THE EFFECT OF A PROSTAGLANDIN SYNTHETASE INHIBITOR, INDOMETHACIN, ON EXCESSIVE UTERINE BLEEDING

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Summary: Indomethacin, a prostaglandin synthetase inhibitor given to 94 women suffering from functional menorrhagia, IUD's and sub mucous fibroid related bleeding, reduced menstrual loss and duration of menstruation in 70 patients (74.5 percent). A significant decrease in duration of menstruation of 2.1 days was obtained in the responding group. In functional bleeding, the mean decrease was 1.7 days, in IUD's related menorrhagia 2.9 days and in menorrhagia due to submucous fibroids 2 days.

Age, parity and duration of menstruation before treatment had no significant effect on the response or reduction of duration of bleeding.

The medication was discontinued only in two patients because of minor gastronntestinal symptoms.

Key words: Menorrhagia, Indomethacin, Functional Bleeding, IUD related Bleeding, Sumucous Fibroids.

INTRODUCTION

Menorrhagia, which takes the form of excessive bleeding or prolonged flow, frequently may cause chronic iron deficiency anemia. The main etiological factors for menorrhagia are uterine and endometrial tumors, endocrinological dysfunctions, systemic diseases, and intra uterine device. However, many women complain of menorrhagia without obvious causes: the functional menorrhagia.

The current management of menorrhagia after endometrial pathology or ovarian dysfunction has been excluded, is usually hormonal therapy taken throughout menstrual cycle.

Recent studies showed that inhibition of prostaglandin synthetase can lead to a significant reduction in menstrual blood loss. Guillebard and coworkers reported on a significant reduction in menstrual blood loss (MBL) in women with IUD during treatment with mefenamic acid ([1, 2]). Other inhibitors of prostaglandin synthesis and release as naproxen, and ibuprofen was found to have the same effect ([3, 4]).

During a clinical trial with indomethacin, a prostaglandin synthetase inhibitor to alleviate dysenorrheic patients suffering from systemic manifestations (cramps, diarrhea, irritability and poor concentration), a significant reduction in MBL and duration of menstruation was reported. For this reason, we initiated a clinical investigation to study the effect of indomethacin on patients suffering from menorrhagia from various etiological factors.

MATERIALS AND METHODS

The study group consisted of 94 healthy women age 19 to 48 years suffering of a prolonged distressing menorrhagia. These patients were treated with indomethacin (Indomed) for 441 cycles. Forty-six patients had no obvious pathology « functional bleeding », 32 with IUD's related bleeding and 16 with sub mucous fibroids objecting surgery.

Individual history and physical examination were carried out before treatment was initiated, patients with a history of gastrointestinal bleeding, blood dyscrasias or bleeding tendency, and pelvic inflammatory disease were excluded. Women were instructed to record carefully the days of bleeding, number of pads or tampons per day

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Table 1. — *Effect of indomethacin on the duration of bleeding in patients with menorrhagia.*

Etiology	No.	Age	Parity	Cycles of treatment	Duration of bleeding		
					Before	During	
Functional	46	29.4 (19-45)	1.4 (0-5)	178 (2-15)	6.9 (3-12)	5.2 (3-10)	$p<0.001$
IUD's Related	32	30.7 (23-43)	2.4 (0-4)	101 (1-8)	8.5 (7-10)	5.6 (4-8)	$p<0.001$
Sub Mucous Fibroids	16	40.0 (38-48)	1.8 (0-7)	162 (2-30)	6.6 (5-10)	4.6 (4-6)	$p<0.001$
Total	94			441	7.4	5.3	

for two consecutive cycles before treatment and during treatment, until the effect was well documented. All patients had a complete blood count before and during treatment. The dose used was 75-100 mg/day, p.o. (1.5 mg/kg body/weight/day). The drug was taken at initiation of menstruation, thus avoiding the use of it in early pregnancy. Patients were told to take the drug throughout the maximal bleeding phase for four or five days.

The patients were followed every month for the first three months of treatment and at three months interval later. The effect of the drug and side effects were recorded.

The duration of treatment was between 1 to 30 cycles, menstrual blood loss was evaluated mainly according to the duration of bleeding but also the daily number of pads or tampons were taken into consideration.

The drug was discontinued if patients complained of gastrointestinal disturbances such as heart burn or gastric pains or any other major side effects.

RESULTS

The effect of indomethacin was pronounced mainly from the second day of treatment. Patients responded within the first or second cycle of treatment, the non responders showed no response if the drug was continued or the dose was increased.

A good correlation was found between the total numbers of days of bleeding and the total number of pads or tampons used. It was therefore decided to evaluate the effect of treatment finally only on the duration of menstruation as presented in table 1.

When evaluating the effect of the treatment, we presumed that the decrease in the number of days of bleeding may very well be dependent on the number of days of bleeding before the treatment, which made it difficult to compare the difference scores, for this reason a non parametric statistical test was chosen - the Sign Test.

Seventy patients (74.5%) had a decrease of bleeding and duration of menstruation concomitantly. The mean number of days of bleeding in the whole group was 7.4 days, and the mean decrease during treatment was 2.1 days (28%) which was statistically significant ($p < 0.001$).

Twenty-two patients had no difference and in two the bleeding increased. In the functional bleeding group, 30 women out of 46 had a decrease in the bleeding days. The mean decrease was of 1.7 days ($p < 0.001$ statistically significant). In the 32 women with IUD's related menorrhagia 23 had a decrease of duration of bleeding of 2,9 days ($p < 0.001$ statistically significant), 7 had no response and in 2 the bleeding increased. In patients with submucous fibroids related bleeding 14 out of 16 had less bleeding days with a mean decrease of 2 days ($p < 0.01$ statistically significant). The 24 patients with non decrease in duration of bleeding during treatment were compared with the responders on age, parity, number of days of bleeding during menstruation before treatment and number of cycles of treat-

Table 2. — *Influence of age, parity, cycles of treatment and number of days of bleeding before treatment on the response to indomethacin.*

Effect of Treatment	Age		Parity		Cycles of Treatment		Days of Bleeding Before Treatment	
	<35	≥35	0	≥ 1	≤ 2	> 2	≤ 7	> 7
Decrease of Bleeding	34	36	28	42	28	42	42	28
No Decrease	20	4	6	18	12	12	18	6
Total	54	40	34	60	40	54	60	24
	x^2 : 3.11 (n.s.)*		x^2 : 0.34 (n.s.)		x^2 : 0.07 (n.s.)		x^2 : 0.34 (n.s.)	

* n.s. = not significant

ment, none of these factors had a significant influence on the response to the treatment as reported in table 2. For those women who had 7 days of bleeding or more before treatment (40 out of 94) a correlation coefficient was computed between cycles of treatment and the decrease in days of bleeding. A very low and not significant was found, i.e. no relation between cycles of treatment and the decrease in bleeding days.

In two patients the medication was discontinued after 2 and 4 cycles, because of heartburn and gastric pain. No gastrointestinal bleeding, mental confusion, psychiatric disturbances, blurred vision, stomatitis or skin reaction occurred.

Repeated blood count showed no decrease in white blood or platelets during treatment.

When medication was discontinued, menorrhagia recurred. The patients treated with indomethacin had additional benefit; some patients reported on a relief of dysmenorrhea or gastrointestinal symptoms associated with menstruation.

DISCUSSION

The effect of indomethacin and different prostaglandin synthetase inhibitors on reduction of menstrual blood loss add a promising therapeutic alternative for menstrual disturbances as previously reported for dysmenorrhea using flufenamic acid, naproxen mefenamic acid ibuprofen and indomethacin ([5, 8]).

The mechanism of action of indomethacin may be attributed to the blocking effect of this drug on the production of prostaglandins in the endometrium. It is well known that various types of prostaglandins mainly E2 and F2α are synthetized in the endometrium throughout menstrual cycle, reaching higher level at menstruation. Relatively higher levels were found in the endometrium of patients with menorrhagia and were suggested to be responsible for this excessive bleeding ([9]). Recent study shows that prostacycline (PGI_2) may be the main responsible factor for menorrhagia. It may influence the degree and duration of menstrual bleeding through its effect on inhibition of platelets aggregation and stimulation of vasodilatation ([10]).

The data in this study were based mainly on duration of menstruation which was already found to correlate positively with the magnitude of menstrual blood loss and with incidence to menorrhagia ([11]). This method is a practical measurable parameters as compared to different quantitative expensive procedure, i.e. chemical determinations of iron, radioisotope techniques and electrical conductivity in collected menstrual loss. The effect of indomethacin in this study was in reducing the duration of menstruation (28%) and the period of excessive bleeding. The

effect was pronounced chiefly from the second or third day of initiation of treatment which correlate to the period of the majority of blood loss during menstruation ([11]). These results agree closely with those previously published on the effect of other antiprostaglandin ([1, 4]). Roy and Shaw found by quantifying menstrual blood loss in 20 women wearing IUD's, a reduction of 25 to 34 percent ([4]). In our study a similar reduction of duration of bleeding in women wearing IUD's (2.9 days - 35%) was observed.

The response to the drug was obvious within the first 2 cycles of treatment and those who had non reduction of bleeding during this period did not respond on successive cycles. It is therefore suggested to discontinue the medication after a trial of two cycles if response is not achieved. Age and parity has no effect on the response to the treatment, as they have little effect on menstrual loss ([12, 13]).

We preferred the use of the drug during the clinical symptoms which was better accepted by the patients and prevented the potential danger of exposing an early embryo to prostaglandin synthetase inhibitors. Theoretically, a prostaglandin synthetase inhibitor should be more effective prophylactically than therapeutically, yet, there was non apparent difference in a previous study concerning dysmenorrhea with respect to whether the medication was started before menses or at the onset of flow ([14]). The short duration of treatment, four to five days, proved to be effective and had negligable side effects.

It is thus suggested that the main indication for further use of indomethacin will be in those women suffering from excessive bleeding secondary to IUD, which is the most common reason for removal of the device. Women with menorrhagia due to sub-mucous fibroid may also benefit from this treatment.

In conclusion, this study as others, shows that reduction of blood flow during menstruation in patients suffering from menorrhagia can be accomplished by a prostaglandin inhibitor and not only by hormonal or antifibrinolytic agents.

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