

TREATMENT OF IUD RELATED MENORRHAGIA BY INDOMETHACIN

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SUMMARY

Indomethacin, a prostaglandin synthetase inhibitor was tested in 9 women wearing a lippe loop IUD. These women suffered from excessive bleeding with a mean menstrual blood loss of more than 100 ml. The effect was studied by quantifying menstrual blood loss in a double blind 4 periods crossover study.

The mean percentage reduction during treatment was of 57 percent. No significant placebo effect was observed.

The effect of indomethacin support the contention that IUD's associated menorrhagia, is connected to an abnormal prostaglandin synthetase in the endometrium.

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INTRODUCTION

Excessive and irregular menstrual bleeding is the most common side effect encountered by women wearing an Intra Uterine Device (IUD). The increased menstrual blood loss (MBL) in these women may be as high as two to three folds over the normal MBL in non users^(1, 2).

The factors that control menstrual blood loss are still unclear. Laboratories and clinical observations offered some explanations for the heavy bleeding: an increase of plasminogen activators was found in the endometrium of women suffering from menorrhagia who responded well to antifibrinolytic agents, such as epsilon amino caproic or tranexamic acid^(3, 4), and a significant increase of prostaglandin E₂ in endometrial tissue during menstruation⁽⁵⁾. IUD users have higher prostaglandin levels in endometrial tissue than non users⁽⁶⁾, and prostaglandin synthetase inhibitors as mefenamic acid, naproxen and ibuprofen can induce a marked reduction in MBL⁽⁷⁻⁹⁾.

Indomethacin, a non steroid anti inflammatory drug, has been used for many years in the treatment of rheumatoid arthritis and osteoarthritis. This drug, a prostaglandin synthetase inhibitor, has been shown to induce pronounced alleviation of dysmenorrhea^(10, 11).

The present study was initiated to determine the ability of indomethacin in reducing menstrual blood loss in IUD related menorrhagia.

MATERIAL AND METHODS

The study group consisted of healthy volunteers between 24 and 36 years of age. They had a normal menstrual history before insertion of IUD. All were fitted with lippe C for at least 3 months, which caused excessive and prolonged menstrual bleeding. Patients were eligible to enter the study only if they had 7 or more days of bleeding. Subjects excluded were those who had a history of pelvic inflammatory disease, dysfunctional uterine bleeding, blood dyscrasia or bleeding tendency and uterine fibroids. The

patients were informed about the study and consent was obtained.

On initial visit each patient had an individual case history and physical examination. Patients with an active peptic ulcer or gastrointestinal lesions and those who were known to be allergic to indomethacin or aspirin were not accepted.

Before entering the study the patients had a blood count, which included hemoglobin, hematocrit, white blood cells and platelets, prothrombin time, bleeding and coagulation time.

Patients entering the study were supplied with sanitary pads and tampons which were collected at the end of each menstruation. Thirty five patients were investigated for two cycles which served as baseline, but only 15 patients having a mean blood loss of more than 100 ml were included in this study. Nine patients completed the study and 6 were lost to follow-up.

The patients received non labelled tablets containing indomethacin 25 mg or placebo and were instructed to take the tablets four times daily, from the first day of menstruation for four consecutive days. The treatment was studied in a double blind 4 periods crossover study: two cycles with indomethacin and the other with placebo; the amount of blood of MLB was evaluated quantitatively using the photometric alkaline hematin method of Hallberg and Nilson⁽¹²⁾. Vaginal tampons or pads were incubated for 48 hours, after incubation absorbance of the brown colored alkaline hematin was measured at 550 nm in Perkin-Elmer Model 124 dual beam spectrophotometer against a blank of 5% sodium hydroxide solution. The optical density of alkaline hematin prepared similarly from the patient's venous blood enabled blood loss to be calculated.

RESULTS

A significant reduction in ML under indomethacin treatment was noted in all 9 patients (table 1). As the sample sizes relatively small, the non parametric Wilcoxon matched pairs-signed rank test was used for analysis⁽¹³⁾. No significant difference in MBL between the baseline and the placebo cycles was observed ($P=0.15$) (table 2). The reduction percentages under indomethacin treatment were found to range between 44 to 73 percent as compared to the pretreatment MBL and between 52 and 68 percent to the placebo cycles. The average reduction percentages was 56.9 which was significant ($P\leq 0.002$).

Table 1. — Menstrual blood loss (ml).

Patient	Baseline cycles		Study cycles			
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
1	120	105	55*	131	144	46*
2	75	124	26*	82	35*	80
3	279	347	190*	147*	260	240
4	150	186	160	45*	52*	114
5	326	290	80*	270	85*	250
6	169	178	195	207	101*	92*
7	132	140	112	67*	62*	105
8	140	161	81*	131	152	75*
9	103	121	130	115	54*	51*

* Indomethacin Cycle.

Table 2. — Mean values and percentage reduction of menstrual blood loss (ml).

Baseline (Cycles)	Placebo (Cycles)	Indomethacin (Cycles)	Percentage reduction
174.7 ±	159.9 ±	75.1 ±	56.9 ±

No significant difference in MBL between the baseline and the placebo cycles was observed ($P=0.15$). A significant reduction was also observed when indomethacin cycles were compared to

placebo + baseline

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($P\leq 0.002$).

The reduction in MBL under indomethacin treatment was not influenced by the sequence of indomethacin-placebo administration.

During the four consecutive study cycles we found no definite tendency in the percentage reduction of MBL when comparing the patients with high MBL (> 150 ml) and the lower value (< 150 ml).

No significant changes in blood count, and coagulation study were noted during the study period. No side effects which could be attributed to indomethacin were observed.

COMMENT

The significant reduction in MBL under indomethacin treatment which was found in all 9 patients in this study may reflect the role of prostaglandins in the pathogenesis of IUD induced menorrhagia⁽⁵⁾.

The mean percentage reduction in MBL in the treatment cycles (56.9%) was higher than that previously reported with other non steroidal anti-inflammatory drugs⁽⁷⁻⁹⁾, with mefenamic acid the average reduction in MBL was 34% (N:15)⁽⁷⁾, with naproxen 33% (N:11)⁽⁸⁾, and with ibuprofen 39% (N:8)⁽⁹⁾.

This difference may be due to larger amount of tissue trauma induced by the larger plastic devices which respond to indomethacin treatment.

When using mefenamic acid⁽⁷⁾, the average reduction was more pronounced in the group of women who had a pre-treatment MBL exceeding 80 ml as compared to those with less than 80 ml; 23% and 34% respectively.

The obvious reduction in MBL in this study was found in a selected group with mean blood loss exceeding 100 ml.

The use of this drug without causing side effects is probably because of short duration of treatment, and the meticulous selection of patients.

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