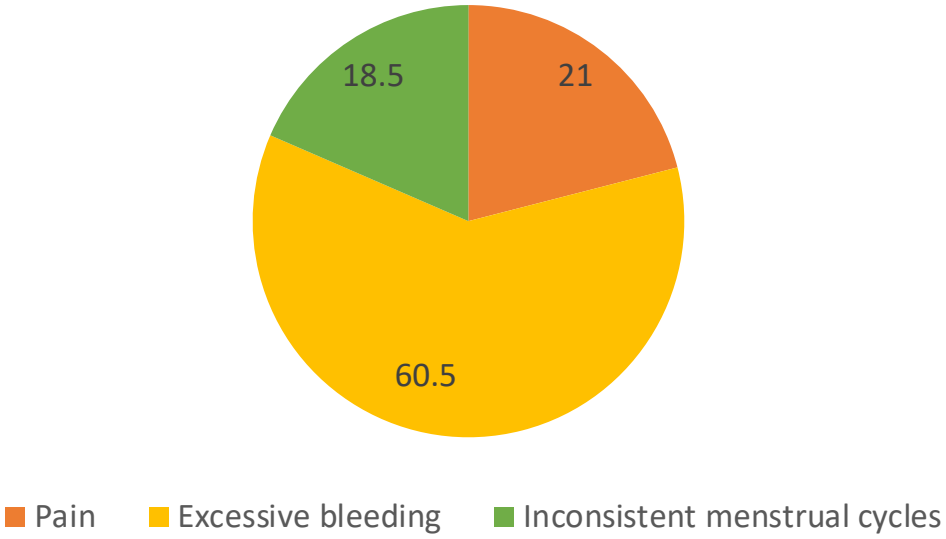
- According to 63% of physicians, AUB patients generally belong to reproductive age group.
- However, 25% of them reported that AUB patients belong to adolescent age group.
- While, 11% of them reported they can be from menopausal age group.
- Similarly, very few of them reported they can be from elderly group.

[3] With which chief complaint do patients of AUB come to your clinic?

A. Pain

B. Excessive bleeding

C. Inconsistent menstrual cycles



- Majority (60.5%) of physicians reported excessive bleeding as the main chief complaint of patients with AUB
- Similarly, 21% of physicians reported pain as the main complaint of their patients in clinical practice.
- However, 18.5% of physicians reported inconsistent menstrual cycle

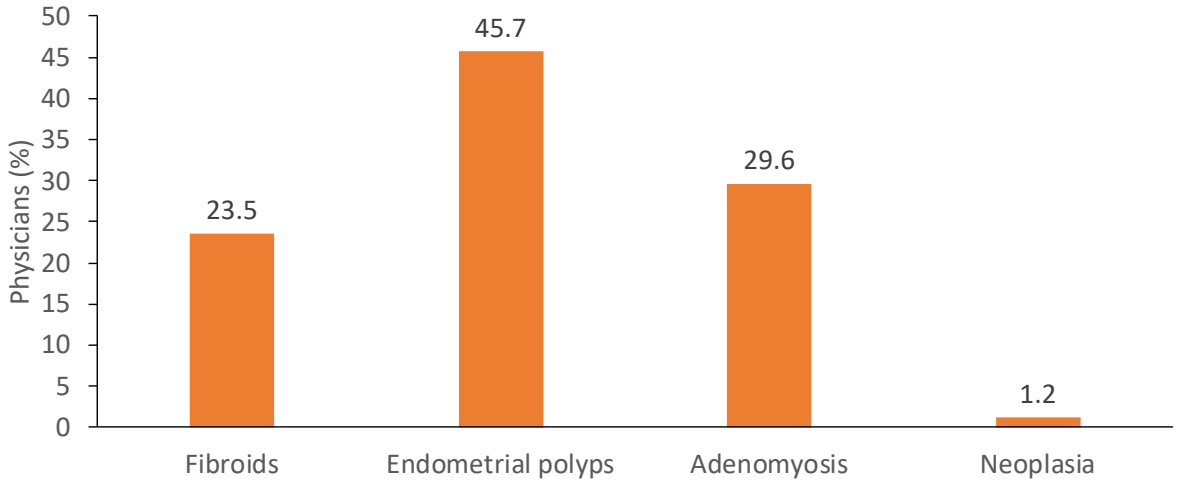
[4] What are the main causes of AUB you encounter in your clinical practice?

A. Fibroids

B. Endometrial polyps

C. Adenomyosis

D. Neoplasia

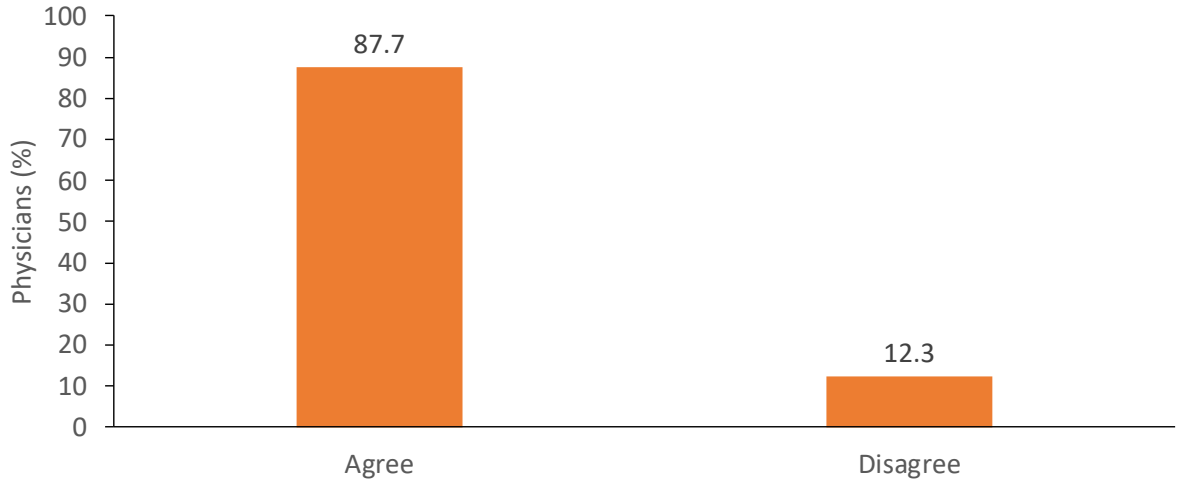


- In clinical practice, most of the (45.7%) physicians reported the main cause of AUB is endometrial polyps.
- Similarly, 29.6% of them found adenomyosis and 23.5% of physicians found fibroids as the main cause of AUB.
- Only few (1.2%) of them reported the main cause of AUB as neoplasia.

[5] For women aged 45 years or older, it is suggested to have endometrial testing to exclude endometrial cancer

A. Agree

B. Disagree



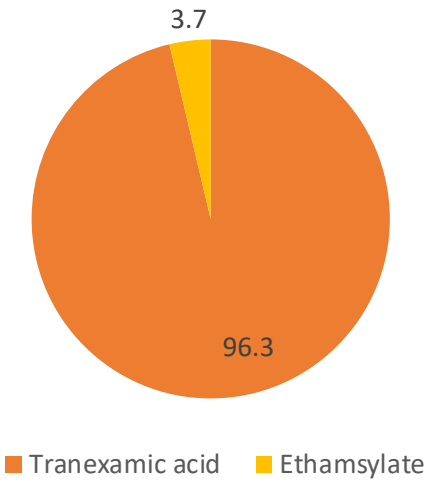
- A total of 87.7% of physicians agreed that women aged 45 years or older are suggested to have endometrial testing to exclude endometrial cancer
- However, 12.3% of physicians disagree with the same.

[6] What is your drug of choice for management of bleeding in AUB?

A. Tranexamic acid

B. Ethamsylate

C. Others please specify

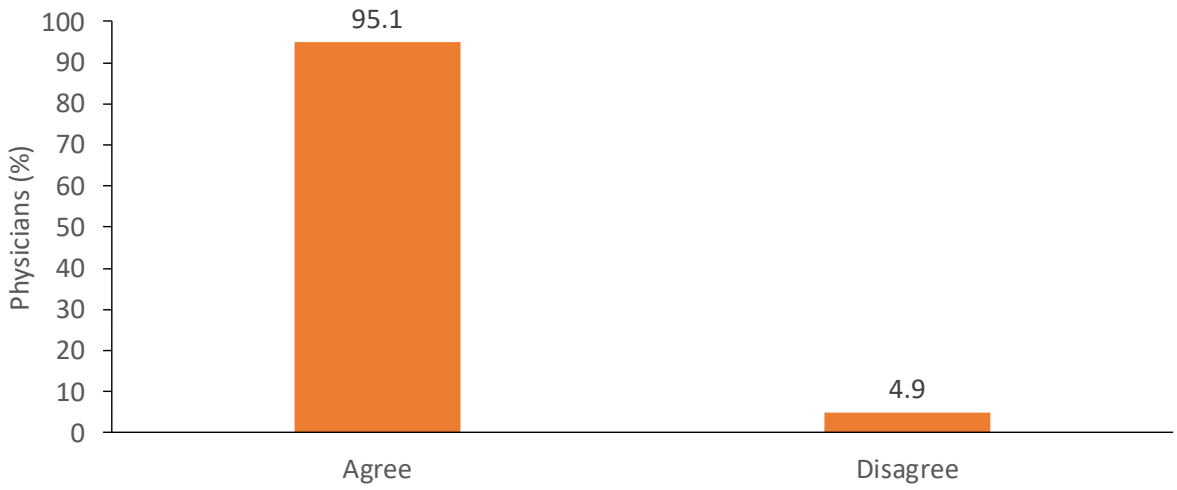


- A total of 96.3% of physicians reported TXA as the drug of choice for management of bleeding in AUB.
- However, only 3.7% of physicians reported ethamsylate as the drug of choice.

[7] Tranexamic acid prevents fibrin degradation and can be used to treat acute AUB:

A. Agree

B. Disagree



- A total of 95% of physicians agreed that TXA prevents fibrin degradation and can be used to treat acute AUB.
- However, 4.9% of physicians disagree with the same.

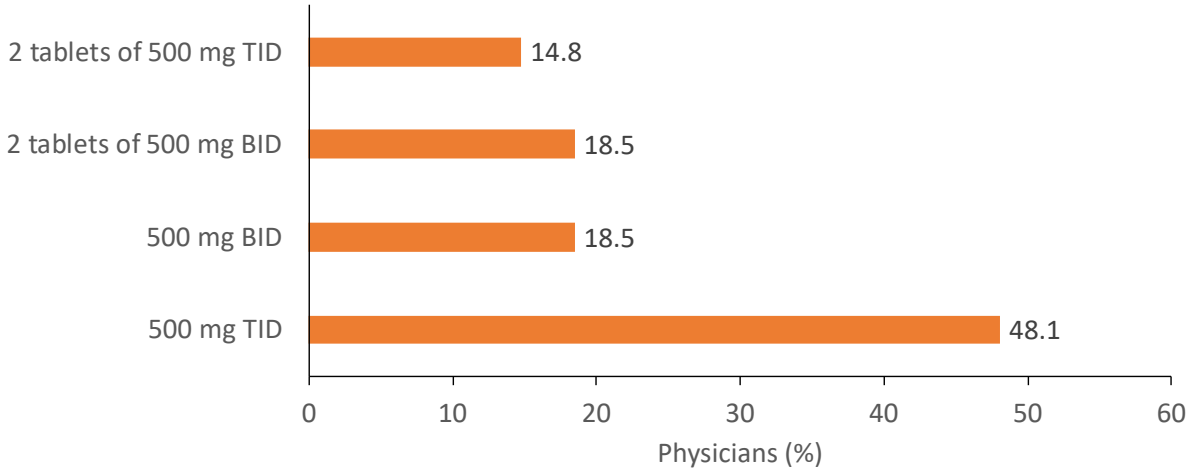
[8] What dose of oral tranexamic acid do you prefer to give in your patients?

A. 500 mg BID

B. 500 mg TID

C. 2 tablets of 500 mg BID

D. 2 tablets of 500 mg TID

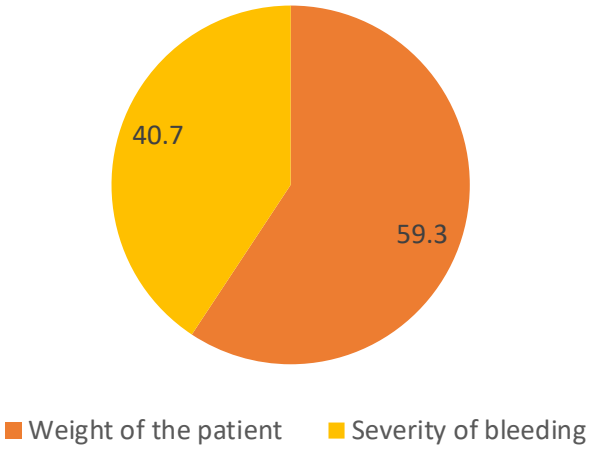


- A total of 48.1% of physicians reported 500 mg TID dose of oral TXA in their patients
- Similarly, 500 mg BID dose and 2 tablets 500 mg BID of TXA was recommended by 18.5% of physicians
- However, 2 tablets 500 mg TID was recommended by 14.8% of physicians

[9] How do you decide the dose of tranexamic acid in patients with AUB?

A. Weight of the patient

B. Severity of bleeding



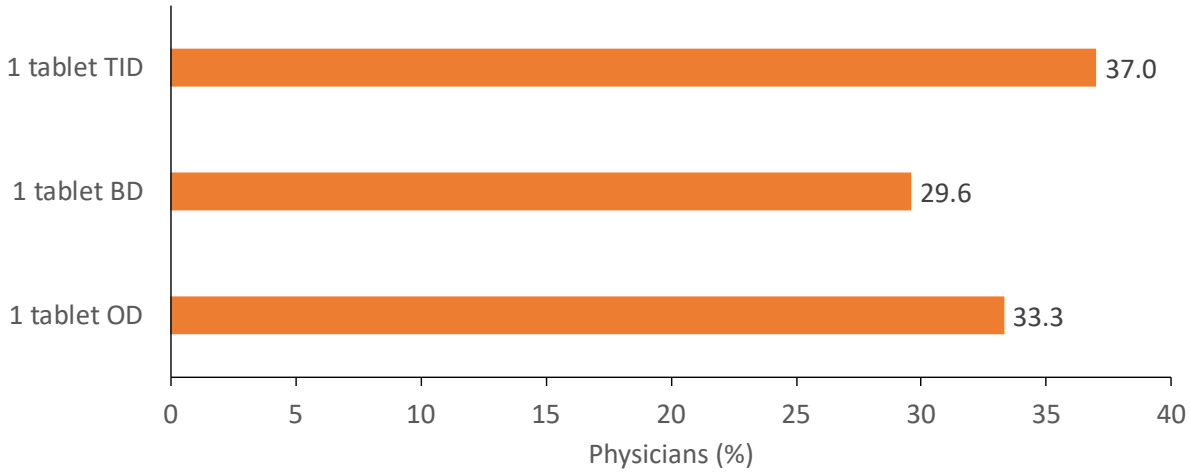
- According to 59.3% of physicians the dose of TXA is decided by weight of the patient
- However, 40.7% of them reported the dose is decided by the severity of bleeding in patients with AUB

[10] In your opinion what should be the frequency of 1000 mg tablet of Tranexamic acid in patients with AUB?

A. 1 Tablet OD

B. 1 Tablet BD

C. 1 Tablet TID

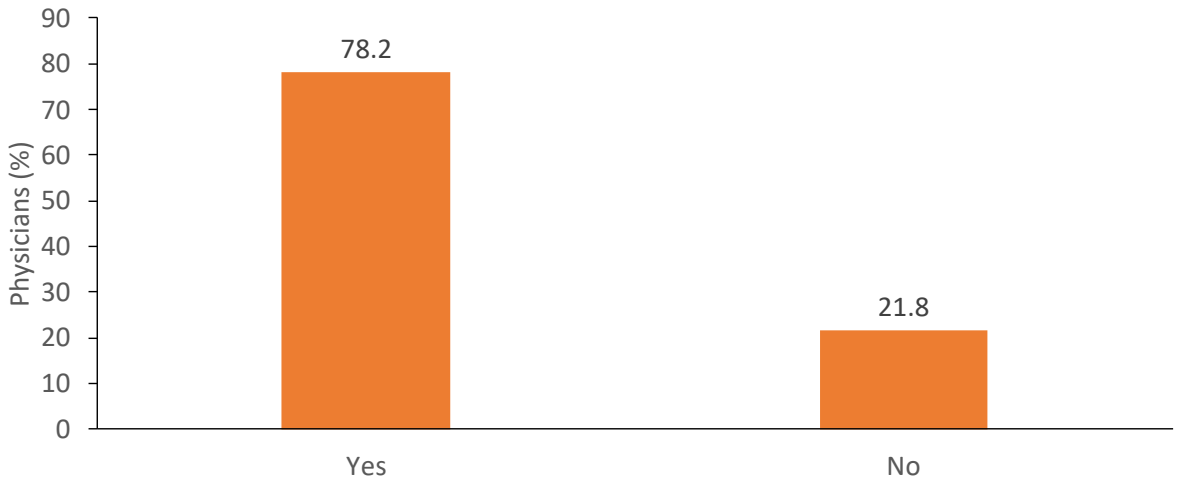


- According to 37% of physicians the frequency of 1000 mg tablet of TXA in patients with AUB is 1 tablet TID
- Similarly, 33% of physicians reported the frequency of 1000 mg tablet as 1 tablet OD
- However, 1 tablet BD of 1000 mg was suggested by 30% of physicians in patients with AUB

[11] Does the dose of tranexamic acid need to be increased or decreased as per the BMI of patient?

A. Yes

B. No



- A total of 78.2% of physicians agreed that dose of TXA should be increased or decreased as per the BMI of patient
- However, 21.8% of them were against the same

6 SUMMARY

The survey revealed that most of the physicians (57%) attend 5 to 10 patients with AUB per week. A total of 26% of physicians attend more than 10 patients per week. According to 63% of physicians, AUB patients generally belong to the reproductive age group. In clinical practice, excessive bleeding is the main commonly reported complaint by patients with AUB. Other complaints include pain, and inconsistent menstrual cycles. The main cause of AUB reported by 46% of physicians is endometrial polyps. However, other causes include adenomyosis, fibroids and neoplasia.

It is suggested by most of physicians that endometrial testing should be performed for women aged 45 years or older to exclude endometrial cancer. Around 96% of physicians prefer TXA for the management of bleeding in AUB patients. Tranexamic acid prevents fibrin degradation and can treat acute AUB. The majority (48%) of physicians recommend a 500 mg TID dose of oral TXA. The dose of the drug is mainly depended on the patient weight. According to 37% of physicians, a 1000 mg tablet of TXA should be given 1 tablet TID in patients with AUB. However, 33% of them suggest 1 tablet OD. Most of the physicians believe dosage should be adjusted based on BMI.

7 DISCUSSION

The study revealed that a majority of physicians (57%) attend to 5 to 10 patients with AUB weekly, while 26% see more than 10 patients. This high frequency underscores the commonality of AUB in clinical practice. Consistent with previous studies, most AUB patients (63%) are of reproductive age, aligning with findings by Fraser et al. (2009), who noted the significant health-related quality of life and economic burden of AUB in this demographic .

Excessive bleeding is the primary complaint reported by patients, as indicated by 60.5% of the surveyed physicians, followed by pain and inconsistent menstrual cycles. This observation is in line with the NICE Clinical Guideline 44, which identifies heavy menstrual bleeding as a prevalent issue . The primary causes of AUB identified include endometrial polyps, adenomyosis, fibroids, and neoplasia, reflecting the PALM-COEIN classification system proposed by Munro et al. (2011) for categorizing AUB causes .

A notable recommendation by the majority of physicians is endometrial testing for women aged 45 and older to exclude endometrial cancer. This aligns with guidelines suggesting heightened vigilance for malignancy in older women presenting with AUB, reinforcing the importance of timely and accurate diagnosis to mitigate cancer risks. The overwhelming preference for TXA in managing AUB highlights its established efficacy and safety profile. TXA's mechanism, which involves inhibiting fibrin degradation, effectively reduces menstrual blood loss, as supported by Okamoto and Okamoto (1962) . Physicians predominantly recommend a 500 mg TID dose of oral TXA, with dosage adjustments often based on patient weight, reflecting a tailored approach to therapy. The diverse dosing strategies, including 1000 mg TID and 1 tablet OD, underscore the need for individualized treatment plans, considering patient-specific factors such as BMI, which most physicians agree should influence dosage decisions.

This study's findings corroborate the results of Lukes et al. (2011), who advocated for TXA's efficacy in treating heavy menstrual bleeding . Additionally, the Cochrane review by Ac et al. (2018) emphasizes antifibrinolytics' role in managing heavy menstrual bleeding, further validating TXA's clinical utility .

The insights gained from this survey can inform clinical practice by emphasizing the need for a standardized yet flexible approach to AUB management. Physicians' reliance on TXA and their varied dosing regimens highlight the importance of individualized treatment strategies tailored to patient characteristics and clinical presentation. Moreover, the emphasis on endometrial testing for older women reinforces the need for comprehensive diagnostic protocols to rule out malignancies, ensuring optimal patient care.

8 CLINICAL RECOMMENDATIONS

- Perform a thorough clinical evaluation for all patients presenting with AUB, including a detailed medical history and physical examination.
- Utilize the PALM-COEIN classification system to identify the underlying causes of AUB, focusing on structural causes like endometrial polyps, adenomyosis, and fibroids, as well as non-structural causes.
- For women aged 45 years and older, recommend endometrial testing to exclude endometrial cancer. This aligns with the survey's finding that most physicians support this practice.
- Use TXA as the first-line treatment for managing heavy menstrual bleeding in AUB patients. TXA is effective in reducing menstrual blood loss by preventing fibrin degradation
- The recommended dosage of TXA varies, but the survey indicates a common practice of prescribing 500 mg TID (three times a day). Adjust the dose based on patient weight and bleeding severity
- Personalize the treatment plan for each patient, considering factors such as BMI, weight, and the severity of bleeding. This tailored approach ensures optimal efficacy and safety
- In cases where a 1000 mg tablet of TXA is used, consider the frequency of 1 tablet TID (three times a day), OD (once a day), or BD (twice a day) based on patient response and clinical judgment

- Regularly monitor patients for response to treatment and any adverse effects. Adjust the dosage of TXA as necessary to achieve the desired therapeutic outcomes
- Schedule follow-up visits to reassess symptoms, ensure compliance with the treatment regimen, and make any necessary modifications to the treatment plan
- For patients who cannot tolerate TXA or do not respond adequately, consider alternative therapies such as hormonal treatments, NSAIDs, or surgical interventions like endometrial ablation or hysterectomy
- Evaluate the risks and benefits of each alternative treatment option, taking into account patient preferences and overall health status
- Educate patients about AUB, including its potential causes, treatment options, and the importance of adherence to the prescribed therapy
- Provide information on lifestyle modifications that may help manage symptoms, such as maintaining a healthy weight and managing stress
- Encourage ongoing research into the long-term safety and efficacy of TXA and other treatment options for AUB
- Promote continuing medical education for healthcare providers to stay updated on the latest guidelines and best practices for AUB management
- By implementing these clinical recommendations, healthcare providers can enhance the management of AUB, improve patient outcomes, and ensure a high standard of care.

9 CONSULTANT OPINION

Develop and validate more sensitive and specific diagnostic tools and biomarkers for identifying the underlying causes of AUB. This could include advancements in imaging technologies and molecular diagnostics. Explore the potential of non-invasive diagnostic methods to reduce patient discomfort and improve compliance. Conduct research to identify genetic, molecular, and environmental factors that influence the development and progression of AUB. This will help in tailoring individualized treatment plans. Investigate the role of pharmacogenomics in predicting patient response to treatments like TXA and other medications, allowing for more personalized and effective therapy.

Perform large-scale, randomized controlled trials comparing the effectiveness and safety of different AUB treatments, including TXA, hormonal therapies, NSAIDs, and surgical interventions. Focus on long-term outcomes and quality of life measures to determine the most beneficial treatment approaches for different patient populations. Explore new therapeutic agents and treatment modalities for AUB, including novel pharmacological compounds, minimally invasive surgical techniques, and emerging technologies such as radiofrequency ablation. Investigate the combination of different treatment modalities to enhance efficacy and reduce side effects.

Develop comprehensive, evidence-based clinical guidelines for the diagnosis and management of AUB, incorporating the latest research findings and expert consensus. Standardize protocols for the use of TXA and other treatments, ensuring consistency in patient care across different healthcare settings.

Conduct qualitative studies to understand patient perspectives on AUB management, including their preferences, concerns, and experiences with different treatments.

Engage patients in the research process to ensure that future studies address relevant clinical questions and improve patient satisfaction. Enhance education and training programs for healthcare providers on the latest advancements in AUB diagnosis and treatment. This includes continuing medical education (CME) opportunities and interdisciplinary collaboration. Promote awareness and education campaigns to inform patients about AUB, its potential causes, and available treatment options.

Investigate the impact of socioeconomic factors, racial and ethnic disparities, and healthcare access on the diagnosis and management of AUB. Develop strategies to address these disparities and improve equity in care. Implement community outreach programs to educate underserved populations about AUB and provide access to timely and appropriate care. Conduct long-term observational studies to track the natural history of AUB and the long-term outcomes of various treatment modalities. This will provide valuable insights into the chronic nature of AUB and its impact on patients' lives. Study the long-term safety profile of TXA and other treatments, particularly in terms of rare but serious adverse effects.

10 MARKET OPPORTUNITIES

- Companies can invest in research and development of more sensitive and specific diagnostic tools for AUB. Innovations in molecular diagnostics and imaging technologies present significant opportunities. There is a growing market for personalized medicine approaches in AUB management, including genetic testing and pharmacogenomics.
- Pharmaceutical companies can explore and market new therapeutic agents, such as novel pharmacological compounds and minimally invasive surgical techniques.
- Develop and distribute evidence-based clinical guidelines and standardized treatment protocols to healthcare providers.
- Develop products and services that focus on patient comfort, preferences, and experiences, such as user-friendly educational materials and support tools.
- Create and market comprehensive education and training programs for healthcare providers on the latest advancements in AUB diagnosis and treatment.
- Develop outreach programs and affordable diagnostic and treatment options to address socioeconomic and racial disparities in AUB care. Develop tools and platforms for conducting long-term observational studies and tracking patient outcomes over time.

11 MARKET POSITIONING

Emphasize the accuracy and non-invasive nature of these new diagnostic tools, highlighting improved patient comfort and early detection capabilities. Position these solutions as cutting-edge and tailored to individual patient profiles, promising more effective and targeted treatment outcomes.

Highlight the effectiveness, reduced side effects, and improved patient recovery times associated with these innovative treatments. Position as authoritative and essential resources that enhance consistency in patient care and improve treatment outcomes. Emphasize the patient-centric approach, improving patient satisfaction and adherence to treatment plans. Promote these programs as essential for continuing medical education and staying updated with cutting-edge medical knowledge.

Highlight the commitment to healthcare equity and improving access to quality care for underserved populations. Position these tools as essential for advancing clinical research and understanding the long-term impacts of AUB treatments. Emphasize the unique technological advancements and innovative nature of diagnostic and therapeutic products. Showcase research-backed evidence demonstrating superior efficacy and patient outcomes. Highlight the focus on patient comfort, preferences, and overall experience. Promote the personalized nature of treatments and diagnostic tools, catering to individual patient needs. Position products and services as high-quality, reliable, and consistent in delivering accurate results and effective treatments. Leverage endorsements from reputable medical organizations and clinical guidelines. Market the company as a leader in medical education and training, providing healthcare professionals with the latest knowledge and skills.

Emphasize collaboration with leading experts and institutions in the field of gynecology and AUB management. Showcase efforts to address health disparities and improve access to quality care for all patient populations. Highlight community outreach programs and affordable care solutions as part of a broader commitment to social responsibility. Position the company at the forefront of clinical research, contributing to the body of knowledge on AUB and influencing treatment guidelines. Use data and outcomes from longitudinal studies to build credibility and trust among healthcare providers and patients.

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