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Review Article

Management of heavy menstrual bleeding in women on long term anticoagulants

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ABSTRACT

Women taking anticoagulants for therapeutic or prophylactic indications has been on the raise since the past few years. Heavy menstrual bleeding (HMB) due to anticoagulant use is also on the raise. Hence, we need to explore various treatment strategies which can reduce or stop the HMB. Various methods that have been tried like reducing the dose of anticoagulants, changing over to a different anticoagulant with lower incidence of HMB, addition of tranexamic acid or progesterone, use of combined oestrogens and progesterone contraceptives etc. In cases of intractable bleeding not controlled with medical measures surgical options like intrauterine balloon tamponade, endometrial ablation or uterine artery embolization may be tried. The last resort is hysterectomy. This review discusses about the various options available that can used in treating women with HMB who are on anticoagulation.

Keywords: HMB, Anticoagulation, Thromboembolism

INTRODUCTION

Heavy menstrual bleeding (HMB) is a common problem in women especially during the perimenopausal period. It is seen in about 33% of women in the general population.[1] Many women need to be started on anticoagulation due to certain medical conditions like placement of prosthetic valve, stroke, and as a treatment for deep vein thrombosis (DVT)/pulmonary embolism (PE). These women experience an increased risk for HMB especially when they already suffer from conditions like fibroid, adenomyosis, polyps and endometriosis. Risk for HMB varies depending on type of anticoagulant used. In general, anticoagulation is associated with HMB in 20-70% of patients.[1] Hepatic/ renal impairment/concomitant use of drugs like aspirin/clopidogrel also increases anticoagulant associated bleeding.

ANTICOAGULANTS

Oral anticoagulants are broadly classified into vitamin K antagonists and direct oral anticoagulants (DOAC). Direct anticoagulants can be direct thrombin inhibitors like dabigatran or direct factor XA inhibitors like apixaban, rivaroxaban, edoxaban and betrixaban.

Vitamin K antagonist (VKA) warfarin is sparingly used in recent years due to its various disadvantages like requirements for frequent monitoring, unpredictable bioavailability and drug interactions. The treatment has to be always in therapeutic doses to achieve the target INR. Also, it takes time and requires frequent monitoring before achieving the target INR.[2] Direct oral anticoagulants are the preferred choice instead. They act rapidly following administration and on stopping the drug the anticoagulant action wears off rapidly. But in a young woman in the reproductive age groups it has an increased risk for heavy menstrual bleeding. Also, it may have teratogenic effects in the fetus if the woman conceives during treatment.[2]

Various theories have been put forth for the increase in menstrual blood loss in women on anticoagulation. It can result from direct action of these drugs on the coagulation factors or it can also alter the proteins in the myometrium

and endometrium responsible for normal menstruation.[3] Increased fibrinolytic action is another reason for HMB.[4]

Caution should be exercised when starting an anticoagulant for women of the reproductive age group especially if they are already having HMB or have risk factors for HMB. In such patients dabigatran seems to be a better choice as compared to other DOACs as it has the least risk for bleeding tendencies.[5,6]

MANAGEMENT OF HMB IN WOMEN ON ANTICOAGULATION

The following treatments can be considered in women with heavy menstrual bleeding who are on anticoagulation-Reducing the dose of the anticoagulant, switch to dabigatran, switch to low molecular weight heparin (LMWH), progesterone, combined oral contraceptive pills, levonorgestrel containing intrauterine device, depo medroxyprogesterone acetate (DMPA), hormonal rings, hormonal implants, patches, tranexamic acid, intrauterine balloon tamponade, endometrial ablation, uterine artery embolization, endometrial curettage and hysterectomy

Reducing the dose of the anticoagulant

Dose reduction seems to be a logical intervention in women who bleed with anticoagulation. It can be done in some patients but not all. Reducing the dose can be considered in patients who no longer require therapeutic anticoagulation and they may be changed to regimens containing prophylactic doses. However, it is advised not to reduce the dose of anticoagulants in patients who are on treatment for venous thromboembolism in the first 3 months as they are at very high risk for thromboembolic complications during this period.[7] Dose adjustments may not be feasible in women on warfarin as it takes a long time for the anticoagulation effect to start and the anticoagulant effect lasts for a few days after stopping the drug. Hence, dose reduction or stopping warfarin for a few days may not have an immediate effect in controlling the bleeding. But with DOACs the anticoagulant effect is decreased immediately on reducing dose or stopping the drug and there is rapid return to therapeutic levels when restarted. As per Einstein choice study, decreasing the dose of rivaroxaban from 20 mg to 10 mg decreased the incidence of heavy menstrual bleeding.[8] Other methods should be considered for treating heavy menstrual bleeding when dose reduction is not an option.

Change to dabigatran

Changing over to dabigatran can be considered in women with HMB who are on other anticoagulants like rivaroxaban or warfarin as dabigatran has the least risk for heavy menstrual bleeding. It may also be the preferred anticoagulant in menstruating women as a first line drug. Use of VKA is associated with increased amount and duration of menstrual flow, passage of clots and intermenstrual bleeding.[1] The incidence of HMB with VKA is up to 66% as compared to DOAC up to 50%.[9]

Rivaroxaban was shown to have the highest risk for heavy menstrual bleeding even more than warfarin. Apixaban has bleeding profiles similar to warfarin[9]. The bleeding episodes according to the German DOAC registry was 32% in rivaroxaban, 28% with apixaban and 25% with edoxaban).[10]

Changing to LMWH

Use of low molecular weight heparin does not cause HMB.[2] But it is usually not used in women who need prolonged anticoagulation. Most often it is used in women during pregnancy, labor and postpartum or when they require anticoagulation for a short span post-surgery. This is because it is costly and has to be given only by subcutaneous injection which is not acceptable to most women in the long term. However, if there is intractable bleeding in women on established anticoagulation, temporary change over to LMWH can be done to control acute bleeding episodes.

Progesterone

Progesterone's like norethisterone and medroxyprogesterone acetate are given in high doses for treatment of heavy menstrual bleeding. Use of high doses of this progesterone are associated with an increased thrombotic episode in at-risk women. The risk for VTE in these women is five times more compared to women not on these drugs. Norethisterone is partly metabolized after oral administration to ethiny lestradiol or norethisterone or norethisterone acetate in humans. This conversion results in an equivalent dose of about 4 to 6 micrograms ethiny lestradiol per 1 mg orally administered norethisterone or norethisterone acetate. The thrombogenic effect of these progesterone is partly due to this estrogenic conversion.

In normal women who are not on anticoagulation, short cyclical tapering regimen of these progesterone (5 mg twice or thrice daily for 7-11 days) was less effective in controlling heavy menstrual bleeding as compared to extended high dose progestin regimen (5 mg twice or thrice daily for 21 days.[11] Short cyclical tapering regimen of these progesterones was also less effective than tranexamic acid, danazol or LNG IUS.[9] Hence for control of bleeding in women on anticoagulation the high dose extended regimen of progesterone should be used. But the risk for VTE is five times more in women using therapeutic doses of oral progesterone (norethisterone and medroxyprogesterone acetate) as compared to nonusers.[9,12] Hence caution should be exercised in women who are started on high dose progestogen for a long duration of time especially in women who are at high risk for thrombosis. However, for women who are already on the therapeutic anticoagulation it can be used safely. But it has to be stopped before the anticoagulation is discontinued.

Progesterone only contraceptives do not increase the risk for VTE and are effective in some patients with heavy menstrual bleeding. This is because they contain lower dose of progestogens. But compliance is poor due to menstrual irregularities during therapy and the need for strict adherence to the time of taking the drug.

Combined oral contraceptive pills

Estrogen increases the production of procoagulants by the liver like factor VII, factor VIII, factor X, VVF and fibrinogen. The effect is highest when estrogen is given orally due to the first pass metabolism. The thrombotic risk can be reduced by giving it transdermal (as implants/patches) or vaginally bypassing the first pass metabolism.[13] Risk of VTE is directly proportional to the dose of estrogen in the COCS. COCs containing 50 mcg or more of ethinylestradiol have a relative risk of 5.2 (3.4-7.9) for thrombosis as compared to COCs with 35 mcg or less where the relative risk is 2.4 (1.8-3.2).[14]

Progesterone in the combined oral contraceptives also can increase the risk of thrombosis. Progesterone in low doses when used alone is not thrombogenic but if combined with estrogens it can modulate the procoagulant effects of estrogen. Desogestrel a third-generation progestin is associated with twofold increased risk for venous thromboembolism when compared with levonorgestrel a second-generation progestin.[15] The risk for thrombosis was six to seven-fold higher in women who used desogestrel containing contraceptives as compared to nonusers. Combined contraceptive pills containing low dose estrogen (<35 mcg) along with a second-generation progestogen like levonorgestrel, norethisterone or norgestimate is preferred over third and fourth generation progestogens.[14,16,17]

Estretol (E4) a weak natural estrogen in combination with second generation progestogen as a COC is undergoing phase 4 trials. It may have lesser thrombotic effects as compared to other estrogens.[13]

Use of combined oral contraceptive pills in women with heavy menstrual bleeding on anticoagulation is a subject of debate in many society groups. This is because the Estrogen in the combined oral contraceptive pills increases the risk for thrombosis.

However, 2 landmark studies done EINSTEIN DVT and EINSTEIN PE study showed that use of COCs in women on anticoagulation for VTE had similar recurrent thromboembolism rates as in women not using COCs (adjusted hazard ratio, 0.56; 95% CI,0.23-1.39).[18] This is because the effect of therapeutic anticoagulation is sufficient to overcome the prothrombotic effect associated with COCs. This has been emphasized by the international society on thrombosis and hemostasis.[19]

Another important consideration is regarding stoppage of hormonal contraception as soon as thrombosis is diagnosed. Even though combined oral contraceptives are known to increase thrombotic episodes, abruptly stopping it would lead to further increase in bleeding with no increase in the thrombosis risk. Hence ISTH (International society on thrombosis and haemostasis) guidelines suggest that COC should not be stopped abruptly in a patient on effective anticoagulation.[19] The rationale behind this suggestion is that any increase in thrombotic tendency will be suppressed by therapeutic intensity anticoagulation. Also holding/stopping anticoagulation early is not proven to reduce menstrual blood loss.

But WHO still categorizes combined oral contraceptives under category 4 even in patients who are on established anticoagulation (Category 4-A condition which represents unacceptable health risk if contraceptive method is used.[20]

Thrombotic episodes during estrogen therapy occur mostly during the first 3 months of its initiation. But the thrombotic effect can persist up to 3 months following discontinuation. So, for women on anticoagulation who are also taking COC it is advisable to stop the COCs at least 3months prior to discontinuing the anticoagulation.

The use of combined oral contraceptives has an additional benefit of reducing the incidence of hemorrhagic cysts in anticoagulated women by inhibiting ovulation.[5]

Levonorgestrel containing intrauterine device

It is preferred treatment in women who also want contraception in addition to treatment for HMB. It results in 50% reduction in blood loss. Some women also become amenorrheic which very beneficial. It is also very effective when there is coexisting pelvic pathology like fibroid or adenomyosis. Along with reduction in blood loss in these patients it also reduces dysmenorrhea. It is a very safe and effective long-term option for women who are on anticoagulation.

Depo medroxyprogesterone acetate

Depo medroxyprogesterone acetate is a common drug used in reproductive age women for postpartum contraception. It is also used in some women with heavy menstrual bleeding. It increases risk for VTE by 2-3 times by unknown mechanisms.[21,22] So it should not be used in women who are at risk for thrombosis. If need arise, its use should be restricted to women on established therapeutic anticoagulation and it should be stopped before stopping therapeutic anticoagulation. However, there is a small risk for hematoma formation in therapeutically anticoagulated women as it is given as a deep intramuscular injection.

Hormonal rings, hormonal implants and transdermal patches

Hormonal rings, implants and patches containing etonogestrel are not associated with VTE, although they haven't been studied specifically women with HMB.[22-24]

Tranexamic acid

As of now its use has not been studied in women on anticoagulation for VTE. Ongoing studies may guide its use in the future.[25] It may be considered for treatment of anticoagulant associated abnormal uterine bleeding with caution.[26] This recommendation is based on various studies that reported that the risk for thrombosis is not increased with tranexamic acid use in women with increased risk for thrombosis. But it should not be used in a patient who is in the acute phase of VTE as it might prevent the fibrinolysis of the existing thrombus.[27]

Intrauterine balloon tamponade

For the management of acute severe bleeding intrauterine balloon tamponade with a Foley catheter can be tried in isolation or in combination with other methods. However, it is a temporary measure and other treatments have to be simultaneously started to have long term hemostatic effect.

Endometrial ablation

Endometrial ablation can be a method of choice in women who have completed their family but wish to conserve the uterus. There was 80% reduction in the menstrual blood loss in women with heavy menstrual bleeding on anticoagulation.[28,29]

Uterine artery embolization

When women wish to conserve the uterus and other conservative measures have been tried, uterine artery embolization may be done to reduce menstrual blood loss.

Endometrial curettage

In extreme cases where there is refractory menstrual bleeding endometrial curettage can be considered to arrest the bleeding.[30]

Hysterectomy

It is done in selected cases when there is intractable bleeding which doesn't respond to any treatment that endangers life of women. It can also be considered in peri-menopausal women who have repeated episodes of heavy menstrual bleeding who do not wish to conserve uterus.

NSAIDS USE IN WOMEN ON ANTICOAGULATION

NSAIDs have been used in women with heavy menstrual bleeding to decrease the blood loss and to treat associated dysmenorrhea. It reduces blood loss by 30-50% in these women. However, its use in an anticoagulated patient can lead to an increased number of bleeding episodes and gastritis. Hence it should not be used in these patients. If the patient is already on NSAIDS it should be discontinued on starting anticoagulants. There is also an increased risk for major bleeding like gastrointestinal bleed, stroke and embolism when NSAIDs are used in this group of women.[1]

CONCLUSION

Heavy menstrual bleeding is a common side effect seen with anticoagulant administration in women. Women who are on established therapeutic anticoagulation any of the hormonal treatment methods can be considered. However, if the patient is on prophylactic dose of anticoagulation or the anticoagulant therapy is a temporary measure, estrogen-containing contraceptives and high depose progestogens are contraindicated. Other methods like changing over to dabigatran or use of LNG IUD can be tried. Hysterectomy may be offered if there is associated uterine pathology or the patient is nor responding to conservative measures.

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