The effect of diclofenac on uterine artery blood flow resistance during menstruation in patients with and without a copper intrauterine device

I.Järvelä¹, A.Tekay and P.Jouppila

Department of Obstetrics and Gynecology, Oulu University Hospital, 90220 Oulu, Finland

¹To whom correspondence should be addressed

The aim was to evaluate the effect of diclofenac on uterine artery blood flow resistance during the first day of menstruation. A total of 28 regularly menstruating women were examined longitudinally with and without a copper intrauterine contraceptive device (IUD) by transvaginal colour Doppler ultrasonography. The uterine artery pulsatility index (PI) was first measured, after which 50 mg of diclofenac was infused i.v. After 15 min the PI was measured again. The patients evaluated their menstrual pain with a scoring system before and after the diclofenac infusion. The mean PI (SD) during menstruation was significantly lower with the IUD [2.13 (0.43)] than without [2.39 (0.62)], P = 0.05. The mean PI in nine patients who had experienced advanced menstrual pain was also lower in the presence of the IUD [2.16 (0.42)] than without it [2.83 (0.78); P < 0.05]. Diclofenac was effective in revealing menstrual pain both with and without the IUD, and reduced the PI in the absence of an IUD [pre-treatment 2.39 (0.62) versus post-treatment 2.12 (0.45); P < 0.001], but had no effect when the IUD was present [pre-treatment 2.13 (0.43) versus post-treatment 2.10 (0.41)]. The results indicate that by inhibiting prostaglandin synthesis one can reduce the resistance to blood flow in the uterine arteries during menstruation. This does not hold true when an IUD is present, however, suggesting that the device might induce the production of vasoactive agents other than prostaglandins in the surrounding tissue.

Key words: diclofenac/intrauterine device/menstrual pain/pulsatility index/uterine artery

Introduction

The most common side-effects of an intrauterine device (IUD) are increased uterine bleeding and menstrual pain, the removal rate for these reasons within the first year of IUD use being 5–15% (Speroff et al., 1994). It is thought that these side-effects are caused by increased uterine secretion of prostaglandins, leading to abnormal uterine activity (Dawood, 1993) and vasoconstriction of the myometrial and endometrial arterioles (Nygren and Rybo, 1983). The production of prostaglandins seems to be increased at least temporarily in the endometrium after IUD insertion (Green and Hagenfeldt, 1975; Hillier and Kasonde, 1976; el-Sahwi et al., 1987) and the rise coincides with the phase of increased bleeding and pain (el-Sahwi et al., 1987). Non-steroidal anti-inflammatory drugs (NSAID), which inhibit prostaglandin synthesis, have been found to be effective in relieving both excessive menstrual bleeding (Davies et al., 1981; Roy and Shaw, 1981) and secondary dysmenorrhoea induced by IUD (Ylikorkala et al., 1978), which further confirms the role of prostaglandins in the pathogenesis of the related side-effects.

There are only a few earlier studies focusing on Doppler findings regarding the uterine blood circulation in relation to endometrial prostaglandin synthesis, dysmenorrhoea, menorrhagia and their treatment (Momtaz et al., 1994; Pirhonen and Pulkkinen, 1995; Battaglia et al., 1997; Dickey, 1997). It has been found that patients suffering from primary dysmenorrhoea have a higher uterine blood flow resistance during menstruation than eumenorrhoeic patients (Pirhonen and Pulkkinen, 1995), and that while the dysmenorrhoeic pain is effectively relieved by NSAID, a concomitant decrease is observed in the uterine blood flow resistance (Pirhonen and Pulkkinen, 1995). In a study of IUD-induced heavy menstrual bleeding, Momtaz et al. (1994) found that the resistance in the uterine artery during menstruation was significantly lower rather than higher in women with IUD-induced heavy bleeding than in those without side-effects or in those not using any kind of contraception.

The aim here was to evaluate the effect of a NSAID (diclofenac) on menstrual pain and the uterine artery pulsatility index (PI) on the first day of menstruation in patients both with and without an IUD.

Materials and methods

The study population consisted of 28 regularly menstruating women with a mean age (range) of 34 years (25–43) and a mean parity of 2 (0–4). Nine of them already had a copper IUD in utero and were willing to change to levonorgestrel-releasing IUD. The remaining 19 were willing to use a copper IUD.

The exclusion criteria for women willing to have a copper IUD were pregnancy, acute or chronic pelvic inflammatory disease, metrorrhagia of unknown cause, cervicitis, dysplasia in the cervix, genital tumour, copper allergy, Wilson’s disease, abnormalities in blood clotting or severe dysmenorrhoeic pains. Contra-indications for NSAID (diclofenac) administration were gastric or duodenal ulceration or allergy to diclofenac or any substances in the preparation. Contraceptive pills should not have been taken during the previous 3 months and any previous IUD must have been removed at least 1 month earlier. The patients were not allowed to take NSAID within 24 h of any examination. All the patients underwent a gynaecological examination and had had a Papanicolaou smear taken during the last 12 months. The patients gave their informed consent, and the trial was approved by the Ethical Committee of the Medical Faculty of Oulu University.
Diclofenac and uterine artery blood flow resistance

Table I. Means (SD) for the uterine artery pulsatility index (PI) before and after diclofenac infusion in patients with \((n = 18)\) and without \((n = 10)\) menstrual pain in the absence of an IUD

<table>
<thead>
<tr>
<th></th>
<th>Uterine artery pulsatility index</th>
<th>(P) value (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before diclofenac</td>
<td>after diclofenac</td>
</tr>
<tr>
<td>No menstrual pain ((n = 18))</td>
<td>2.44 (0.60)</td>
<td>2.16 (0.42)</td>
</tr>
<tr>
<td>Menstrual pain ((n = 10))</td>
<td>2.31 (0.67)</td>
<td>2.05 (0.52)</td>
</tr>
</tbody>
</table>

Table II. Means (SD) for the uterine artery pulsatility index (PI) before and after diclofenac infusion in patients with \((n = 15)\) and without \((n = 13)\) menstrual pain with an IUD \(in situ\)

<table>
<thead>
<tr>
<th></th>
<th>Uterine artery pulsatility index</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before diclofenac</td>
<td>after diclofenac</td>
</tr>
<tr>
<td>No menstrual pain ((n = 13))</td>
<td>2.01 (0.43)</td>
<td>2.01 (0.42)</td>
</tr>
<tr>
<td>Menstrual pain ((n = 15))</td>
<td>2.23 (0.43)</td>
<td>2.18 (0.39)</td>
</tr>
</tbody>
</table>

NS = not significant.

Table III. Mean (SD) for the uterine artery pulsatility index (PI) before and after diclofenac infusion in patients with \((n = 9)\) and without \((n = 19)\) IUD-induced menstrual pain in the absence of the IUD

<table>
<thead>
<tr>
<th></th>
<th>Uterine artery pulsatility index</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before diclofenac</td>
<td>after diclofenac</td>
</tr>
<tr>
<td>No IUD-induced pain ((n = 19))</td>
<td>2.19* (0.40)</td>
<td>2.09 (0.37)</td>
</tr>
<tr>
<td>IUD-induced pain ((n = 9))</td>
<td>2.83 (0.78)</td>
<td>2.29 (0.58)</td>
</tr>
</tbody>
</table>

*\(P < 0.01\) versus IUD-induced pain.

Table IV. Means (SD) for the uterine artery pulsatility index (PI) before and after diclofenac infusion in patients with \((n = 9)\) and without \((n = 19)\) IUD-induced menstrual pain with the IUD \(in situ\)

<table>
<thead>
<tr>
<th></th>
<th>Uterine artery pulsatility index</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before diclofenac</td>
<td>after diclofenac</td>
</tr>
<tr>
<td>No IUD-induced pain ((n = 19))</td>
<td>2.12 (0.45)</td>
<td>2.05 (0.40)</td>
</tr>
<tr>
<td>IUD-induced pain ((n = 9))</td>
<td>2.16 (0.42)</td>
<td>2.23 (0.41)</td>
</tr>
</tbody>
</table>

NS = not significant.

Results

The uterine artery PI (SD) was 2.39 (0.62) without the IUD and 2.13 (0.43) with it \((P = 0.05; n = 28)\), the figures for the 19 patients who did not experience any advanced menstrual pain induced by IUD being 2.19 (0.40) and 2.12 (0.45) (NS) respectively and those for the nine patients who experienced advanced menstrual pain 2.83 (0.78) and 2.16 (0.42) \((P < 0.05)\). There was no difference in PI between these groups when the IUD was present, but in its absence the PI was higher in those who experienced advanced menstrual pain with it \((P < 0.01)\).

Without the IUD 18 patients had no pain before diclofenac, five mild pain, two moderate pain and three severe pain, whereas after diclofenac 27 had no pain and one mild pain \((P < 0.01)\). With the IUD 13 patients had no pain before diclofenac, seven had mild pain, five moderate pain and three severe pain, whereas after diclofenac, 24 had no pain, three mild pain and one moderate pain \((P < 0.01)\).

The uterine artery PI (SD) decreased from 2.39 (0.62) to 2.12 (0.45) after diclofenac administration without the IUD \((P < 0.05)\).
< 0.001), but only from 2.13 (0.43) to 2.10 (0.41) (NS) when the IUD was present. There was no correlation between pain level and the mean PI with or without the IUD.

In order to evaluate the effect of diclofenac in the different subgroups, the patients were first divided according to whether they had menstrual pain before diclofenac infusion or not. 18 patients were pain-free and ten had menstrual pain in the absence of the IUD; 13 were pain-free and 15 had menstrual pain with an IUD. The effects of diclofenac on the uterine artery PI in the absence of the IUD are shown in Table I and those in its presence in Table II.

The effect of diclofenac was also evaluated in two groups defined according to whether the patients experienced IUD-induced advanced menstrual pain (n = 9) or not (n = 19). The effects of diclofenac in these two groups in the absence of the IUD are shown in Table III and those in its presence in Table IV.

Discussion

The main purpose was to elucidate the haemodynamic effects of NSAID administered during menstruation on the uterine arteries and to relate the results to the presence or absence of the IUD. This topic is of interest because NSAID are commonly used to relieve the side-effects of IUD even though the uterine vasoactive effects of both of these agents are poorly understood.

The results showed first that diclofenac reduced the uterine artery blood flow resistance during menstruation in the absence of the IUD in both dysmenorrheic and eumenorrheic patients. Secondly, the uterine artery pulsatility index was lower in the presence of the IUD than in its absence, and finally, diclofenac did not have any significant effect on the uterine blood flow circulation with the IUD in situ, nor was it dependent on the presence of menstrual pain or on its intensity.

The non-effectiveness of diclofenac on uterine artery blood flow resistance in patients using an IUD is surprising. This gives us reason to speculate that the IUD probably induces some production of vasoactive substances other than prostaglandins in the surrounding tissue which could be responsible for the vasodilatory changes we have observed and which are not affected by the NSAID. There is no earlier evidence that IUD could induce the production of any vasoactive agent into the systemic circulation. Similarly, since ovarian hormonal function is unaffected by the IUD (Faundes et al., 1980; Anttila et al., 1991), any haemodynamic changes related to it are probably induced by a locally excreted vasodilatory agent.

Among the various locally vasoactive substances, a possible agent that could be implicated is nitric oxide (NO), which is a potent vasodilator produced by the vascular endothelium and formed from L-arginine by nitric oxide synthase (NOS). NOS has been identified in the human endometrium and myometrium, and it is assumed that NO may play a role in the paracrine control of the uterine vascular bed (Telfer et al., 1995). NO is present in the foreign body inflammatory reaction around loosened joint replacement implants (Moilanen et al., 1997) and, as the insertion of an IUD induces a foreign body reaction in the surrounding endometrium (Sheppard, 1987), it is possible that this may also lead to an increase in NO synthesis. The literature does not, however, provide any information on the effect of an IUD on NO production by the endometrium.

In addition, NO interacts directly with cyclooxygenase (COX), which is responsible for prostaglandin (PG) synthesis, to cause an increase in the enzymatic activity (Salvemini et al., 1993). Selective inhibitors of NOS, such as dexamethasone, N-iminoethyl-L-lysine or NG-nitro-L-arginine methyl ester, are anti-inflammatory agents that inhibit both NO and PG synthesis (Salvemini et al., 1995). Inhibition of PG synthesis by a NSAID blocks PG release but does not have any effect on NO release (Salvemini et al., 1994). In cases of arthritis, for example, indomethacin blocks PG production but not NO and thereby alleviates the symptoms associated with the inflammatory insult but does not modify the course of the disease (Flynn, 1994).

In the light of these observations and our present findings, it is possible that IUD induces a foreign body reaction in the surrounding tissue and a subsequent increase in NO synthesis, leading to a decrease in uterine blood flow resistance. At the same time the effects of PG on the uterine blood flow are further attenuated, since while NSAID selectively inhibit PG production, they do not affect NO synthesis or release.

In conclusion, an IUD seems to be associated with a decrease in uterine blood flow resistance during menstruation relative to the non-IUD situation. Administration of a NSAID, although effective in relieving menstrual pain in patients both with and without an IUD, reduces uterine blood flow resistance only in the absence of the IUD and not in its presence. This observation indicates that an IUD may induce a local effect in the surrounding tissue and a subsequent change in the vasoactive agents controlling the uterine haemodynamics. The identity of these agents, however, remains to be determined.

References


Received on January 19, 1998; accepted on June 5, 1998