and the Metropolitan Police for their unfailing co-operation; Dr Eva Alberman for survival rates of infants in England and Wales given in table I; and Dr Ann Stewart for her helpful advice.

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Aminocaproic acid and menstrual loss in women using intrauterine devices

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Summary

A controlled study of the effect of aminocaproic acid 3 g six-hourly taken by mouth during menstruation was carried out on 56 women for eight months from the time of insertion of a Lippes D intrauterine device (IUD). Thirty-five women presenting with menorrhagia in association with an IUD were also treated during three out of six consecutive menses. A highly significant reduction in menstrual loss was observed during treatment in both groups.

Introduction

Excessive menstrual bleeding is the commonest complication of intrauterine contraceptive devices (IUDs) and is responsible for their discontinuance in up to 20% of users.¹⁻⁴ Since aminocaproic acid (EACA), an antifibrinolytic agent, effectively controls menorrhagia not related to IUDs we have studied its effects on menstrual blood loss in women using IUDs.

Patients and method

Two groups of women were studied, all of whom gave full and informed consent. The first group consisted of 56 women requesting intrauterine contraception. They had one menstrual collection measured before insertion and eight consecutive collections measured after insertion. The patients were allocated to treatment and control groups matched for pre-insertion menstrual loss and stratified to cover a range of losses from 5 to 100 ml (table I). All were fitted with Lippes D IUDs. The treated women received 3 g EACA four times a day for seven days from the date of insertion, then 3 g four times a

day during menstruation for the subsequent four periods. For the next four periods they took the treatment during cycles 6 and 8 only. The second group consisted of 35 women presenting with IUD menorrhagia, irrespective of the type of device. These women were studied through six consecutive menstrual collections. The first was a baseline measurement; the next three were treatment periods during which they received 3 g EACA four times a day taken as a powder dissolved in water. The last two periods were without treatment.

TABLE I—Pre-insertion blood loss in 56 treated women and controls

No. of Patients	Blood Loss (ml)		
	Range	Treated Women (n = 28)	Controls (n = 28)
16	5-20	5.4	7.9
		8.7	10.7
		9.0	12.2
		9.2	12.3
		11.8	15.9
		14.2	16.2
		16.9	16.6
		19.8	17.6
16	>20-40	20.3	20.7
		20.6	21.6
		22.2	24.4
		23.2	25.5
		23.4	26.5
		29.7	29.8
		30.1	30.3
		35.4	33.7
10	>40-60	46.1	40.6
		49.6	40.9
		49.9	43.2
		53.2	47.4
		60.0	51.8
6	>60-80	62.9	64.9
		63.2	71.6
		67.7	80.0
4	>80-100	96.9	84.8
		99.0	87.2
4	>100	124.7	103.2
		131.3	157.4
Mean		43.0	42.7

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All patients gave a full medical history and underwent clinical examination, including gynaecological assessment. All tampons and sanitary towels used were collected in polyethylene bags numbered for each day of bleeding. Blood loss was measured by a modified alkaline haematin method.⁵ The pads and tampons were soaked in 5% sodium hydroxide for 48 hours. The

TABLE II—Mean menstrual blood loss (ml) $\pm$ SD before and after Lippes D IUD insertion

	Before Insertion	Cycles after Insertion							
		1	2	3	4	5	6	7	8
Control group (n = 28)	42.7 $\pm$ 34.7	121.1 $\pm$ 104.6	99.5 $\pm$ 67.0	93.5 $\pm$ 69.2	97.0 $\pm$ 75.9	91.4 $\pm$ 59.3	89.5 $\pm$ 65.7	81.7 $\pm$ 47.7	81.6 $\pm$ 54.7
EACA treatment group (n = 28)	43.0 $\pm$ 34.9	49.2 $\pm$ 26.3	50.2 $\pm$ 28.5	48.3 $\pm$ 26.6	54.1 $\pm$ 28.6	78.4 $\pm$ 45.7	49.7 $\pm$ 28.2	84.4 $\pm$ 47.2	52.0 $\pm$ 23.6
P (log values)	N.S.	0.001	0.001	0.001	0.005 > P > 0.001	0.5	0.005	0.7	0.025

In view of the skewed distribution of menstrual blood loss the original values were converted to logarithms for tests of significance (Student's *t* test). In cycles 5 and 7 the women in the treatment group received no EACA. The mean losses in these cycles showed no significant difference.

TABLE III—Mean duration of periods (Days) $\pm$ SD before and after insertion of Lippes D IUD

	Before Insertion	Cycles after Insertion							
		1	2	3	4	5	6	7	8
Control group (n = 28)	4.9 $\pm$ 1.3	6.6 $\pm$ 1.8	5.6 $\pm$ 1.4	5.5 $\pm$ 1.3	5.4 $\pm$ 1.6	5.2 $\pm$ 1.2	5.3 $\pm$ 1.4	5.1 $\pm$ 1.4	5.0 $\pm$ 1.3
EACA treatment group (n = 28)	5.1 $\pm$ 0.9	6.1 $\pm$ 1.5	5.6 $\pm$ 1.4	5.4 $\pm$ 1.3	5.6 $\pm$ 1.4	6.1 $\pm$ 1.9	5.7 $\pm$ 2.1	5.5 $\pm$ 2.7	5.0 $\pm$ 1.3
P	0.6	0.3	0.5	0.7	0.7	0.1	0.3	0.5	0.9

optical density of the resulting solution of alkaline haematin was measured with a Vitatron photometer and compared with the reading obtained from the patient's venous blood mixed with a known volume of 5% sodium hydroxide. For quality control a known volume of venous blood was placed on a sanitary towel (without the knowledge of the technician) for measurement of blood loss; 5 ml was used on four occasions and the experiment was repeated with 10, 15, and 20 ml. The results of the 16 experiments showed a range of error from 0.5% to 11.2% with an average recovery of 97%.

Results

PROPHYLACTIC STUDY

Total Blood Loss—The mean pre-insertion blood loss for the 28 women in the untreated group was 42.7 ml, while for the treated group it was 43.0 ml (table II). After insertion of the IUD the menstrual loss for the control group rose to a mean of 121.1 ml, decreasing to 81.6 ml by the eighth post-insertion period. By contrast the treated group showed a slight rise to 54.1 ml, falling only slightly with time, except for the two non-treatment cycles, when the blood loss rose to 78.4 and 84.4 ml respectively, which was similar to that in the untreated group. The difference in losses between the EACA group during treatment and the control group was highly significant ($P < 0.001$).

Duration of Periods—Both the treated and control groups showed a significant increase in the duration of menses after insertion of the IUD ($P < 0.005$) with no significant difference between the groups (table III).

Intermenstrual Bleeding—The number of days on which intermenstrual bleeding ("spotting") occurred was recorded on "menstrual calendar" cards kept by the patients. Altogether 16 women in the treated group and 18 in the control group experienced spotting (table IV). With successive cycles after insertion of the IUD, however, significantly fewer women in the treated group continued to have intermenstrual spotting ($P < 0.05$). Furthermore, the total number of days of spotting was significantly lower in the treated women ($P < 0.01$; Wilcoxon's signed rank test).

THERAPEUTIC STUDY

The 35 women with IUD menorrhagia given EACA had a mean menstrual loss before treatment of 100.4 ml (table V). This was reduced to 41.1–49.8 ml during treatment, returning to the previous levels when treatment was stopped. The reduction was highly significant ($P < 0.001$; Student's *t* test on logarithmic values).

SIDE EFFECTS

In 49 (77.8%) of the 63 women taking EACA mild to moderate side effects occurred. The commonest were nausea, headache, and dizzi-

ness. The following three patients were unable to continue the trial because of side effects.

Case 1—A 31-year-old para-1 had nausea but not vomiting during the first treatment period, which lasted five days, and in view of this she discontinued treatment.

Case 2—A 32-year-old para-2 experienced severe nausea followed by vomiting and headache on the third day of the fourth cycle of treatment with EACA. She also complained of dizziness to the extent of losing her balance, and treatment was stopped.

Case 3—A 36-year-old para-1 developed gross oedema of the legs and face on the third day of treatment with EACA. Biochemical tests of renal function gave normal results and venography showed no abnormality of the venous system in the lower limbs. An allergic type of reaction was suspected. After a year she still had bilateral leg oedema. A cause-effect relationship with her EACA treatment was not established and we are not aware of any previous report of this complication.

TABLE IV—Incidence of intermenstrual bleeding in the EACA-treated women and controls

Cycles after Insertion	EACA Group (n = 28)			Control Group (n = 28)		
	No. of Women	No. of Days	Women-Days	No. of Women	No. of Days	Women-Days
Insertion -1	16	81	1296	18	90	1620
1-2	12	30	360	15	61	915
2-3	12	37	444	10	44	440
3-4	9	33	297	11	48	528
4-5	8	35	280	11	37	407
5-6	5	8	40	8	39	312
6-7	4	18	72	10	32	320
7-8	3	14	42	10	39	390
Total		256	2831		390	4932

Differences between the two groups of women were significant for numbers with intermenstrual bleeding ($P < 0.05$) and numbers of days of intermenstrual bleeding ($P < 0.01$).

TABLE V—Fall in menstrual blood loss (ml) with EACA in 35 women using various IUDs*

Cycle after Insertion	EACA Treatment					
	1	2	3	4	5	6
Arithmetic mean	100.4	41.1	48.4	49.8	90.5	83.6
SD	66.8	33.5	38.4	44.5	71.5	53.8
SE	11.3	5.7	6.5	7.5	12.1	9.1

* Lippes D (3 women), Saf-T-coil (23), Dalkon shield (6), Copper 7 (3). Significance of reduction in blood loss $P < 0.001$ (Student's *t* test with logarithmic transformation of individual values).

Discussion

A role for fibrinolysis in the pathogenesis of menorrhagia was first suggested by Whitehouse,⁶ and other workers subsequently

produced confirmatory evidence.⁷ The relevance of endometrial fibrinolysis to IUD menorrhagia was suggested by finding high fibrinolytic activity around IUDs removed from women with excessive bleeding.⁸ The use of EACA in the treatment of IUD menorrhagia therefore has a rational basis. Our results show that EACA reduces menstrual blood loss in women using IUDs. This effect is limited to the days of treatment and no carry-over to the next period was found. The duration of periods does not appear to be affected. A steady rise in the menstrual loss during treatment periods appeared to be due to failure to maintain adequate dosage in successive periods.

We concluded that EACA is effective in controlling IUD menorrhagia and that intermenstrual bleeding is reduced.

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Vitamin E deficiency and platelet functional defect in a jaundiced infant

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Summary

A 16-month-old infant with hepatic fibrosis, cholestasis, and chronic jaundice had signs of vitamin E deficiency, including mild acanthocytosis, thrombocytosis, increased peroxide haemolysis, and absent serum vitamin E. Abnormal prothrombin consumption and platelet ristocetin aggregation suggested the presence of defective platelet function, and correction studies indicated that this was due to a plasma defect. The abnormality was corrected by treatment with vitamin E, and the findings suggest a possible role of this vitamin in platelet reactions.

Introduction

Little is known about the role of Vitamin E in thrombopoiesis or platelet function. High platelet counts are a recognized feature of vitamin E deficiency in premature infants and there is evidence suggesting that vitamin E may play a part in platelet aggregation induced by hydrogen peroxide.¹ We report here on an infant with hepatic fibrosis and cholestatic jaundice who developed vitamin E deficiency and impaired platelet function.

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Case Report

A male infant weighing 3.55 kg was born by forceps delivery in May 1973 after a full-term pregnancy. The haemoglobin level at birth was 20.5 g/dl; his blood group was B+; and the direct antiglobulin test on cord blood was negative. The mother was a primigravida, her blood group was B-, but the antibody screen at 32 weeks' pregnancy gave negative results. The only medication received during pregnancy was oral iron.

Clinical examination of the infant at birth showed no abnormality. On day 2 twitching of face and limbs was noted. This subsided without treatment. On day 6 jaundice was noted. The serum bilirubin was 61.5 μ mol/l (3.6 mg/100 ml), serum aspartate aminotransferase (SGOT) 38 IU/l, serum alanine amino-transferase (SGPT) 36 IU/l, and serum alkaline phosphatase 55 IU/l. On day 16 he was still jaundiced and the serum bilirubin was 46.2 μ mol/l (2.7 mg/100 ml). The Wasserman reaction and virus agglutination tests were negative. Sweat sodium concentration was 17 mmol/l. The thyroid profile was normal. He was treated with prednisone 7.5 mg every six hours but the jaundice persisted.

At six weeks he was transferred to the University Hospital of Wales. He was pale, feverish, and jaundiced with hepatomegaly but no splenomegaly. The urine was dark and stools pale but not completely colourless. Investigations showed: haemoglobin 11.9 g/dl, reticulocytes 3%, platelets 699×10^9 /l, total bilirubin 85.5 μ mol/l (5.0 mg/100 ml), conjugated bilirubin 17.1 μ mol/l (1 mg/100 ml), SGOT 126 IU/l, SGPT 158 IU/l, and alkaline phosphatase 37 IU/l. The urine contained no excess urobilinogen or bile salts. Serum immunoglobulins were normal. The Rose-Bengal excretion test showed that 18% was excreted in 48 hours and 21.6% in 72 hours. Though excretion was impaired it was more than that usually found in biliary atresia. Hepatitis was diagnosed and no specific treatment was recommended.

At 12 months his general condition remained the same but with slight clinical improvement; hepatomegaly of 1 cm persisted and he had developed pruritus. Serum bilirubin concentration was 58 μ mol/l (3.4 mg/100 ml), SGOT 274 IU/l, alkaline phosphatase >150 IU/l, haemoglobin 10.1 g/dl, and reticulocyte count 4%. Oral iron treatment was begun and the haemoglobin rose to 11.0 g/dl. Because of the persistent jaundice laparotomy was considered for liver biopsy and the exclusion of biliary obstruction.

At 16 months, before laparotomy, several investigations were performed. Ultrasonic scan showed a normal gall bladder. Serum bilirubin concentration was 80.3 μ mol/l (4.7 mg/100 ml), SGOT 247 IU/l, and alkaline phosphatase 160 IU/l. Blood urea and electrolytes were normal. Tests for hepatitis-associated antigen and antibody