ROLE OF ANTI PROSTAGLANDINS IN DYSFUNCTIONAL UTERINE BLEEDING

By

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SUMMARY

Dysfunctional uterine bleeding (DUB) continues to be one of the most frequently encountered and perplexing problems in Gynaecology. The increasing demand for I.U.C.D. insertions and sterilisation techniques have put D.U.B. on an increase. Instead of the drastic measure like hysterectomy and the cumbersome hormonal therapy, a simpler and effective therapy in D.U.B. is aimed at.

Keeping in mind that the link between endocrine control and vascular participation in normal and abnormal menstrual bleeding may lie in the effect of hormones on prostaglandin production in the vascular endothelium, the use and efficacy of antiprostaglandin drugs in reduction of blood loss in D.U.B. was studied.

Discussion

Prostaglandins are present in almost all organs of reproductive system and their secretories. Prostaglandins, Prostacyclins, thromboxanes are synthesized in the endometrium and may be vasoactive substance of Markee (1940) the menotoxin of Smith and Smith (1950) and the menstrual stimulant of Pickles (1957).

The findings that—

(a) Prostaglandin F2 and E2 are present in endometrium increase during the luteal phase and are maximum at menstruation (Downie *et al,* 1974).

(b) Infusion of PG F2 in human volunteers induce menstruation (Wisquist *et al,* 1971).

(c) The amounts of Pg E2 and PG F2 and in endometrium in luteal phase are increased in patients with menorrhagia and dysmenorrhea (Haynes *et al,* 1980).

(d) Treatment with prostaglandin synthatase inhibitors reduces menstrual blood loss. Anderson *et al,* 1976, Haynes *et al,* 1980, all suggest that prostaglandins play a major role in normal and abnormal menstruation.

Prostaglandin E2 causes relaxation of vascular smooth muscle and dilatation of both resistance and capacitance of vessels whereas PG F2 causes constriction of capacitance of resistance of vessels in low doses. Prostaglandin (PG E2) is a potent vaso dilator. Prostaglandins are essentiallv local hormones synthesised and acting locally in tissues.

Willman *et al* (1976) showed a disproportionate increase in PG E2 as compared with PG F2 in patients with menorrhagia and it is tempting to postulate that it is the

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excessive vasodilatory effect of PG E2 on spiral arteriosis which is responsible for excessive blood loss. Inhibition of this vasodilatory effect of excessive PG E2 by prostaglandin synthesize inhibitors would then help to reduces the menorrhagia.

The preliminary observations by Anderson *et al* (1976) suggest a new treatment in menorrhagia using the prostaglandin synthesize inhibitor.Haynes *et al* observed significant reduction in menstrual blood loss on Mefemamic acid therapy (Prostaglandin synthesize inhibitor).

Excessive menstrual bleeding in patients with I.U.C.D. induced menorrhagia returned to normal bleeding pattern after use of antiprostaglandins as reported by Usha Krishna *et al* and A. J. Davies *et al*, 1981.

The drugs used in the study.

(1) *Tromaril*: M B' Phenyl ethyl anthranitic acid (enfenamic acid) is a prostaglandin synthetaise inhibitor. Dosage: 800 mg twice or thrice a day for 4-7 days during menstrual period.

(2) *Naproxene*: 6 methoxyamethyl—2—napthal is a potent prostaglandin synthetase inhibitor and has a thromboxane action. Dose: 500 mg twice a day with 250 mg in afternoon for 5 days during periods. Low dose schedule was 500 mg as loading dose followed by 250 mg thrice a day for 5 days.

Material and Methods

This prospective drug trial of antiprostaglandin agents was conducted at Govt. Medical College on 50 cases attending the Gynaec. department and diagnosed as D.U.B.

History, general and local pelvic examinations with necessary laboratory investigations were carried out in all cases. D & C was undertaken in cases of premenopausal age group to rule out malignancy. Patients having post I.U.C.D. menorrhagia were excluded from this study. The patients were distributed in 3 groups as follows:

Group I: 25 cases treated with the Tromaril. (Engenamic acid).

Group II: 25 cases treated with Naprotis and Naproxen.

Control group: 25 cases having blood loss during periods. Patients with estimated blood loss of more than 80 ml before therapy were considered for the study.

The estimation of blood loss was done in 4 consecutive cycles in both groups, one estimation before and 3 estimations after therapy.

Estimation of Blood Loss: The method was adopted from the ringthal method of Hallberg and Nilsson.

All the patients were supplied with specially made cotton gauze sanitory pads. The patients were instructed to collect all their menstrual pads in plastic bags and report soon after cessation of menstruation with the pad, a sample of peripheral venous blood 1 ml was collected in Wintrobe tube and Hb% was estimated.

Principle

A volume of menstrual blood loss was determined by measurement of alkali haematin. In this the pads were treated with a 5% NaOH solution of a measured volume in a blender to convert the blood Hb to alkali haematin. The optical density of the alkaline haematin solution was spectrophotometrically determined. Similarly alkaline haematin optical density prepared from the patients peripheral venous blood was measured. The readings so obtained were used in an equation to calculate the blood loss.

$$\text{Blood loss (M1)} = \frac{\text{O.D. at 550 mm of the homogenate} \times (V)}{\text{O.D. at 550 mm of the homogenate} \times (V)}$$

where O.D. is the optical density obtained from the tables and Vs is the volume of 5% NaOH solution added to the bag with sample. Vv is the volume of 5% NaOH solution added with peripheral venous blood.

Observations

Total cases, under these drug-trial are 50, which were divided into two groups for study. Group I includes 25 cases treated with Tromaril and Group II includes 25 cases treated with Naproxane.

The largest number of cases were found to belong to parity group 1-4 in Group I and parity Group 1-4 in Group II as well.

Maximum cases presented with cyclical menorrhagia.

This was used to standardise the method of blood loss estimation. Blood loss in 25 cases over 3 consecutive menstrual cycles was estimated.

Hence patients who had blood loss more than 80 ml were considered in the study.

TABLE I
Agewise Distribution of Cases

Years	15-20	21-25	26-30	21-35	36-40	41-45	Total
Group I	2	3	8	3	5	4	25
Group II	1	6	8	5	3	2	25

Maximum patients belonged to 26-30 years age group, in Group I and in Group II.

TABLE II
Showing Marital Status

	Married	Unmarried	Total
Group I		2	25
Group II	24	1	25

Maximum number of cases belonged to married group in both the series.

TABLE III
Showing Parity Distribution

	Nulliparous	1-4	More than 4	Total
Group I	3	16	6	25
Group II	1	14	10	25

TABLE IV
Showing Symptom—Complex

Symptom-complex	Group I	Group II
Cyclical Menorrhagia	8	7
Puberty Menorrhagia	2	1
Polymenorrhagia	2	6
Polymenorrhoea	0	1
Metrorrhagia	1	0
Post abortal	2	2
Post partum	5	6
Perimenopausal	5	2
Total	25	25

TABLE V
Showing Normal Blood Loss

Blood loss in ml.	<30	30-35	36-40	41-45	46-50	51-55
No. of cases	1	0	5	6	10	3

Minimum: 18.3 ml Maximum: 53.14 ml.

Estimations were done 4 times: Once before therapy and in 3 consecutive cycles when on therapy.

was 51-60 ml. However maximum number of cases i.e. 10 cases had a reduction to the level of 61-70 cases.

TABLE VI
Showing Blood Loss in Menorrhagia Cases

Blood loss in ml.	80-100 ml	101-120	121-140	More than 140
Group I	12	5	8	2
Group II	9	10	5	1

Maximum: 140-150 ml was estimated in 2 cases. One case had blood loss between 71-80 ml and was omitted from study Group I, Group II maximum blood loss estimated in 10 patients was in 101-120 ml range.

Graph showing pretreatment blood loss and estimated blood loss over 3 consecutive cycles when on treatment follows. From this graph we learn that the blood loss range for both the groups was 80-152 ml in pre-treatment cycle. Cases in Group I had average pretreatment loss of 101.98 ml and in Group II 108.530 ml.

After starting Tromaril therapy in Group I the average loss reduction was 65.936 ml with average difference of 36.044 ml. In Group II after starting Naproxane therapy this loss was reduced to 70.530 ml i.e. with average difference of 38.192 ml. These figures of reduction in blood loss are statistically significant. In Group I S.D. is 49.03 whereas in Group II it is 40.439.

The above table shows that in Group I maximum blood loss reduction achieved

TABLE VII
Estimated Blood Loss in Cases of Each Group With Treatment

No. of cases				With treatment blood loss in ml.
Group I		Group II		
No.	Percentage	No.	Percentage	
6	24	1	4	51-60 ml
10	40	13	52	61-70 ml
8	32	10	40	71-80 ml
1	4	1	4	81-90 ml
25	100	25	100	Total

On the other hand in Group II only 1 case reached 50-60 ml reduction but 15 cases had reduction in blood loss between 61-70 ml.

Blood loss was reduced to 61-70 ml in maximum cases. Standard deviation as per Group I is 49.03 which is highly significant and Standard deviation in Group II is 40.439.

TABLE VIII
Post Therapy Blood Loss in Cases Each Group

Group I	Group II	Post therapy blood loss in ml
6	1	50-60 ml
10	13	61-70 ml
8	10	71-80 ml
1	1	81-90 ml
25	25	Total

Blood loss was reduced to 61-70 ml in maximum cases.

Conclusion

An accurate objective method Hallberg and Nilsson's method of estimating blood loss was used in this study to know the use and efficacy of the antiprostaglandins in reducing the blood loss in D.U.B. cases.

In the Tromaril group blood loss reduction was 65-93 ml with average difference of 36.04 ml. In the Naproxane group reduction in blood loss was to 70.53 ml with average difference of 39.19 ml. This reduction of blood loss by these two drugs were statistically significant.

Group I SD is 49.03
Group II SD is 40.439.

The study therefore proves the efficacy of the antiprostaglandin in the treatment of D.U.B. and can be added in the armamentrium of conservative management of D.U.B

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