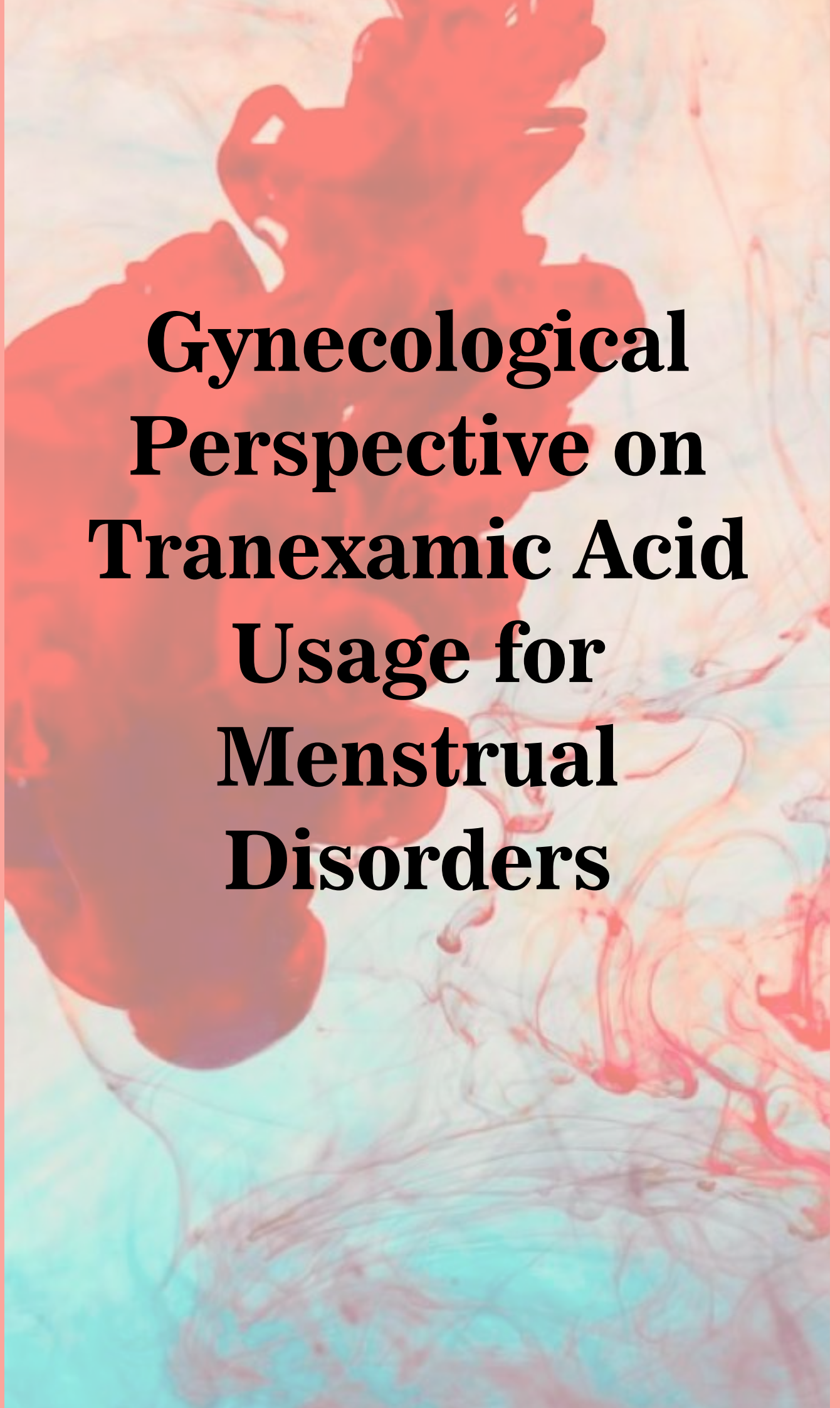


Gynecological Perspective on Tranexamic Acid Usage for Menstrual Disorders

Table of Content

Background and Objective of the Survey

Tranexamic acid (TXA) holds a significant place in gynecological practice for the management of various menstrual disorders, offering effective symptom relief and improved quality of life for women experiencing heavy menstrual bleeding (menorrhagia) or other related conditions.

In the context of menorrhagia, TXA is often prescribed as a first-line or adjunctive therapy to reduce menstrual blood loss and alleviate associated symptoms such as fatigue, anemia, and menstrual pain. TXA works by inhibiting the breakdown of fibrin blood clots, thereby reducing the duration and severity of menstrual bleeding without affecting hormonal levels or menstrual regularity.

Gynecologists may recommend TXA for women with primary menorrhagia (excessive menstrual bleeding without an underlying medical condition) or secondary menorrhagia (excessive menstrual bleeding due to underlying conditions such as fibroids, adenomyosis, or hormonal disorders). TXA can be used as a short-term treatment during menstruation to control acute episodes of heavy bleeding or as a longer-term treatment to manage chronic or recurrent menorrhagia.

The objective of the survey is:

To understand gynecological perspective on tranexamic acid usage for menstrual disorders

Methodology of the Survey

A survey was conducted to understand gynecological perspective on tranexamic acid usage for menstrual disorders. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Causes of menorrhagia
- Diagnostic approach to menorrhagia
- Treatment of menorrhagia
- Tranexamic acid
- Pharmacodynamic Properties
- Pharmacokinetic Properties
- Therapeutic Use
- Dosage and Administration

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Menorrhagia is subjectively defined as a ‘complaint of heavy cyclical menstrual bleeding occurring over several consecutive cycles’. Objectively it is a total menstrual blood loss (MBL) equal to or greater than 80 ml per menstruation. This degree of blood loss can cause disturbances of the woman's social, occupational or sexual life, concern about possible underlying serious disease (especially cancer), as well as medical risks such as chronic iron deficiency anemia. It is estimated that approximately 30% of women complain of menorrhagia. Excessive bleeding is the main presenting complaint in women referred to gynecologists and it accounts for two-thirds of all hysterectomies, and most of endoscopic endometrial destructive surgery. Thus, menorrhagia is an important healthcare problem.

Causes of menorrhagia[1]

Menorrhagia may be the result of systemic or pelvic pathology, or iatrogenic causes. The classic causes of menorrhagia are detailed in Table 1, however, there has been little confirmation with objective MBL measurement.

Table I. Causes of menorrhagia

(a) Uterine causes: organic, functional (dysfunctional uterine bleeding)
(b) Systemic causes: endocrinologic disorders, hematological disorders
(c) Iatrogenic causes: IUDs', use of anticoagulants

Occasionally it may be the result of systemic disease such as hypothyroidism or hematological disorders like bleeding diatheses such as von Willebrand's disease, deficiencies of factors V, VII, X and XI, or idiopathic thrombocytopenic purpura.

Although various pathologies have been implicated in menorrhagia, in 50% of cases of objective menorrhagia no pathology is found at hysterectomy. Although ‘unexplained’

menorrhagia is a very appropriate term this state is often labeled less clearly as dysfunctional uterine bleeding, which implies endocrine abnormalities.

Anovulation might be associated with menorrhagia close to menarche and to menopause. In ovulatory cycles excessive menstrual loss has been ascribed to abnormal uterine levels of prostaglandins. During menstruation higher levels of prostaglandin E2 and prostaglandin F2α in menstrual fluid are found in menorrhagic women when compared with those with normal menses. Furthermore release of prostaglandin E2, prostaglandin F2α and prostacyclin by endometrium and myometrium during menstruation is elevated from tissues obtained from menorrhagic women. Moreover increased concentrations of prostaglandin E receptors are found in myometrium collected from menorrhagic women. In addition, fibrinolytic activity is significantly elevated in the endometrium of most women with ovulatory dysfunctional uterine bleeding.

Diagnostic approach to menorrhagia[1]

Menstrual history

Evaluation begins with a detailed menstrual history focusing on length and subjective assessment of blood flow, intermenstrual intervals, and changes from previous bleeding patterns. Women presenting with ovulatory bleeding are likely to have heavy regular menstruation over several consecutive cycles without any intermenstrual or postcoital bleeding. They may also have dysmenorrhea with passage of clots. Presumptive evidence of ovulation can be gained from a history of premenstrual symptoms. Anovulatory bleeding is frequently not associated with any of these symptoms and occurs unpredictably.

Assessment of menstrual blood loss

Women seeking treatment for menorrhagia often do not have greater blood losses than average. It has been estimated in hospital practice that only 40% of women complaining of menorrhagia have measured losses greater than 80 ml. Therefore, objective verification of menstrual blood loss is essential, which is difficult in routine clinical practice. The number of sanitary pads or tampons used or the duration of bleeding has little or no correlation with blood loss. Women with true menorrhagia may not necessarily drop their hemoglobin concentration, as losses of 800–1000 ml can occur without anemia. Furthermore, assessment of menstrual blood loss should be undertaken over two menstruations because of cycle to cycle variation.

Although not available routinely, MBL can be quantified using the noninvasive 'alkaline hematin method', where sanitary devices are soaked in 5% sodium hydroxide to convert the blood to alkaline hematin and optical density is measured.

In order to obtain a semiquantitative measurement of the menstrual blood loss, better suited to general practice or nonresearch gynecologic out-patient settings, a pictorial blood loss assessment chart (PBAC) has been developed. The charts indicate not only the number but also the degree of soiling of items of sanitary wear. The patient scores the daily number of lightly, moderately, or heavily soiled tampons or sanitary towels used. Although in wide general use, results of studies correlating PBAC scores and menstrual blood loss are conflicting.

More recently, the measurement of total menstrual fluid using a weighing technique was described as sufficiently accurate for clinical purposes. This simple inexpensive technique might have considerable clinical potential but certainly needs further evaluation.

Clinical assessment

An abdominal and pelvic examination is recommended in all women complaining of menorrhagia. Cervical cytology should be up to date in accordance with local screening programs. A full blood count is needed to determine the degree of anemia. Ferritin is not recommended as a routine test in women complaining of menorrhagia. Testing for bleeding disorders should only be undertaken if clinically indicated, e.g. menorrhagia since the menarche and a history of bleeding after dental extractions and childbirth. Thyroid function tests should only be undertaken if clinically indicated. No other endocrine investigations are warranted.

Transvaginal ultrasound scanning

Transvaginal ultrasound scanning has become a routine procedure. Its use should be implemented as a first-step investigation in patients with abnormal uterine bleeding to select those in need of further diagnostic evaluation. Transvaginal ultrasound scan is a noninvasive, nonpainful method and represents a very good test for the diagnosis of endometrial pathologies including polyps, submucous fibroids and hyperplasia. Transvaginal sonography enables to assess endometrial thickness and detects polyps and myomata with a sensitivity of 80% and specificity of 69%.

There is evidence that endometrial thickness may be indicative of pathology in postmenopausal women. A meta-analysis of 35 studies showed that in menopausal women, endometrial thickness (endometrial double layer) of 5 mm at ultrasound has a sensitivity of more than

92% for detecting endometrial disease (polyp, atypical hyperplasia or cancer) and 96% for detecting endometrial cancer. This was independent from hormonal therapy.

No such correlations are firmly established in the premenopausal patient. The British 'RCOG Guideline Development Group' reviewed a number of studies involving premenopausal women and concluded that 10–12 mm represented a reasonable cut-off when using transvaginal ultrasound scanning as the method prior to more invasive procedures of endometrial assessment.

Ideally, transvaginal ultrasound scanning should be performed after menstruation in the follicular phase of the menstrual cycle. Ultrasound can sometimes miss small polyps particularly when performed in the late secretory phase when the endometrium is thicker.

Detection of benign lesions such as endometrial polyps and submucous fibroids can be enhanced by sonohysterography. By instillation of saline into the uterine cavity an interface between the fluid and an endometrial mass can be defined more clearly.

Some studies suggest that transvaginal ultrasound scanning in combination with color flow Doppler may assist in the diagnosis of endometrial cancer, as blood flow is increased in malignancies). However, increased blood flow has also been reported in benign conditions and results are conflicting whether Doppler sonography improves diagnosis of premalignant and malignant endometrial lesions).

Although transvaginal ultrasound may be a useful screening procedure, it is insufficient on its own to establish a histological diagnosis: this requires endometrial sampling.

Endometrial sampling

The principal purpose of endometrial sampling in women with menorrhagia is to obtain a histological diagnosis to exclude malignant and premalignant disease.

Endometrial sampling should be considered in all women with abnormal bleeding aged more than 40 years and in women who are at increased risk of endometrial cancer. Risk factors include nulliparity with a history of infertility, obesity (≥90 kg), a family history of endometrial or colonic cancer, abnormal PAP-smear and tamoxifen therapy).

Younger women may also need endometrial sampling if abnormal bleeding does not resolve with medical treatment. In certain conditions, such as polycystic ovary syndrome in which endometrial hyperplasia is more common, endometrial assessment may be necessary if abnormal bleeding is a presenting feature, or unusual sonographic endometrial appearances are discovered

The most common methods of endometrial sampling in current clinical use are:

- (a) Dilatation and curettage (D & C)
- (b) Endometrial biopsy
- (c) Hysteroscopy

In a meta-analysis Spencer et al. reviewed 142 studies to determine the value of endometrial sampling methods in women with menorrhagia. However, the results do not support a uniform recommendation for which method to choose for endometrial evaluation. Nevertheless, although the choice of sampling device may affect accuracy, no existing method will sample the entire uterine cavity. Therefore in most cases endometrial sampling methods have to be complementary to other techniques to increase sensitivity. Hysteroscopically directed sampling, for example, detects a higher percentage of abnormalities when compared with 'blind' D & C and if no pathology is observed during diagnostic hysteroscopy, the endometrium should be sampled, as hysteroscopy alone is insufficient to exclude endometrial neoplasia.

Dilatation and curettage (D & C)

The classic method of obtaining endometrium is by D & C. Despite having been considered as the 'gold standard', D & C does not sample the whole uterine cavity. As D & C is essentially a blind procedure it can miss lesions such as polyps, submucous fibroids, hyperplasia and carcinoma. It is estimated that in more than 50% of cases D & C does not uncover endometrial pathology.

For many years D & C has erroneously been considered to be a therapeutic as well as a diagnostic procedure. The reason is that traditionally follow up after any gynecologic procedure is at 6 weeks when most women will have only had one postoperative period. Objective menstrual blood loss measurement has shown that while the first period after D & C is lighter, subsequent ones are no different.

D & C requires general anesthesia and is associated with surgical complications including perforation in 0.6–1.3% of cases, hemorrhage in 0.4% of cases, infection in 0.3–0.5% of cases and cervical damage. Extensive curettage may cause intrauterine synechiae. D & C is therefore being increasingly replaced by outpatient procedures which avoid general anesthesia and are also less costly.

Available evidence suggests that, traditional D & C no longer has a place in either the treatment or the investigation of abnormal uterine bleeding. D & C should be reserved for those cases where office biopsy or directed hysteroscopic biopsy are not feasible.

Endometrial biopsy

The advantage of endometrial biopsy is that it avoids general anesthesia and has fewer complications than D & C. The technical skills required for outpatient endometrial biopsy are similar to those needed to fit an intrauterine contraceptive device and there is an argument in favor of its use in primary care.

The Pipelle sampler is a flexible polypropylene suction catheter that has an outer sheath of 23.5 cm in length and 3.1 mm in diameter. The device is inserted through the cervical canal to the uterine fundus and a piston within the sheath is withdrawn to create a vacuum inside the uterus. The tissue sample is obtained by twirling the catheter while moving it up and down within the uterine cavity.

The Vabra curette is a stainless-steel cannula of 24 cm in length and 3 mm in diameter with a chamber for collecting of the specimens at one end. The attached plastic chamber is connected to an electrically powered vacuum pump.

The Pipelle device obtains an adequate endometrial specimen in up to 99% of women in studies with large numbers of premenopausal patients. The Vabra aspirator is reliable in detecting endometrial pathology in 95% of cases.

A recent meta-analysis of Dijkhuizen et al. including 39 studies with 7914 patients reported the 'Pipelle' endometrial biopsy device with detection rates of 91% for endometrial carcinoma and atypical hyperplasia in premenopausal women to be superior to D & C and hysteroscopy.

The 'RCOG Guideline Development Group' also cited studies comparing the Pipelle sampler with formal D & C and with other endometrial sampling devices including Vabra. The group concluded that Pipelle was the preferable device in terms of diagnostic ability, patient acceptability and cost

However, a dilemma exists if there is a negative initial biopsy and menorrhagia persists. One study followed up 263 patients with a negative initial endometrial biopsy or D & C (either benign histology or insufficient sample). One-third underwent further sampling of which 2% were diagnosed with uterine malignancy and 2% were found to have complex hyperplasia. As a result of the high risk (more than 10%) of an existing lesion having been overlooked the authors recommended a repeated biopsy or a transvaginal ultrasound scan in patients with persistent symptoms after a negative initial biopsy.

While endometrial biopsy represents the method of choice for diagnosis or exclusion of malignancy and premalignancy, it is also acknowledged that blind endometrial biopsy is insensitive in diagnosing benign and organic causes of menorrhagia. The two principal

techniques of investigating the uterine cavity to detect pathologies such as polyps and fibroids are transvaginal ultrasound and hysteroscopy.

Hysteroscopy

Hysteroscopy allows direct visualization of the uterine cavity. It is known to be a superior method for the detection of endometrial polyps and submucosal myomas, which can be easily missed by endometrial biopsy procedures, ultrasonography or 'blind' curettage. Diagnostic hysteroscopy can be performed either as an outpatient procedure without anesthetic or as a formal theater procedure.

Hysteroscopy has been advocated by many as the standard for the diagnosis of abnormal uterine bleeding. However, results of various studies are conflicting whether this method improves upon the sensitivity of D & C in the detection of endometrial hyperplasia or carcinoma).

In addition, caution is advised in the uncritical use of hysteroscopy in patients suspected of having endometrial cancer. It has been shown that hysteroscopy can cause dissemination of malignant cells into the abdominal cavity from uteri containing endometrial carcinoma and that these cells are functionally viable. Consequently, hysteroscopy seems to affect prevalence of positive peritoneal cytology, especially in those patients with high-risk cell types. At least four case reports have described the hysteroscopic dissemination of endometrial cancer cells and it was suggested that hysteroscopy should be reserved for patients in whom prior endometrial sampling failed to demonstrate malignancy).

Treatment of menorrhagia

Medical treatment: introduction

Medical therapy is indicated when there is no obvious pelvic abnormality and the woman wishes to retain her fertility. Medical treatment avoids major surgery, but may have side-effects and must be taken long-term. Thus the drug regimen chosen must be effective, have few or mild side-effects and must be acceptable to the patient.

The aims of therapy are to reduce blood loss, reduce the risk of anemia and improve quality of life. Menorrhagia is the commonest cause of iron deficiency anemia in Western women and thus iron therapy is often indicated as well as the options discussed later. It could be argued that MBL should be reduced to be within the normal range (i.e. less than 80 ml per period). However women who are keen to avoid surgery may accept a higher loss if they can cope with the flow and any anemia is controlled with iron.

It is important to assess drug therapies in terms of reduction of measured MBL, because, as already mentioned earlier, there is poor correlation between objective and subjective assessment. Well-designed randomized controlled trials provide the best evidence of the efficacy of any intervention, as any differences between groups can be more confidently attributed to differences in treatment.

Treatment options

Medical treatments for menorrhagia can be divided into two main classes (Table II).

Table II. Medical treatments of menorrhagia

1. Non-hormonal treatments for menorrhagia
Non-steroidal anti-inflammatory drugs
mefenamic acid
meclofenamic acid
naproxen
ibuprofen
flurbiprofen
diclofenac
Antifibrinolytics
tranexamic acid
Reducers of capillary fragility
ethamsylate
2. Hormonal treatments for menorrhagia
Oral progestogens
norethisterone
medroxyprogesterone acetate
dydrogesterone
Intrauterine progestogens
levonorgestrel IUCD
progestasert IUCD
Combined estrogen/progestogens
oral contraceptives
hormone replacement therapy

Other
danazol
gestrinone
GnRH analogs

Non-hormonal treatments of menorrhagia

Non-steroidal anti-inflammatory drugs

Discovery of the relationship of endomyometrial prostaglandins to the genesis of menorrhagia provided an opportunity to evaluate therapy with cyclooxygenase inhibitors. Frequently referred to as nonsteroidal anti-inflammatory drugs (NSAIDs) they reduce endometrial prostaglandin levels by inhibiting cyclooxygenase, the enzyme largely responsible for conversion of arachidonic acid to prostaglandins.

Non-steroidal anti-inflammatory drugs (NSAIDs) can be chemically classified into five main groups: salicylates (aspirin), indolacetic acid analogs (indomethacin), aryl proprionic acid derivatives (naproxen, ibuprofen), fenamates (mefenamic acid, flufenamic acid, meclofenamic acid) and coxibs (celecoxib, rofecoxib). The first four groups inhibit cyclooxygenase-1 (COX-1) and the last cyclooxygenase-2 (COX-2).

NSAIDs have been evaluated in numerous studies, which to date have been limited to COX-1 inhibitors. Patients' subjective perception of improvement and decrease of blood loss was shown in placebo-controlled trials (see for example). A meta-analysis including 16 randomized studies has provided no evidence that one NSAID is superior to the other.

Of the NSAIDs, the fenamates (e.g. mefenamic acid) have been the most extensively studied. The fenamates have the unique property that they inhibit prostaglandin synthesis and also bind to prostaglandin receptors, which are significantly increased in women with menorrhagia. In addition, fenamates are thought to improve endometrial hemostasis. Reductions in menstrual blood flow range from 22 to 46%. With regards to long-term therapy, a follow up of 12–15 months after commencing treatment showed that mefenamic acid continued to be effective.

Reductions in menstrual loss have also been documented for other NSAIDs such as naproxen, ibuprofen, sodium diclofenac and flurbiprofen. The percentage reduction in blood loss varied from 25 to 47% depending on the agent and dosage used.

Optimal doses and schedules are difficult to define, although most studies analyzed regimens that started with the first day of the menstrual cycle and continued for 5 days or until cessation of menstruation. Mefenamic acid and naproxen are typically prescribed in a dosage of 250–

500 mg two to four times/day, ibuprofen has been studied in dosages ranging from 600 to 1200 mg/day.

A common side-effect of NSAIDs are gastro-intestinal symptoms. NSAIDs are therefore contraindicated in women with peptic ulceration. Gastro-intestinal effects are less likely with mefenamic acid than naproxen. Apart from that, NSAIDs have a low profile of adverse effects in otherwise healthy women.

Randomized studies comparing NSAIDs with other agents for dysfunctional uterine bleeding suggest both danazol and tranexamic acid to be superior with respect of decreasing blood loss. However, danazol and tranexamic acid are more likely to cause adverse events when compared with NSAIDs.

In summary, NSAIDs can be an effective first-line treatment in essential menorrhagia. The degree of reduction of menstrual blood loss is modest, but NSAIDs have a low profile of adverse effects in otherwise healthy women. Furthermore, NSAIDs are also effective in women with a copper or nonhormonal intrauterine contraceptive device. An additional beneficial effect is that these drugs also alleviate menstrual pain.

Antifibrinolytics

The endometrium possesses an active fibrinolytic system. An increase in the levels of plasminogen activators, a group of enzymes that cause fibrinolysis, has been found in the endometrium of women with heavy menstrual bleeding compared with those with normal menstrual loss. Plasminogen activator inhibitors (antifibrinolytic agents) have therefore been promoted as a treatment for menorrhagia.

Tranexamic acid, a synthetic derivate of the amino acid lysine, exerts its antifibrinolytic effect through the reversible blockade of plasminogen. Tranexamic acid reduces MBL by up to 50%. Comparative studies have shown tranexamic acid to be superior to NSAIDs, oral progestogens and ethamsylate in reducing menstrual blood loss.

Side-effects of antifibrinolytic drugs are reported by approximately one-third of patients. These are mainly gastrointestinal and dose-dependent. Adverse effects can be reduced by limiting the number of days on which the drug is taken. As approximately 90% of menstrual blood is lost during the first 3 days, medication could be limited to that time.

One factor limiting the widespread acceptance of antifibrinolytic therapy has been the fear of increased thrombotic activity fueled by single case reports about cerebral sinus thrombosis and central venous stasis retinopathy. Long-term studies in Scandinavia, however, have shown that

the incidence of thrombosis in women treated with tranexamic acid is comparable to the spontaneous frequency of the condition in the female population.

Thus antifibrinolytics should be considered as a first-line treatment for menorrhagia. Tranexamic acid is also effective in women with a copper or nonhormonal intrauterine contraceptive device.

Tranexamic acid

Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.

Intravenously administered tranexamic acid (most commonly 10 mg/kg followed by infusion of 1 mg/kg/hour) caused reductions relative to placebo of 29 to 54% in postoperative blood losses in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), with statistically significant reductions in transfusion requirements in some studies. Tranexamic acid had similar efficacy to aprotinin 2×10^6 kallikrein inhibitory units (KIU) and was superior to dipyridamole in the reduction of postoperative blood losses. Transfusion requirements were reduced significantly by 43% with tranexamic acid and by 60% with aprotinin in 1 study. Meta-analysis of 60 trials showed tranexamic acid and aprotinin, unlike ε-aminocaproic acid (EACA) and desmopressin, to reduce significantly the number of patients requiring allogeneic blood transfusions after cardiac surgery with CPB.

Tranexamic acid was associated with reductions relative to placebo in mortality of 5 to 54% in patients with upper gastrointestinal bleeding. Meta-analysis indicated a reduction of 40%.

Reductions of 34 to 57.9% versus placebo or control in mean menstrual blood loss occurred during tranexamic acid therapy in women with menorrhagia; the drug has also been used to good effect in placental bleeding, postpartum haemorrhage and conisation of the cervix. Tranexamic acid significantly reduced mean blood losses after oral surgery in patients with haemophilia and was effective as a mouthwash in dental patients receiving oral anticoagulants. Reductions in blood loss were also obtained with the use of the drug in patients undergoing orthotopic liver transplantation or transurethral prostatic surgery, and rates of rebleeding were reduced in patients with traumatic hyphaema. Clinical benefit has also been reported with tranexamic acid in patients with hereditary angioneurotic oedema.

Tranexamic acid is well tolerated; nausea and diarrhoea are the most common adverse events. Increased risk of thrombosis with the drug has not been demonstrated in clinical trials.

Tranexamic acid is useful in a wide range of haemorrhagic conditions. The drug reduces postoperative blood losses and transfusion requirements in a number of types of surgery, with

potential cost and tolerability advantagesover aprotinin, and appears to reduce rates of mortality and urgent surgery in patients with upper gastrointestinal haemorrhage. Tranexamic acid reduces menstrual blood loss and is a possible alternative to surgery in menorrhagia, and has been used successfully to control bleeding in pregnancy.

Pharmacodynamic Properties

Tranexamic acid exerts its antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules and thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Although plasmin can still be formed under these circumstances, it is unable to bind to and degrade fibrin.

Tranexamic acid is 6 to 10 times more potent in terms of binding to plasminogen/plasmin than the other synthetic antifibrinolytic agent ε-aminocaproic acid (EACA). Suppression of fibrinolysis by tranexamic acid is manifested in surgical patients by reductions in blood levels of D-dimer, but the drug has no effect on blood coagulation parameters. Concurrent administration of heparin does not influence the activity of tranexamic acid.

Pharmacokinetic Properties

Maximum plasma concentrations of tranexamic acid are attained within 3 hours of an oral dose; the presence of food in the gastrointestinal tract has no effect on the pharmacokinetic parameters of the drug. Elimination after intravenous administration is triexponential, and over 95% of each dose is eliminated as unchanged drug in the urine. The total cumulative excretion after an intravenous dose is approximately 90% after 24 hours.

Of the total amount of circulating tranexamic acid, 3% is bound to plasminogen. The drug crosses the blood-brain barrier and the placenta, but excretion into breast milk is minimal. Tranexamic acid is not detectable in saliva after systemic (oral) administration, and mouthwashing with 5% w/v aqueous solutions of the drug results in plasma drug concentrations below 2 mg/L.

Therapeutic Use

Cardiac Surgery

Perioperative treatment with tranexamic acid (most commonly as an intravenous loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/hour) resulted in significant reductions in postoperative blood losses (mostly measured over 12 to 24 hours) in randomised, double-blind comparisons with placebo in patients undergoing cardiac surgery with cardiopulmonary bypass

(CPB). Losses via mediastinal drains were reduced by 29 to 54% relative to placebo, and statistically significant reductions in red blood cell transfusion requirements were reported in some but not all studies. Inconsistency in results with respect to reduction or elimination of transfusions may have been caused in part by variation between institutions in transfusion criteria.

The protease inhibitor aprotinin has been the most frequently used comparator in randomised but nonblind studies of tranexamic acid in patients undergoing cardiac surgery with CPB. Postoperative blood losses (over 6 hours) were reduced to a similar extent by tranexamic acid 10 mg/kg intravenously followed by infusion of 1 mg/kg/hour and aprotinin 2×10^6 kallikrein inhibitory units (KIU) intravenously in 1 study, with both treatments being superior to dipyridamole. Similar effects on postoperative blood losses with the 2 drugs were reported in 2 further studies. Both agents significantly reduced postoperative transfusion requirements in one of these trials (by 43 and 60% with tranexamic acid and aprotinin, respectively; both $p < 0.05$ *vs* control group). Other studies have shown greater reductions in 24-hour blood losses with aprotinin or EACA than with tranexamic acid, but definitive conclusions cannot be drawn from these trials because of inconsistent transfusion data and small patient numbers.

A meta-analysis of 60 randomised clinical trials of haemostatic agents in cardiac surgery with CPB showed tranexamic acid to be associated with a significant decrease (relative to placebo or no treatment) in the proportion of patients requiring allogeneic blood transfusions. A similar effect was found with aprotinin but not with EACA or desmopressin.

Acute Upper Gastrointestinal Bleeding

Reduction of blood transfusion requirements with tranexamic acid therapy in patients with upper gastrointestinal bleeding was first described in 1973. In randomised double-blind studies, predominantly in patients with peptic ulceration or erosion, reductions relative to placebo in mortality rates have ranged from 5 to 54% with tranexamic acid (4.5 to 6g daily for 5 to 7 days in most studies); statistical significance between tranexamic acid and placebo was obtained in the largest published trial.

Meta-analysis of studies of tranexamic acid in patients with upper gastrointestinal haemorrhage showed the drug to be associated with reductions relative to placebo of 20 to 30% in rates of rebleeding, 30 to 40% in the need for surgery and 40% in mortality rates.

Oral Surgery

Proportions of patients with postoperative bleeding complications ranged from 0 to 6.7% when mouthwashes of tranexamic acid were used after oral surgery in patients receiving oral anticoagulant therapy. The corresponding range in patients who received placebo was 13.3 to 40%. In patients with haemophilia, 5 days' treatment with tranexamic acid 1g 3 times daily orally resulted in a mean blood loss after oral surgery of 61.2ml, compared with an 84.1ml loss with placebo, and reduced consumption of clotting factors (14.3 *vs* 78.6% of patients).

Other Surgery

Substantial and statistically significant reductions relative to placebo in mean postoperative blood losses (57 and 65.9%) were reported in 2 trials after perioperative tranexamic acid therapy in patients undergoing total knee arthroplasty, with significant reductions in transfusion requirements. Clinical benefit relative to placebo was obtained after intravenous infusion of tranexamic acid 40 mg/kg/hour in 1 study in patients undergoing orthotopic liver transplantation, with no episodes of hepatic artery or portal vein thrombosis occurring within 1 month of surgery.

Four-week incidences of haemorrhage after transurethral prostatic surgery in a randomised study in 100 men were 24% after treatment with tranexamic acid (1g 3 times daily orally) and 56% in patients who received no antifibrinolytic therapy.

Gynaecology

Reductions of 34 to 57.9% versus placebo or control in mean menstrual blood loss were reported in women with menorrhagia receiving 2 to 3 cycles of treatment with tranexamic acid. The drug was at least as effective as nonsteroidal anti-inflammatory therapy and more effective than etamsylate (ethamsylate) or norethisterone. Efficacy of tranexamic acid in the control of bleeding has also been reported in individual patients with placental abruption or postpartum haemorrhage. A mean 71% reduction in postoperative blood loss was noted in a double-blind study in patients who received tranexamic acid 1.5g daily orally for 12 days after conisation of the cervix. In another double-blind study, 1 of 38 patients who received tranexamic acid and 4 of 37 who received placebo experienced late bleeding after cervical conisation with suturing; the difference between groups was not statistically significant.

Other Indications

An oral dosage of tranexamic acid lg 3 times daily significantly reduced the frequency of secondary ocular haemorrhage after traumatic hyphaema in controlled trials; further data from a case series of 340 children showed rates of rebleeding of 1.1% and 9.6% in patients who received tranexamic acid and no antifibrinolytic therapy, respectively.

Reductions versus placebo in number and severity of attacks of oedema in patients with hereditary angioneurotic oedema were reported in 2 randomised, double-blind studies of tranexamic acid, and clinical benefit was obtained with the drug (1.5g orally 3 times daily) in 6 of 7 patients described in a case series.

There was a significant reduction (from 24% with placebo to 9% with tranexamic acid therapy for up to 4 weeks) in the rate of rebleeding in a randomised double-blind placebo-controlled study in 479 patients with subarachnoid haemorrhage. However, overall outcome was not improved with tranexamic acid after 3 months; this was attributed to an increase in incidence of cerebral ischaemia.

Tolerability

Tranexamic acid is well tolerated. Adverse events are uncommon and usually manifest as nausea or diarrhoea, or occasionally as orthostatic reactions. Results of controlled clinical studies have not confirmed concerns over the possibility of an increased thrombotic tendency in patients treated with inhibitors of fibrinolysis. No increases in incidence of thrombotic events were reported with tranexamic acid in studies of patients undergoing cardiac surgery with CPB or in a retrospective case analysis of 256 women with bleeding disorders in pregnancy. No muta-genic activity or harmful fetal effects of tranexamic acid have been reported.

Retinal changes seen in dogs after very high dosages of tranexamic acid for 1 year have not been reported in humans receiving the drug at therapeutic dosages. However, disturbances in colour vision have been documented, and patients who develop this symptom should discontinue therapy.

Dosage and Administration

Tranexamic acid is presented in a variety of formulations for oral (tablets and syrup) or intravenous use. A dosage of 500mg to 1g by slow intravenous injection 3 times daily or 1 to 1.5g 2 to 3 times daily orally is recommended for local fibrinolysis. For general fibrinolysis, a single dose of 1g or 10 mg/kg by slow intravenous injection is recommended.

Patients undergoing cardiac surgery have most commonly received tranexamic acid intravenously as a 10 mg/kg dose before CPB and an infusion of 1 mg/kg/hour thereafter. A daily dosage of 4.5 to 6g daily (divided into 3 to 6 doses) for 5 to 7 days (intravenous followed by oral therapy) has been used most frequently in patients with upper gastrointestinal bleeding. Patients with haemophilia who are about to undergo oral surgery require 1 to 1.5g orally every 8 hours, and a 4.8 to 5% mouthwash, used for 2 minutes 4 times daily for 7 days, has shown good efficacy in dental patients receiving anticoagulant therapy.

Intravenous infusion of 10 mg/kg before release of tourniquet may be used in patients undergoing knee arthroplasty, and treatment with oral tranexamic acid 6 to 12g daily for 4 days has been used in patients undergoing transurethral prostate surgery. Intravenous infusion of 40 mg/kg/hour has been used to good effect in patients undergoing orthotopic liver transplantation.

Women with menorrhagia should receive tranexamic acid 1 to 1.5g 3 to 4 times daily orally for 3 to 4 days. Dosages of 1.5g or 1 to 1.5g orally 3 times daily are recommended for conisation of the cervix or traumatic hyphaema, respectively, and oral treatment with 1.5g 3 times daily is recommended for the management of hereditary angioneurotic oedema.

Tranexamic acid is contraindicated in patients with a history of thromboembolic disease, and dosage reductions are recommended in patients with renal insufficiency.

References:

1. Oehler MK, Rees MC. Menorrhagia: an update. *Acta Obstet Gynecol Scand*. 2003;82(5):405-422.
2. Dunn, C.J., Goa, K.L. Tranexamic Acid. *Drugs* **57**, 1005–1032 (1999).

Survey Form

1. How often do you prescribe Tranexamic Acid for menstrual disorders in your gynecological practice?

a) Very frequently

b) Frequently

c) Occasionally

d) Rarely

2. What menstrual disorders do you primarily prescribe Tranexamic Acid for?

a) Menorrhagia

b) Dysmenorrhea

c) Metrorrhagia

d) None of the above

3. How effective do you find Tranexamic Acid in managing menstrual bleeding in your patients?

a) Very effective

b) Effective

c) Moderately effective

d) Not very effective

4. What are the main factors that influence your decision to prescribe Tranexamic Acid for menstrual disorders?

a) Severity of bleeding

b) Patient's medical history

c) Presence of underlying conditions

d) All of the above

5. How do you assess the risk of thrombosis when considering Tranexamic Acid for a patient with menstrual disorders?

a) Evaluate patient's medical history and risk factors

b) Perform coagulation studies

c) Consult with a hematologist

d) Patient history

6. How do you assess the risk of thromboembolic events before initiating Tranexamic Acid?

a) Reviewing patient's medical history

b) Conducting thrombophilia screening tests

c) Assessing other risk factors

d) Not applicable, I do not routinely assess thromboembolic risk

7. Have you encountered any adverse effects associated with Tranexamic Acid usage in your patients with menstrual disorders?

a) Yes, frequently

b) Yes, occasionally

c) No, never

d) Not sure

8. What alternative treatments do you consider before prescribing Tranexamic Acid for menstrual disorders?

a) Hormonal therapy

b) Nonsteroidal anti-inflammatory drugs (NSAIDs)

c) Surgical interventions

d) None of the above

9. How satisfied are you with the overall outcomes of Tranexamic Acid treatment in managing menstrual disorders?

a) Very satisfied

b) Satisfied

c) Neutral

d) Dissatisfied

10. How frequently do you review patients' response to Tranexamic Acid treatment during follow-up visits?

a) Regularly, at every visit

b) Occasionally, as needed

c) Only when patients report issues

d) Not applicable, I do not routinely follow up on Tranexamic Acid treatment

11. What dosage of Tranexamic Acid do you typically initiate for the management of menstrual disorders?

a) 500 mg orally three times daily

b) 1000 mg orally twice daily

c) 1300 mg orally twice daily

12. How do you counsel patients regarding the timing of Tranexamic Acid administration for optimal efficacy?

a) At the onset of menstrual bleeding

b) Before expected heavy bleeding episodes

c) Throughout the menstrual cycle

13. What patient-reported outcomes do you consider when assessing the effectiveness of Tranexamic Acid?

a) Reduction in menstrual bleeding volume

b) Improvement in menstrual pain severity

c) Decrease in duration of menstrual bleeding

14. Have you encountered any adverse effects associated with Tranexamic Acid usage in your patients with menstrual disorders?

a) Yes, frequently

b) Yes, occasionally

c) No, never

d) Not sure

15. On a scale of 1 to 10, how likely are you to recommend Tranexamic Acid to your colleagues for managing menstrual disorders?

a) 1-3 (Not likely)

b) 4-6 (Neutral)

c) 7-8 (Likely)

d) 9-10 (Very likely)

Survey Findings

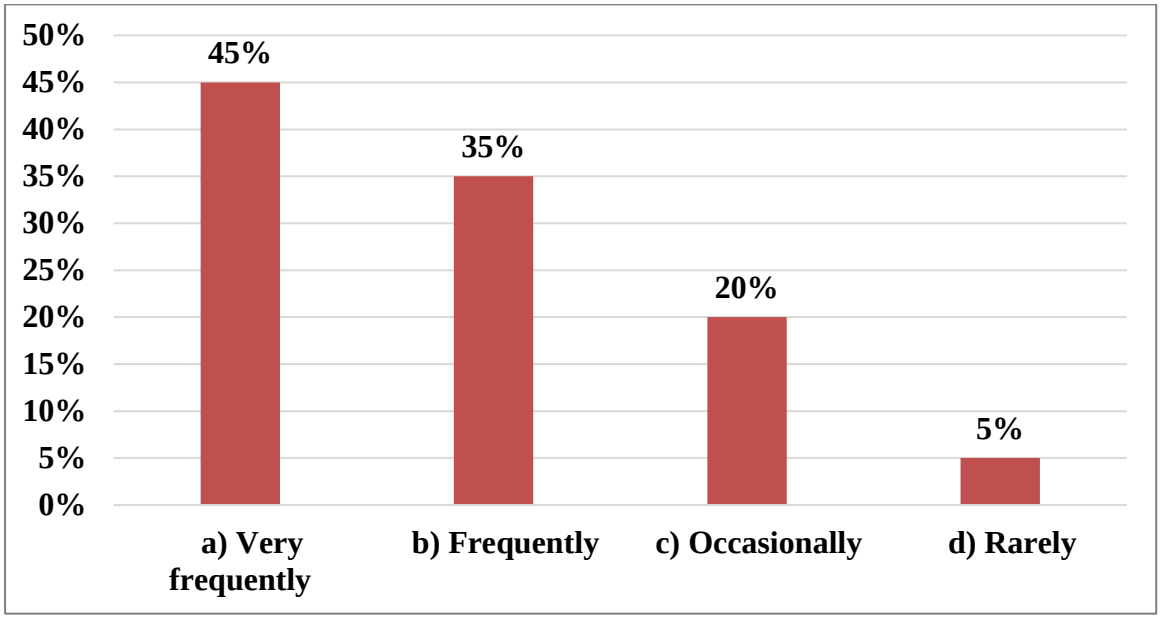
1. How often do you prescribe Tranexamic Acid for menstrual disorders in your gynecological practice?

a) Very frequently

b) Frequently

c) Occasionally

d) Rarely



45% of doctors very frequently prescribe Tranexamic Acid for menstrual disorders in their gynecological practice.

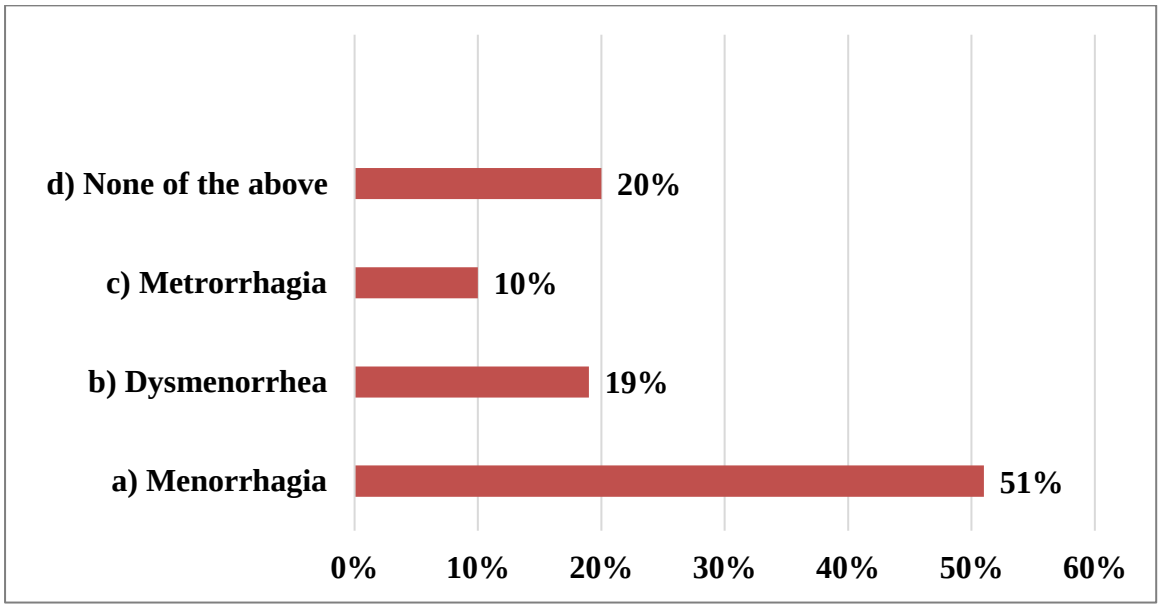
2. What menstrual disorders do you primarily prescribe Tranexamic Acid for?

a) Menorrhagia

b) Dysmenorrhea

c) Metrorrhagia

d) None of the above



51% of doctors primarily prescribe Tranexamic Acid for menstrual disorders of menorrhagia.

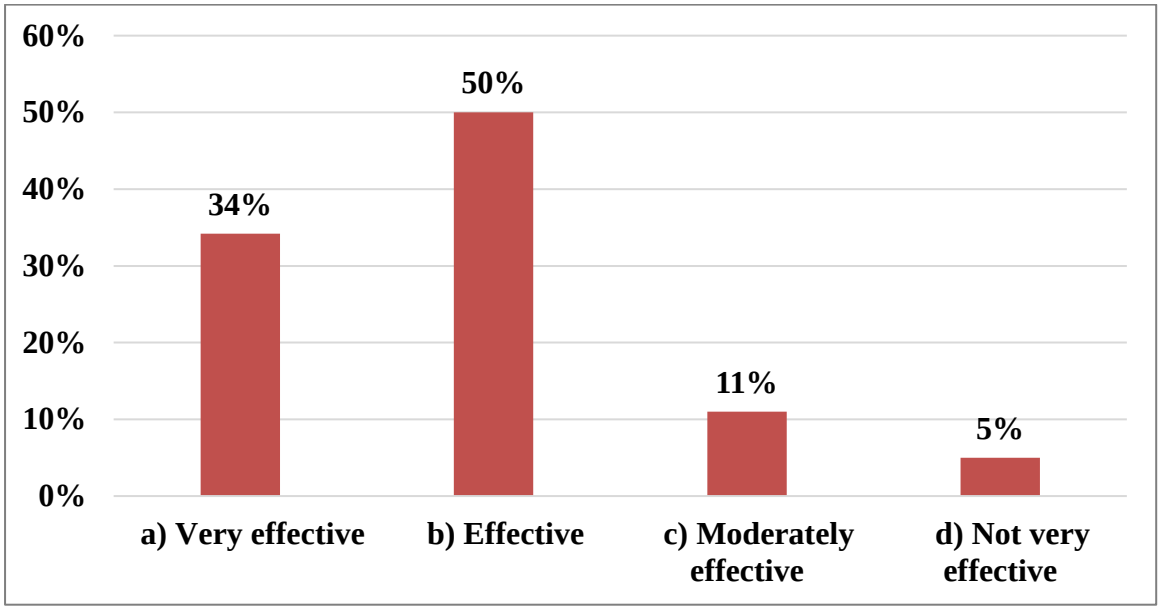
3. How effective do you find Tranexamic Acid in managing menstrual bleeding in your patients?

a) Very effective

b) Effective

c) Moderately effective

d) Not very effective



Half the doctors, 50%, find Tranexamic Acid effective in managing menstrual bleeding in their patients.

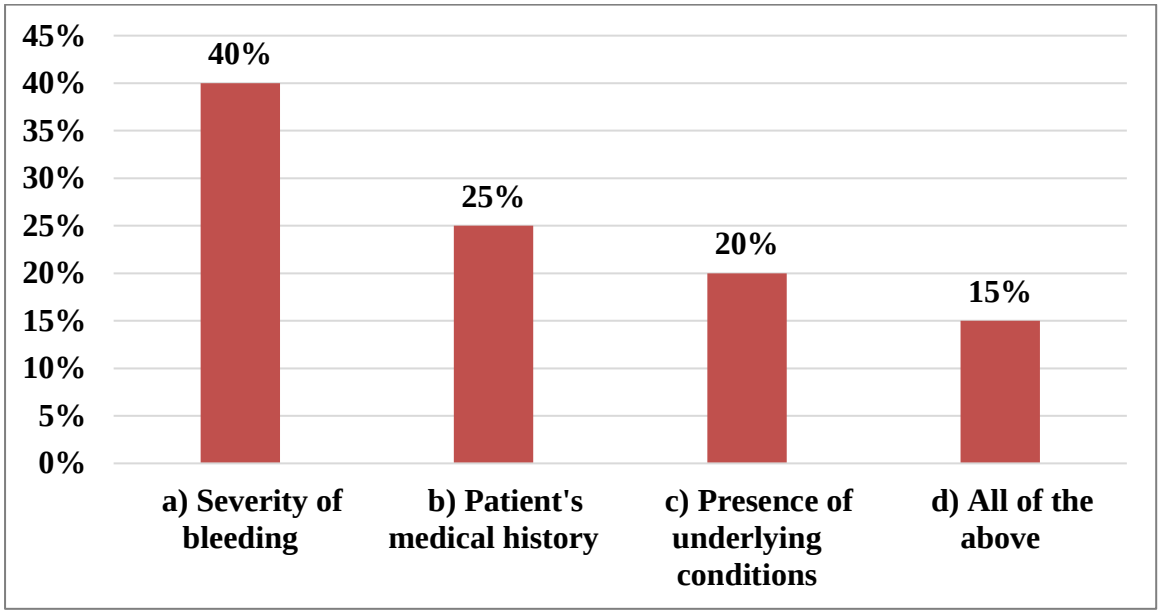
4. What are the main factors that influence your decision to prescribe Tranexamic Acid for menstrual disorders?

a) Severity of bleeding

b) Patient's medical history

c) Presence of underlying conditions

d) All of the above



According to 40% of doctors, the main factor that influence their decision to prescribe Tranexamic Acid for menstrual disorders is severity of bleeding.

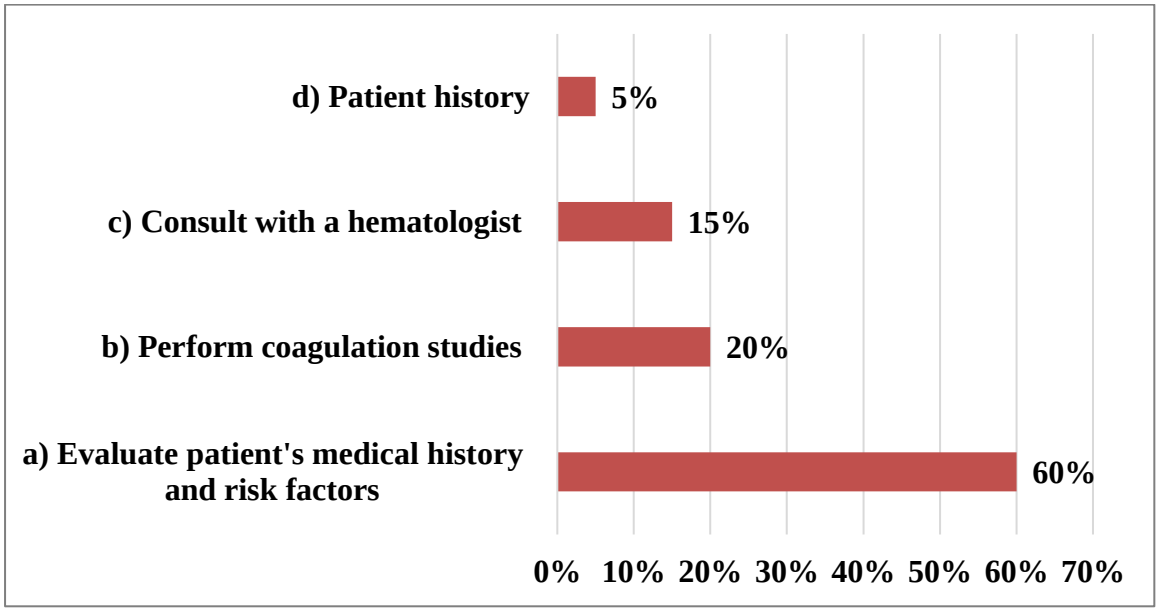
5. How do you assess the risk of thrombosis when considering Tranexamic Acid for a patient with menstrual disorders?

a) Evaluate patient's medical history and risk factors

b) Perform coagulation studies

c) Consult with a hematologist

d) Patient history



Majority of doctors (60%) assess the risk of thrombosis when considering Tranexamic Acid for a patient with menstrual disorder by evaluating patient's medical history and risk factors.

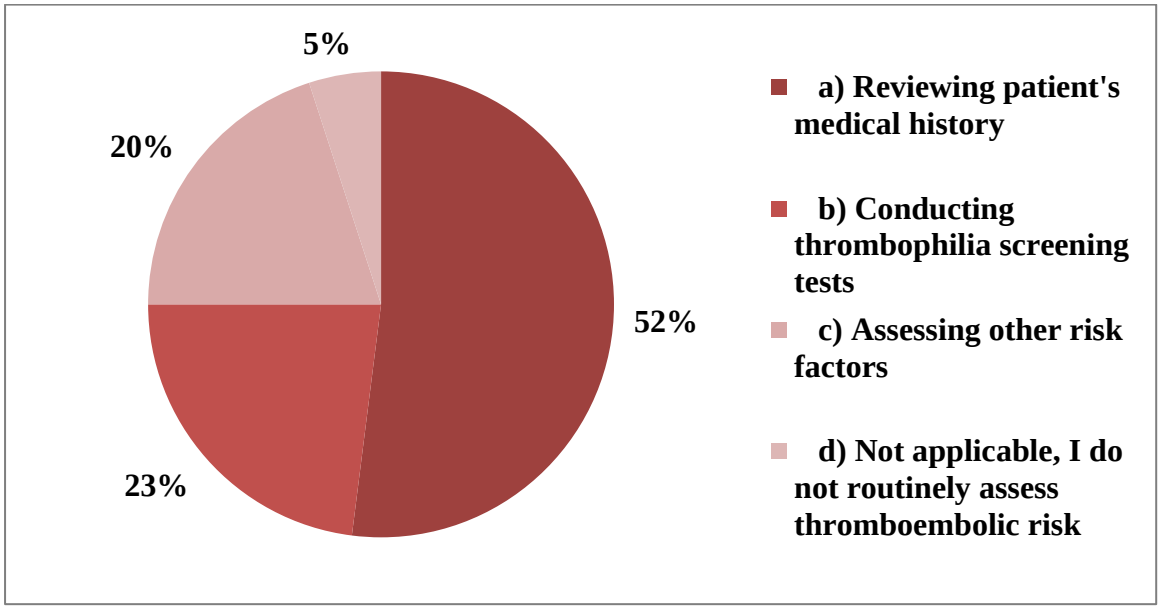
6. How do you assess the risk of thromboembolic events before initiating Tranexamic Acid?

a) Reviewing patient's medical history

b) Conducting thrombophilia screening tests

c) Assessing other risk factors

d) Not applicable, I do not routinely assess thromboembolic risk



52% of doctors assess the risk of thromboembolic events before initiating Tranexamic Acid by reviewing patient's medical history.

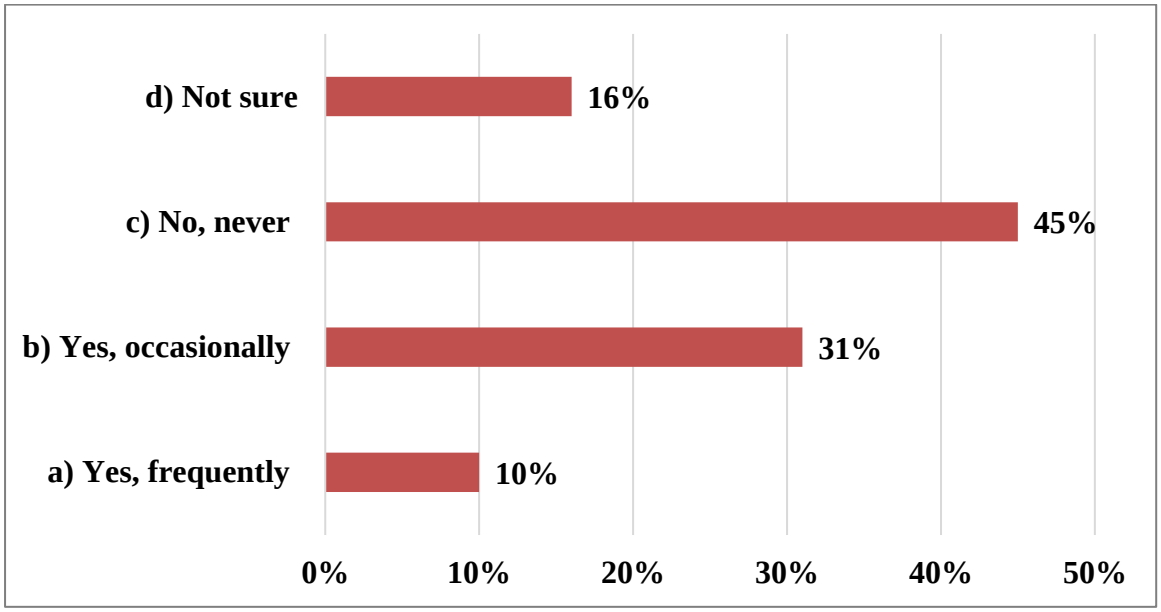
7. Have you encountered any adverse effects associated with Tranexamic Acid usage in your patients with menstrual disorders?

a) Yes, frequently

b) Yes, occasionally

c) No, never

d) Not sure



According to 45% of doctors have never encountered any adverse effects associated with Tranexamic Acid usage in their patients with menstrual disorders.

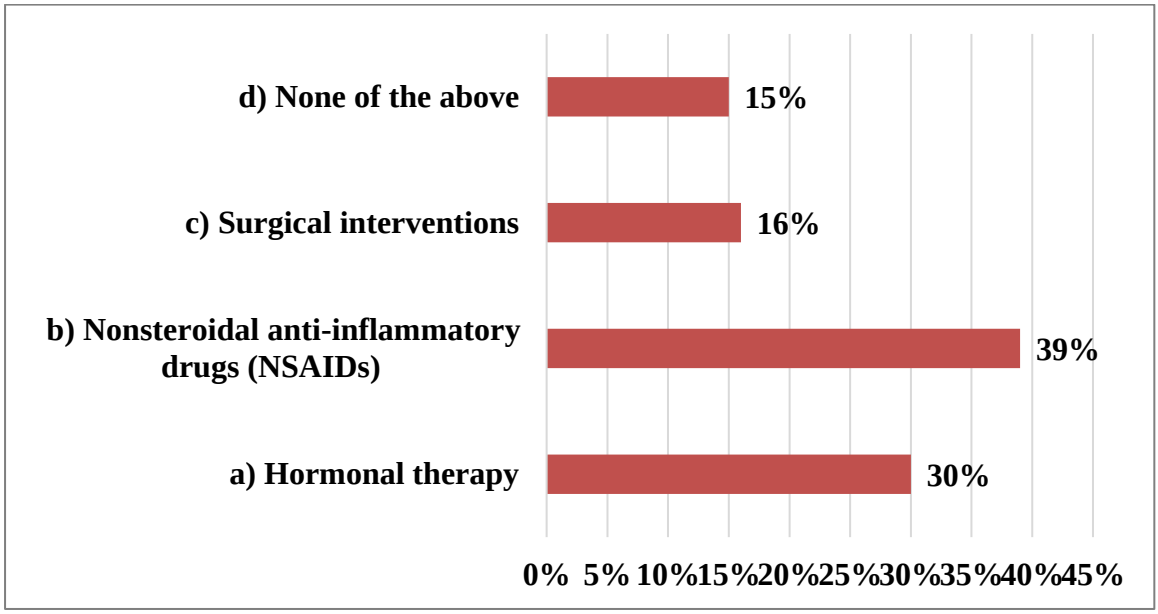
8. What alternative treatments do you consider before prescribing Tranexamic Acid for menstrual disorders?

a) Hormonal therapy

b) Nonsteroidal anti-inflammatory drugs (NSAIDs)

c) Surgical interventions

d) None of the above



39% of doctors consider the alternative treatment of Nonsteroidal anti-inflammatory drugs (NSAIDs) before prescribing Tranexamic Acid for menstrual disorders.

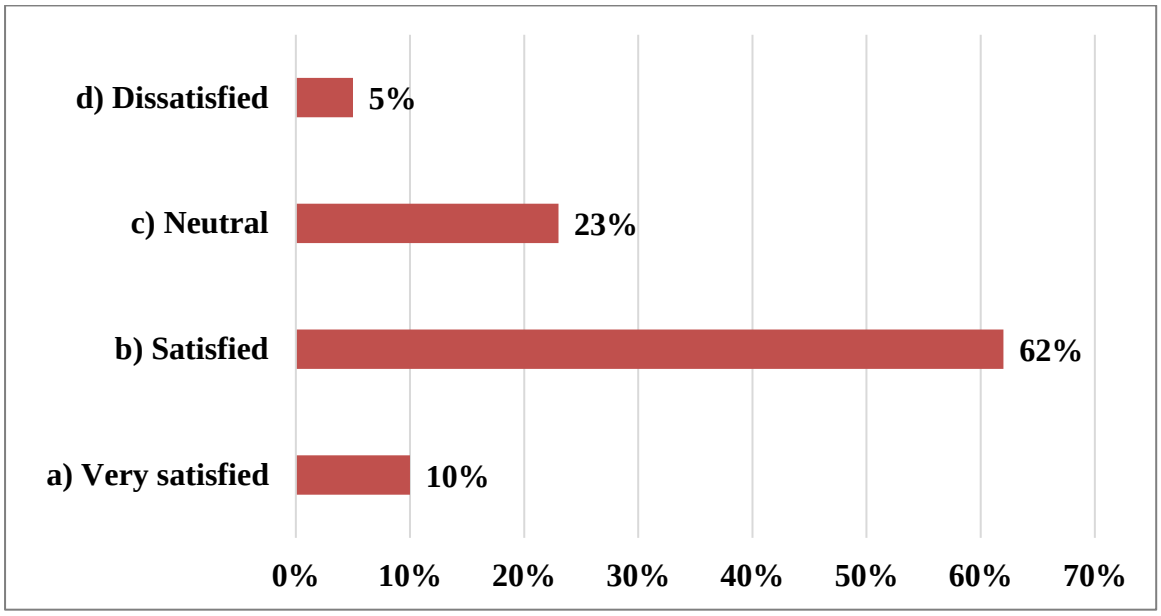
9. How satisfied are you with the overall outcomes of Tranexamic Acid treatment in managing menstrual disorders?

a) Very satisfied

b) Satisfied

c) Neutral

d) Dissatisfied



Majority of doctors (63%) are satisfied with the overall outcomes of Tranexamic Acid treatment in managing menstrual disorders.

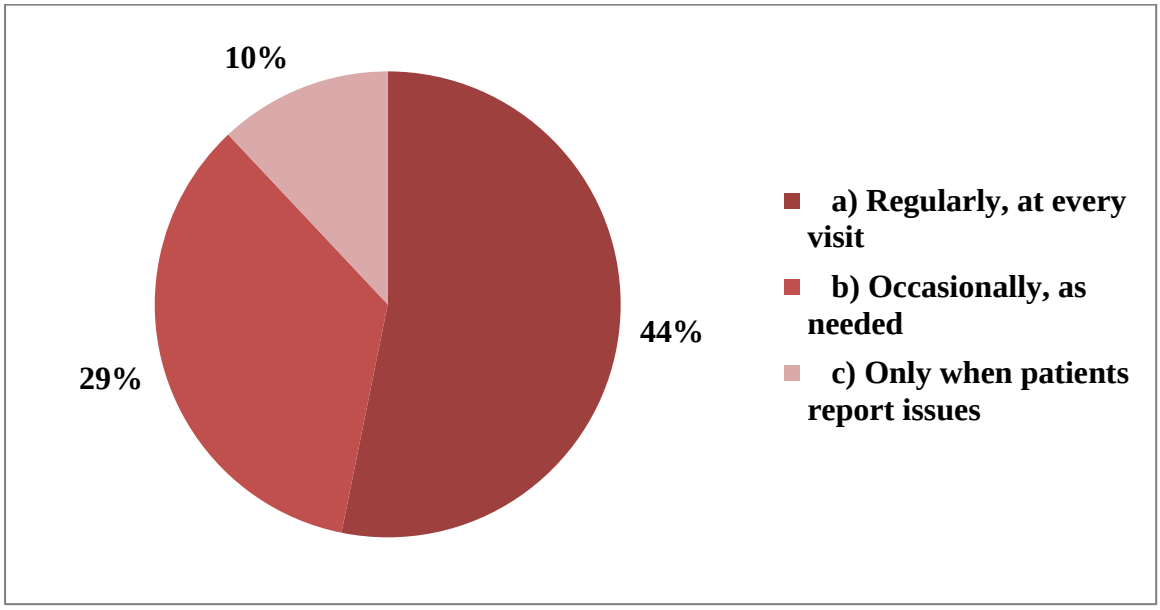
10. How frequently do you review patients' response to Tranexamic Acid treatment during follow-up visits?

a) Regularly, at every visit

b) Occasionally, as needed

c) Only when patients report issues

d) Not applicable, I do not routinely follow up on Tranexamic Acid treatment



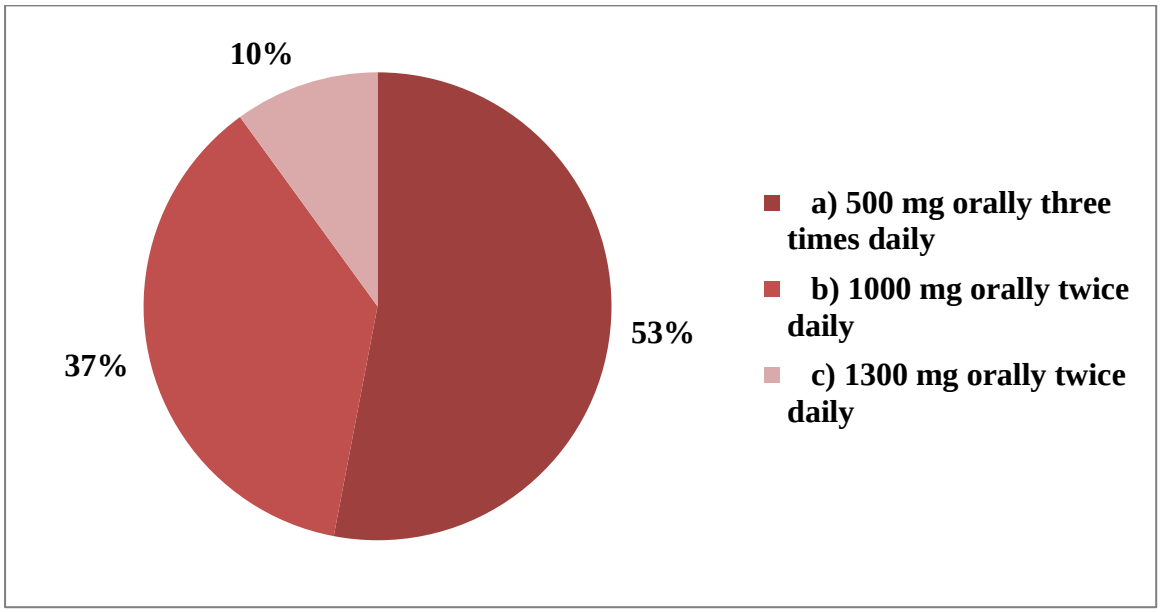
44% of doctors review patients' response to Tranexamic Acid treatment during follow-up visits regularly, at every visit.

11. What dosage of Tranexamic Acid do you typically initiate for the management of menstrual disorders?

a) 500 mg orally three times daily

b) 1000 mg orally twice daily

c) 1300 mg orally twice daily



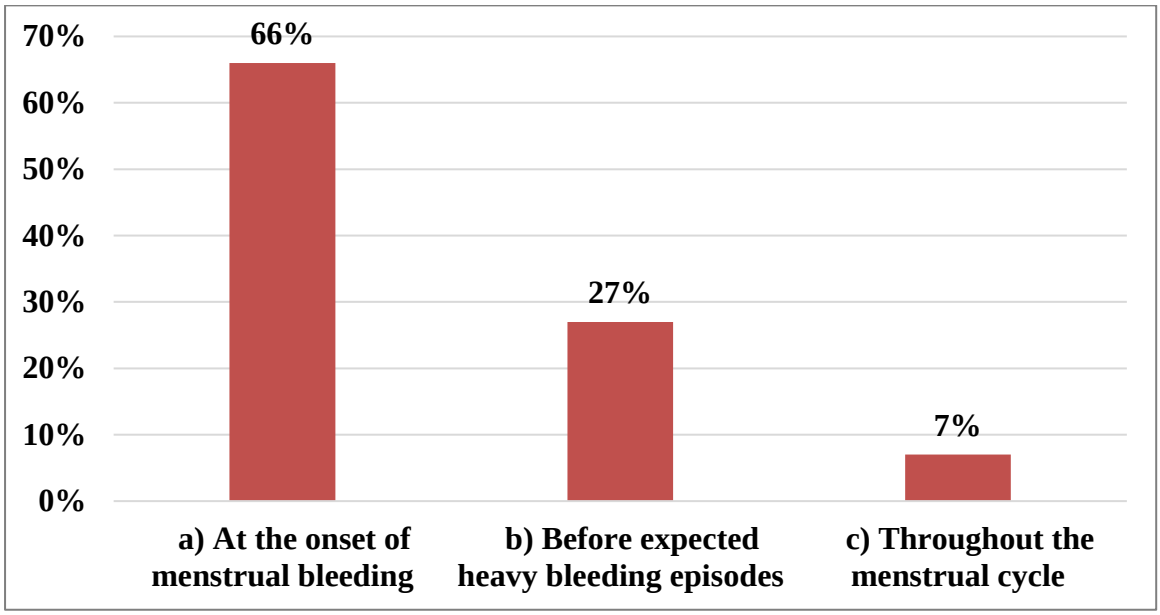
According to 53% of doctors, they typically initiate the dosage of 500 mg orally three times daily of Tranexamic Acid for the management of menstrual disorders.

12. How do you counsel patients regarding the timing of Tranexamic Acid administration for optimal efficacy?

a) At the onset of menstrual bleeding

b) Before expected heavy bleeding episodes

c) Throughout the menstrual cycle



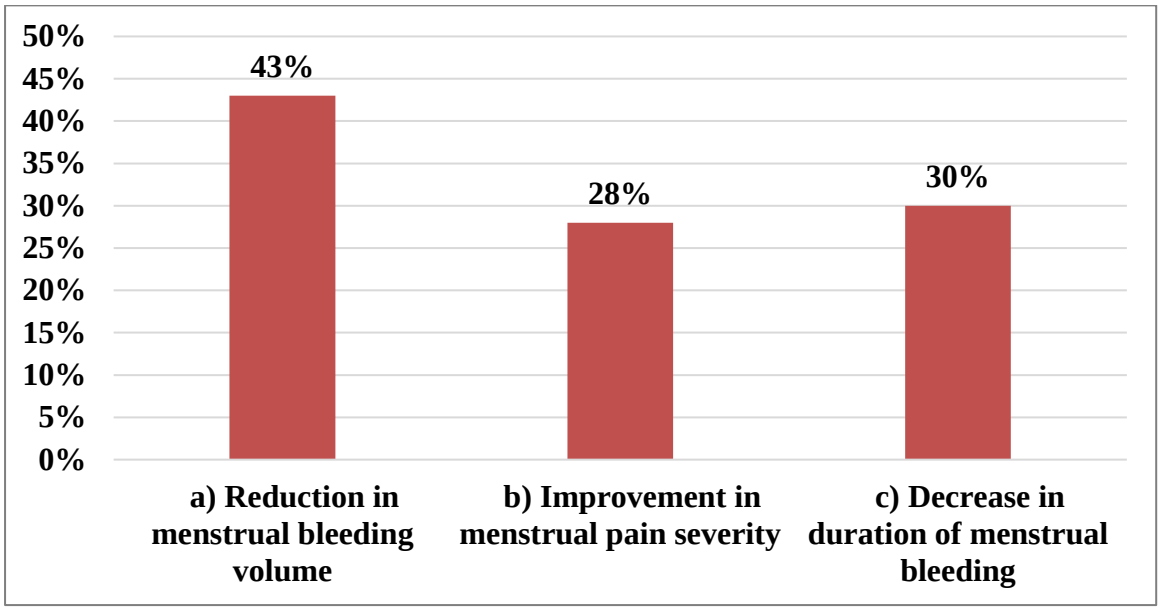
As per majority of doctors, 66%, they counsel patients regarding the timing of Tranexamic Acid administration for optimal efficacy at the onset of menstrual bleeding.

13. What patient-reported outcomes do you consider when assessing the effectiveness of Tranexamic Acid?

a) Reduction in menstrual bleeding volume

b) Improvement in menstrual pain severity

c) Decrease in duration of menstrual bleeding



When assessing the effectiveness of Tranexamic Acid, 43% of doctors consider the of patient-reported outcomes reduction in menstrual bleeding volume.

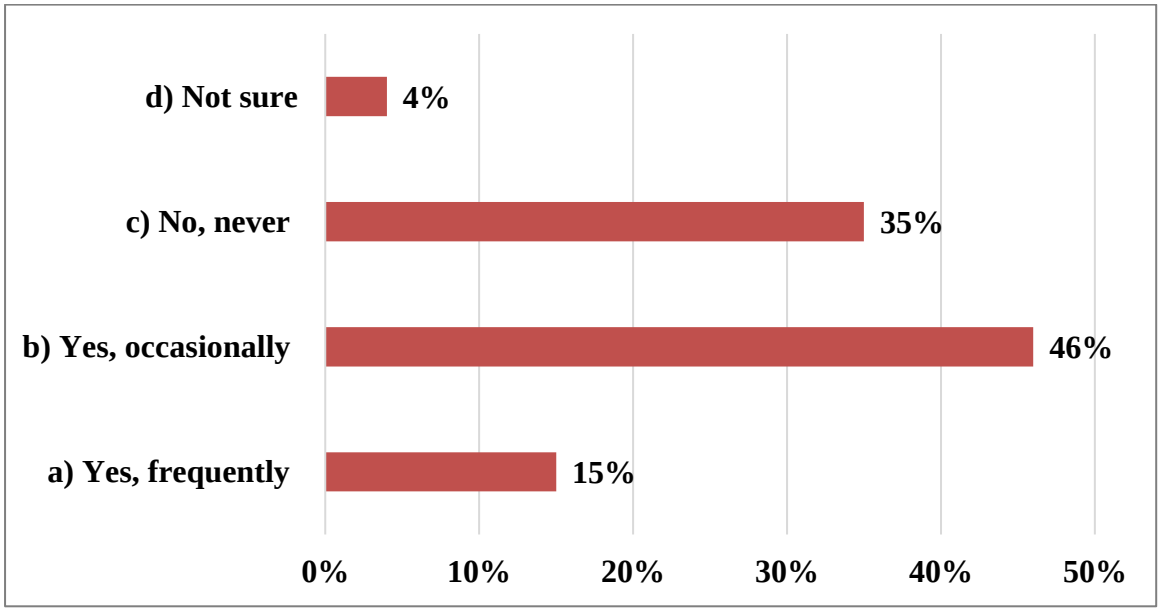
14. Have you encountered any adverse effects associated with Tranexamic Acid usage in your patients with menstrual disorders?

a) Yes, frequently

b) Yes, occasionally

c) No, never

d) Not sure



46% of doctors have occasionally encountered any adverse effects associated with Tranexamic Acid usage in their patients with menstrual disorders.

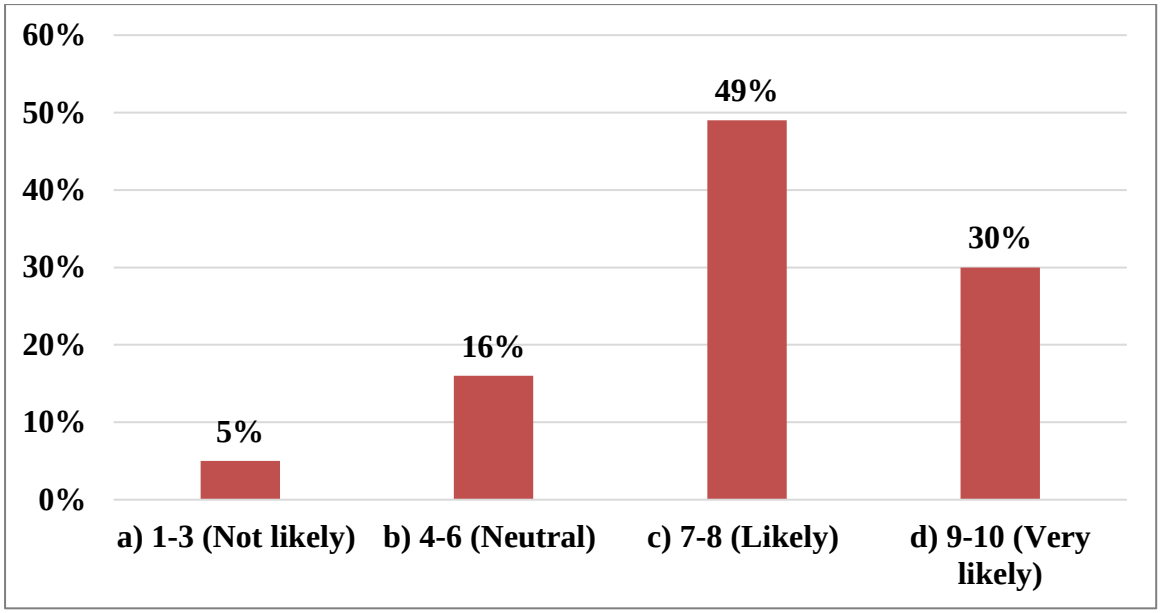
15. On a scale of 1 to 10, how likely are you to recommend Tranexamic Acid to your colleagues for managing menstrual disorders?

a) 1-3 (Not likely)

b) 4-6 (Neutral)

c) 7-8 (Likely)

d) 9-10 (Very likely)



49% of doctors are likely to recommend Tranexamic Acid to their colleagues for managing menstrual disorders 7-8 (Likely) on a scale of 1-10.

Summary

- 45% of doctors very frequently prescribe Tranexamic Acid for menstrual disorders in their gynecological practice.
- 51% of doctors primarily prescribe Tranexamic Acid for menstrual disorders of menorrhagia.
- Half the doctors, 50%, find Tranexamic Acid effective in managing menstrual bleeding in their patients.
- According to 40% of doctors, the main factor that influence their decision to prescribe Tranexamic Acid for menstrual disorders is severity of bleeding.
- Majority of doctors (60%) assess the risk of thrombosis when considering Tranexamic Acid for a patient with menstrual disorder by evaluating patient's medical history and risk factors.
- 52% of doctors assess the risk of thromboembolic events before initiating Tranexamic Acid by reviewing patient's medical history.
- According to 45% of doctors have never encountered any adverse effects associated with Tranexamic Acid usage in their patients with menstrual disorders.
- 39% of doctors consider the alternative treatment of Nonsteroidal anti-inflammatory drugs (NSAIDs) before prescribing Tranexamic Acid for menstrual disorders.
- Majority of doctors (63%) are satisfied with the overall outcomes of Tranexamic Acid treatment in managing menstrual disorders.
- 44% of doctors review patients' response to Tranexamic Acid treatment during follow-up visits regularly, at every visit.
- According to 53% of doctors, they typically initiate the dosage of 500 mg orally three times daily of Tranexamic Acid for the management of menstrual disorders.
- As per majority of doctors, 66%, they counsel patients regarding the timing of Tranexamic Acid administration for optimal efficacy at the onset of menstrual bleeding.
- When assessing the effectiveness of Tranexamic Acid, 43% of doctors consider the of patient-reported outcomes reduction in menstrual bleeding volume.

- 46% of doctors have occasionally encountered any adverse effects associated with Tranexamic Acid usage in their patients with menstrual disorders.
- 49% of doctors are likely to recommend Tranexamic Acid to their colleagues for managing menstrual disorders 7-8 (Likely) on a scale of 1-10.

Consultant Opinion

Market Opportunities:

The high frequency of prescription (45%) indicates a significant market opportunity for pharmaceutical companies manufacturing Tranexamic Acid formulations. Companies could focus on developing patient-friendly formulations or delivery methods to enhance the ease of use and compliance with Tranexamic Acid therapy for menstrual disorders.

Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the appropriate use of Tranexamic Acid for managing menstrual disorders. Continuing medical education programs can help ensure that healthcare professionals stay updated on the latest evidence-based practices and guidelines for Tranexamic Acid therapy.

Adverse Effect Management:

While many doctors (45%) have not encountered adverse effects associated with Tranexamic Acid usage, healthcare professionals should remain vigilant in monitoring patients for potential adverse reactions. Regular follow-up visits and assessments can help detect and manage adverse effects promptly, ensuring the safety and well-being of patients.

Withdrawal Management:

Clear guidelines should be established for the duration and dosage of Tranexamic Acid therapy for menstrual disorders to prevent overuse and minimize the risk of adverse effects. Healthcare professionals should assess the need for continuation or discontinuation of Tranexamic Acid treatment based on patient response and ongoing monitoring of menstrual bleeding.

Market Positioning:

Pharmaceutical companies can capitalize on the effectiveness of Tranexamic Acid in managing menstrual bleeding by emphasizing this benefit in their marketing strategies. Highlighting the safety profile and patient satisfaction with Tranexamic Acid therapy can help position it as a preferred treatment option for menstrual disorders, particularly menorrhagia.

Personalized Treatment Decisions:

Healthcare professionals should consider individual patient factors, such as the severity of bleeding, medical history, and risk of thrombosis, when deciding whether to prescribe Tranexamic Acid for menstrual disorders. Personalized treatment decisions can optimize outcomes and minimize the risk of adverse effects.

Improving Patient Outcomes:

Patient education is essential to ensure optimal outcomes with Tranexamic Acid therapy for menstrual disorders. Patients should be informed about the potential benefits and risks of treatment, as well as the importance of adherence to prescribed regimens. Additionally, healthcare professionals should regularly assess patient response and adjust treatment plans as needed to achieve optimal reduction in menstrual bleeding volume and overall satisfaction.

NOTES

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

CTS-77, Shop No.11, Swapna Siddhi CHS LTD, Akurli Road Near Malad Sahakari Bank
Kandivali (E), Mumbai - 400101. M: 9322615653 I W: www.wmefi.co.in