ACTION OF A PROSTAGLANDIN SYNTHETASE INHIBITOR ON IUD ASSOCIATED UTERINE BLEEDING

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Summary: The Authors treated twenty-eigth women using IUD, who suffered from increased menstrual blood loss and pelvic pain, with a prostaglandin synthetase inhibitor, Suprofen, in an attempt to reduce their symptomatology, in a double blind crossover study.

The drug produced an important reduction of the menstrual blood loss and pains. These observations suggest that prostaglandins are involved in the etiology of excessive menstrual blood loss and pains, and that prostaglandin inhibitors may be useful for reducing these symptoms.

INTRODUCTION

The increase of menstrual blood loss and pelvic pain, are the most frequent side effects of intrauterine contraceptive devices, and constitute the main medical reason of IUD removal ([1, 2, 3, 4]).

It has been shown that prostaglandins (PGs) may be produced by several means, and that there is an increase of them in the endometrium of laboratory animals and women using intrauterine devices ([5, 6]). If prostaglandins, locally generated, contribute to increased menstrual blood loss and pains in some patients, their inhibitors could be useful for reducing these syptoms.

Therefore, we have done a double blind crossover study to investigate the real effectiveness of a prostaglandin synthetase inhibitor, suprofen, in twenty-eight women using IUDs.

MATERIALS AND METHODS

The study was done on twenty-eight patients using IUDs for six months minimum to a maximum of ten months (Eighteen users of Gravigard and ten users of Copper T).

The twenty-eight volunteers were divided into two groups of fourteen patients each, and a double blind crossover study was made using a placebo and the actual drug. The patients were studied for three months. The first month was employed only in observation. During the second month, the first group of 14 patients (group "A") took Suprofen (Suprol-Cilag S.p.A.) (200 mg), four times the first day, and then three times daily after that; the second group (group "B") took placebo. The third month the patients, who previously took Suprofen received placebo and vice-versa.

The patients received Suprofen or placebo at the first sign of bleeding and/or pains, and continued receiving it until the symptoms ceased, or for a maximum of seven days.

Each woman received a card on which to note down the intensity of the uterine bleeding and pains, the results of the therapy, and side effects of the drug, if any.

The increased menstrual blood loss was specified by three degrees of different intensity:

I degree - slightly increased menstrual blood loss;

II degree - moderately increased menstrual blood loss;

III degree - intensely increased menstrual blood loss.

In order to see the effectiveness of the therapy, the degree of relief was also charted in the following way:

— slight reduction of menstrual blood loss (I degree);
— moderate reduction of menstrual blood loss (II degree);
— intense reduction of menstrual blood loss (III degree);
— no reduction of menstrual blood loss (IV degree).

The intensity of the pain associated with uterine bleeding and the therapeutic efficacy were classified as follows:

— moderate to intense pain;
— slight pain to no pain at all;
— moderate to intense relief;
— slight relief to no relief at all.

The patients were within 21 and 33 years of age.

Group « A » was made up of 10 women with increased menstrual blood loss of III degree, 3 of them classified in the II degree, and 1 of them classified in the I degree; in the second group (« B »), 10 patients had uterine bleeding of III degree, 2 patients of II degree, and 2 patients of I degree (tab. 1).

Table 1. — *Composition of the group "A" and "B".*

		No. of patients	
		Group "A"	Group "B"
Increased menstrual blood loss of	*I degree*	1	2
	II degree	3	2
	III degree	10	10

RESULTS

All twenty-eight patients cooperated fully with the test.

Twenty women (71.42%) showed an intense increase in the menstrual blood loss; five patients showed a moderate increase (17.85%); three patients (10.71%) had a slight increase.

With the use of suprofen, twelve women obtained a strong decrease of menstrual blood loss (42.85%), while ten (35.71%) had a moderate decrease. Two subjects (7.14%) noted only a slight decrease of uterine bleeding, and the remainder showed no results.

In detail, within group "A" of ten patients – III degree symptoms –, all using suprofen, five of them had great improvement, and the other five a moderate one; concerning three patients with moderate symptoms (II degree), one had a moderate improvement and two had only a slight reduction of uterine bleeding. The last woman of "A" group, with slight symptoms, showed no improvement.

In group "B"of ten patients with intense menstrual blood loss, seven showed a third degree improvement and three obtained a second degree improvement using Suprofen, whereas only one of two patients with moderate uterine bleeding showed a moderate improvement, and patients with slightly increased menstrual blood loss had no improvement through Suprofen (tab. 2).

Table 2. — *Results by the drug.*

Uterine bleeding degree		No. of patients	No. of patients with reduction of uterine bleeding			
			slight	moderate	intense	no reduction
Group "A"	I	1	—	—	—	1
	II	3	2	1	—	—
	III	10	—	5	5	—
Group "B"	I	2	—	—	—	2
	II	2	—	1	—	1
	III	10	—	3	7	—

No patients treated with placebo showed an intense or a moderate decrease in uterine bleeding, two had a slight improvement and twenty-six no improvement.

Regarding the pain as opposed to the bleeding, twenty-six subjects experienced pains from moderate to intense, and two from slight to none.

The intensity of pain decreased moderately or greatly in twenty-three women using Suprofen, while in five patients the drug had slight or no effects.

Placebo, on the other hand, showed few or no results in twenty-seven patients, while in one subject it obtained moderate to intense effects (tab. 3).

Table 3. — *Relief by drug and placedo.*

Intensity of the pain or relief	No. of patients with pain	Relief	
		with drug	with placebo
Moderate to intense	26	23	1
Slight to nothing	2	5	27

One patient referred stomach cramps, regarding side effects, and two subjects reported nausea and headaches, after taking the drug.

DISCUSSION AND CONCLUSION

A certain percentage of women (5%–15%) asked for removal of the intrauterine devices, during the first year, because of increased menstrual blood loss, and/or pelvic pain ([2, 3, 4]). In fact inert IUD could be associated with an intrauterine bleeding ranging from 70 ml to 100 ml, while with a copper IUD the menstrual bleeding could range from 40 ml to 60 ml ([7, 8, 9]); an average increase of menstrual blood loss of around 150% with Lippes Loop D, and 60% with copper 7 has been found by other researchers also ([10]).

Electron microscope studies showed both endometrial surface modifications and stromal degeneration in many patients with IUDs ([11, 12]). In fact, on the endometrial surface, erosions, degenerative changes in the areas of haemorrage, loss of red blood cells, and fibrin formation around the copper part of the devices have been observed. Breaks in the epithelial basement membrane, with polimorphonuclear leukocytes appeared adjacent to the copper part of the IUDs.

In the endometrial stroma, in direct contact with intrauterine devices, necrosis of the subepithelial capillaries, microthrombosis, platelets, fibrin hemostatic plugs filling endhothelial gaps have been shown. These stromal modifications appeared to a lesser extent far away from the IUDs, but in these areas the hemostatic response was not evident ([11, 12]).

Intrauterine contraceptive devices are able to determine a chronic sterile inflammatory process. Polimorphonuclear leukocytes, lymphocytes, macrophages and mast cells were observed in uterine fluid and adherent to IUD ([13, 14, 15]). Using an electronmicroscope it was revealed that the mast cells showed features of degranulation, as a response to low level but constant stimulation ([14]).

IUD associated haemorrhage may be the result of various mechanisms: the erosions of capillaries could occurr either by a direct mechanism, or by mechanical forces transmitted by uterine muscle contraction around the IUD ([16]); another mechanism could be the release of vasoactive and vasopermeable mediators, with subsequent effects on local blood flow, as histamine, heparin, SRS, and other factors from the inflammatory cells ([14, 17]). During these events, prostaglandin synthesis may take place at various levels. In fact, Piper and Vane ([18]), demonstrated that tissue distortion, in our case determinated by uterine muscle contraction around the non flessible IUD, increases prostaglandin production; in addition, the endothelial lesion, however produced, can activate through coagulation, and with subsequent thrombin production, prostaglandin synthesis in endothelial cells. Moreover, a type of prostaglandin, PGH_2, by prostacyclin synthase, may be trasformed in PGI_2, and makes a remarkable vascular dilator ([19]).

In the final analysis, the process of coagulation, because of the endothelial damages, is responsible for local release of prostacyclin.

Prostaglandins, that are produced during every inflammatory process, are present in the uterus owing to the chronic sterile inflammatory process induced by IUD.

The PGs, the release of chimical mediators from leukocytes, macrophages and mast cells, the process of coagulation whith subsequent fibrinolytic activity, could all be responsible for vascular modifications of haemostasis, and for the increased menstrual blood loss.

In a large percentage of the patients observed, the use of a prostaglandin synthetase inhibitor, Suprofen, determined a remarkable improvement of the symptoms.

Moreover we noticed that patients with symptomatology of greater intensity obtained better results from therapy. This is in accord with other researchers, who obtained a greater decrease in menstrual blood loss in patients with more intense IUD symptomatology ([20, 21]).

We think that the most complete response to treatment concerning patients with intense symptoms associated with IUD, could be attributed to the preeminent role in these patients of prostaglandins.

PG inhibitors significantly lower $PGF_{2\alpha}$ concentration in menstrual endometrium ([22]).

It may be affirmed that although the role of prostaglandins is not completly clear, the use of Suprofen, in the treatment of the increased menstrual blood loss and pelvic pains associated with IUDs, seems to be a rational therapeutic approach. Its efficacy is attributable certainly to the inhibitor effect of prostaglandin synthetase enzymatic complex.

BIBLIOGRAPHY

1) Shaw S. T. Jr., Moyer D. L.: "Uterine bleeding from intrauterine devices: clinical aspects and pathogenesis". In: *Human Reproduction Conception and Contraception.* 2nd ed., edited by E.S.E. Hafez, Hagerstown, MD, Harper & Row, 682, 1979.
2) Lukkainem T., Allonen H., Nielsen N. C., Nygren K. G.: *Am. J. Obst. Gyn., 147,* 885, 1983.
3) Data collected from O. M. S., 1981.
4) Burdick C. L., Anderson M. V.: *Delawere Med. J., 45* (9), 253, 1973.
5) Chauduri G.: *Prostaglandins, 3,* 773, 1973.
6) Hillier K., Kasonde J. M.: *Lancet, 1,* 15, 1976.
7) Israel R., Shaw S. T. Jr., Martin M. A.: *Contraception, 10,* 63, 1974.
8) Liedholm P., Rybo J.: *Contraception, 12,* 317, 1975.
9) Guillebaud J., Bonnar J.: "Estimation and prediction of IUD related increased duration and amount of menstrual blood loss". In: *Progress in Contraceptive Delivery Systems. IUD Pathology and Management,* Lancaster, England, vol. 3, MTP Press, 1980.
10) Guillebaud J., Bonnar J., Morehead J., Mattews A.: *Lancet, 1,* 387, 1976.
11) Brian L., Sheppard, Phil D., Bonnar J. M. D.: *Am. J. Obst. Gyn., 146* (7), 829, 1983.
12) Aparicio S. R., Bradbury K., Bird C. C., Foley M. E. *et al.*: *Br. J. Obst. Gyn., 86,* 314, 1979.
13) Bertil Casslen: *Acta Obst. Gyn. Scand., 98* (Suppl.), 10, 1983.
14) Tursi A., Mastrorilli A., Loiudice L., Ribatti D., Contino R., Claudatus L.: *Am. J. Obst. Gyn., 148* (8), 1064, 1984.
15) Sheppard B. L., Bonnar J.: *Am. J. Obst. Gyn., 87,* 155, 1980.
16) Subir Roy, Shaw S. T.: *Obst. Gyn., 58,* 101, 1981.
17) Shaw S. T. Jr.: "The enigma of uterine bleeding and IUDs, IUD pathology and management", Vol. 3, *Progress in Contraceptive Delivery Systems,* edited by E.S.E. Hafez, W. A. A. Lancaster, MTP Press, 31, 1980.
18) Piper P., Vane J.: *Ann. N. Y. Acad. Sci., 180,* 363, 1971.
19) Czervionke R. L., Smith J. B. *et al.*: *Thromb. Res., 14,* 781, 1979.
20) Guillebaud J., Anderson A. B. M., Turnbull A. C.: *Br. J. Obst. Gyn., 85,* 53, 1978.
21) Davies A. J.: *Int. J. Gyn. Obst., 17,* 353, 1980.
22) Sander S., Shapiro, Ray V., Haning J. R.: *Current Therapeutic Research, 33,* 380, 1983.