Effectiveness and mechanism of action of desmopressin in the treatment of copper intrauterine device-related menorrhagia: a pilot study

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BACKGROUND: Desmopressin, a synthetic analogue of the natural hormone vasopressin, stimulates endogenous haemostasis and exerts a powerful myometrial and vasoconstrictor action in a variety of pharmacological preparations. Both mechanisms of action may have therapeutic value for the treatment of intrauterine device (IUD)-related menorrhagia, which is believed to be caused not only by altered local haemostasis but also—according to a new hypothesis—by decreased vascular uterine resistance. The aim of this prospective study was to evaluate the effect of vasopressin drug on menstrual blood loss and on changes, if any, in uterine flow impedance. Mefenamic acid, which is commonly used to treat IUD-related menorrhagia, was administered as a comparison. METHODS: Twenty-four women with IUD-induced menorrhagia were recruited and randomly allocated to treatment with either desmopressin or mefenamic acid. Menstrual blood loss (measured by pictorial blood loss assessment chart) and uterine artery resistance (measured with transvaginal colour Doppler) performed in two pretreatment periods were compared with 3-month treatment periods. RESULTS: Menstrual blood loss was significantly reduced in both treatment groups. In the desmopressin group, the effect was clinically useful in all subjects, but in the mefenamic group menstrual blood loss was consistently menorrhagic in two patients. No significant differences were observed in the uterine artery pulsatility index before and during treatment. CONCLUSIONS: Desmopressin may be a useful therapeutic tool for many women with IUD-related menorrhagia. Its mechanism of action lies in an ability to enhance local haemostasis, without affecting uterine blood flow.

Key words: desmopressin/IUD-related menorrhagia/uterine artery resistance

Introduction

Abnormal uterine bleeding, including menorrhagia and intermenstrual bleeding, is one of the most frequent side effects of intrauterine device (IUD) use, and the main cause for discontinuation of this type of contraceptive (Bergsjo, 1992). Several factors have been suggested to explain IUD-related bleeding, including increased vascularity of the endometrium and capillary permeability (Hillier and Kasonde, 1976), reduced platelet aggregation (Moncada et al., 1976) and enhanced fibrinolytic activity of uterine fluid (Larsson et al., 1974). A direct correlation between the uterine artery pulsatility index (PI) and amount of menstrual blood loss has suggested that vascular factors might be involved in the pathogenesis of IUD-related menorrhagia (Momtaz et al., 1994). Indeed, one hypothesis is that menorrhagic women may have decreased uterine artery resistance due to a lack of balance between the vasoconstrictor and vasodilator effects of prostaglandins (Smith et al., 1981). The above-mentioned derangement of the haemostatic process, as well as the altered uterine haemodynamics, suggest a novel approach to the treatment of IUD related menorrhagia by means of vasopressin.

Besides its well-known antidiuretic properties, vasopressin is known for its ability to enhance the haemostatic process by mediating the release of von Willebrand factor (vWF) from endogenous storage sites, thereby increasing plasma levels of Factor VIII and platelet adhesiveness, as well as reducing bleeding time (Mannucci, 1998). These properties have made this drug effective also for the treatment of bleeding disorders in women (Lethagen, 1999; Edlund et al., 2002). A further action of vasopressin, which is similar to that of its counterpart oxytocin, is the powerful uterine muscle-contracting and vasoconstricting actions which occur as a result of direct excitatory effects on the specific receptor sites that cause vascular spasms (Townsend, 1991; Frederick et al., 1994). This
8-D-arginine; this compound is known as desmopressin acetate.

Materials and methods

Patient population

Between December 1999 and March 2002, women attending the Family Planning Clinic for IUD-associated menorrhagia were evaluated for inclusion in the study. In order to quantify menstrual blood loss, women were asked to complete a pictorial blood loss assessment chart (PBAC) for two pretreatment periods, as devised previously (Higham et al., 1990). This method does not yield an exact flow volume in millilitres; a score is calculated taking into account the degree to which each item of sanitary protection is soiled with blood, as well as the total number of pads or tampons used. A monthly score ≥100 on this chart, which is equivalent to a uterine blood loss ≥80 ml as measured by the alkaline haematin method, is defined as menorrhagia. The method has been validated and refined (Janssen et al., 1995), but its use was recently challenged (Reid et al., 2000). The values of menstrual blood loss thus obtained, estimated before treatment was started, were used as baseline control values.

Twenty-four women with a menstrual blood loss objectively judged as menorrhagic were invited to participate in the study. Those patients with menorrhagia caused by pelvic pathologies evaluated by gynaecological examination and transvaginal ultrasonography were excluded, as were patients with a family or personal history of bleeding. None of the patients had previously taken mefenamic acid or any other drug to treat this pathology.

The mean age of the women was 28.9 (median 31; range 20–40) years. All women were parous (mean parity 2.3; range 2–4) and all were using an IUD (No-Gravid; Irmet Verona-Italia). The device had a copper surface area of 384 mm2 and released 100 µg Cu over a 24-h period.

Patients provided their fully informed consent, and the study was approved by the hospital ethics committee.

Treatments and investigations

The subjects were allocated to either the desmopressin or mefenamic acid group according to a schedule provided by an envelope system developed using computer analysis.

Each patient in the desmopressin group received a single daily dose of high-concentration intranasal desmopressin (HCIN-DDAVP; Minirin; Ferring s.p.a, Milan, Italy) administered as a morning 300 µg dose (one intranasal spray in each nostril) for the first 5 days of menstruation, irrespective of the duration of the menstrual period.

Patients in the mefenamic acid group were instructed to take one 500 mg tablet every 8 h for 5 days from the onset of menstrual bleeding, irrespective of the duration of the menstrual period.

In order to assess the effect of treatments on menstrual blood loss measured by the PBAC score, patients were seen monthly for 3 months during the treatment period, and asked to complete a new menstrual chart every month before each follow-up, when a gynaecological examination and evaluation of their PABC score and of any adverse reaction was carried out.

In order to evaluate possible haemodynamic uterine changes during the 3-month period, transvaginal colour Doppler was conducted in each patient in order to measure flow impedance of the uterine arteries; the data obtained were compared with the two monthly pretreatment values.

An ultrasound scan was carried out during each menstrual phase of the cycle (days 3–4), measuring uterine blood flow indices using a transvaginally directed pulsed colour Doppler system (POWERVISION 8000; Toshiba, Tokyo) equipped with a 6.5 MHz vaginal probe. All examinations were performed by one gynaecologist, who was blinded to the clinical purpose of the study. Examinations were conducted between 08:00 and 10:00 in order to reduce the effect of circadian variation on the PI (Zaidi et al., 1995).

Blood flow velocity waveforms were evaluated in the main branch of the uterine artery on either side at the level of the inner cervical os. The PI was calculated electronically according to the formula [(A–B)/ ‘mean’], where A is the peak systolic Doppler shift frequency, B the
end-diastolic shift frequency, and ‘mean’ the mean maximum Doppler shift frequency. When adequate colour signals were obtained, three similar and optimal consecutive waveforms of the left and right uterine arteries were analysed, and the mean value was obtained for statistical analysis.

Statistical analysis

All data processing and statistical analyses were carried out using SPSS 9.0 (SPSS Inc., Chicago, IL, USA) and a personal computer. For each variable, the arithmetic mean of the two pretreatment periods, as well as of the three treatment periods, was calculated. A linear analysis of variance (ANOVA) model was then fitted to the difference in mean values. If the overall F-test was significant, tests for differences between treatment groups were carried out.

Results

A statistically significant reduction in PABC score was found in each treatment group compared with baseline pretreatment values. The inter-group difference was not statistically significant, however (Figure 1).

In the desmopressin group, the mean reduction in PBAC score during the 3-month treatment period was 110 (40.5%), and ranged from 174 (72%) to 62 (43%). In the mefenamic acid group, the mean reduction was 95 (45.7%), and ranged from 169 (73.4%) to 1. Individual percentage changes in PBAC score in both treatment groups are illustrated in Figure 2. Two patients in the mefenamic group experienced reductions of 3.1% and 0.8%, with respective mean PBAC scores during treatment of 155 and 130.

An inter-group comparison of pre- and post-treatment values of mean uterine artery PI showed there to be no significant inter-group differences.

No serious adverse effects were reported during the study, and none of the patients discontinued treatment. Three patients (25%) in the desmopressin group reported headache and insomnia during treatment, but these were mild in intensity and not considered to be related to desmopressin administration.

Discussion

In the present study, both desmopressin and mefenamic acid reduced menstrual blood loss in patients with IUD-related menorrhagia, though there was no statistically significantly difference in the reduction in PBAC score after either treatment. Desmopressin treatment was shown to reduce menstrual blood loss to normal levels in all subjects. However, in the mefenamic acid group the effect was variable and not clinically useful in all cases; a reduction in PBAC score within normal limits was achieved in all patients but two, in whom the mean PBAC score during treatment clearly exceeded the limit used to define menorrhagia.

These results suggest that in women fitted with an IUD, altered local coagulation factors are the major determinants of menorrhagia, and that desmopressin has an important selective activity in restoring the altered coagulation pattern caused by increased prostaglandin synthesis.

The mechanism by which desmopressin promotes haemostasis in women with presumably normal haemostatic function is unclear. It has been suggested that such an effect might be mediated by the attainment of supranormal plasma concentrations of the von Willebrand factor (vWF)/Factor VIII involved in fibrin formation, though others have suggested that vWF is not involved in this process (Cattaneo et al., 1989).

Although the results of the present study demonstrated the effectiveness of desmopressin in promoting haemostasis, confirmation should be sought in a larger series of patients as, in the present authors’ opinion, this drug is potentially of major clinical value, despite its well-known fibrinolytic action which is exerted through the release of plasminogen activator from the vascular endothelium (Lethagen et al., 1990). This (theoretically) untoward action not only diminishes the ultimate therapeutic effect of the drug, but also casts some doubts on the role of fibrinolysis in the pathogenesis of IUD-related menorrhagia (Rybo et al., 1981).

No significant changes in flow impedance of the uterine arteries was demonstrated during treatment with either desmopressin or mefenamic acid; therefore, the therapeutic action of both drugs in reducing menstrual blood loss is not mediated through changes in uterine vascular tone.

It has been shown (Momtaz et al., 1994) that some women are more prone to develop IUD-induced menorrhagia than...
others, and this tendency might be due to a decreased vascular resistance in the uterine artery. In this respect, it has been suggested that vasoactive substances such as prostaglandins might play an important role in regulation of uterine blood flow and menstrual blood loss.

The limitations of the present study were clear, in that uterine artery PI is not a precise indicator of the endometrial vascular bed. However, two subordinate conclusions may be drawn in that: (i) there is no association between the impedance of uterine arteries and the successful reduction of menstrual loss; and (ii) further evidence is needed to place in perspective the relationship between diminished uterine vascular tone and menorrhagia.

The results of the present study confirmed previous reports that drugs believed to inhibit prostaglandin synthetase would significantly reduce menstrual blood loss in women fitted with IUDs (Guillebaud et al., 1978). The results also supported the use of desmopressin as a therapeutic tool in many women with IUD-related menorrhagia, even if larger case series are needed to provide a solid basis for recommending the use of one drug over another. It is possible that the mechanism of action of desmopressin lies in its ability to enhance local haemostasis, without imparting any haemodynamic effect on uterine blood flow.

References


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