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The effect of parenteral iron administration in the control of anaemia of pregnancy

BY S. K. SOOD,* K. RAMACHANDRAN, KAMLA RANI, V. RAMALINGASWAMI, V. I. MATHAN, J. PONNIAH AND S. J. BAKER†

Department of Pathology and Biostatistics, All-India Institute of Medical Sciences, New Delhi and Wellcome Research Unit, Christian Medical College Hospital, Vellore, Tamil Nadu, India

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1. The relative efficacy of oral and parenteral iron administration in the prophylaxis and treatment of Fe-deficiency anaemia of pregnancy has been studied.

2. Intravenous administration of Fe by total dose infusion of Fe dextran was not superior to oral Fe 120 mg/d, 6 d/week for 10–12 weeks.

3. Intramuscular Fe dextran, 100 mg twice per week for 10–12 weeks, produced a significantly greater rise in mean haemoglobin concentration than oral Fe therapy.

4. The superiority of intramuscular Fe as compared with intravenous Fe is probably related to the different handling of the Fe dextran by the reticulo-endothelial system.

5. In spite of the better response to intramuscular Fe dextran, it is not recommended for public health practice because of the risks associated with its use and the much higher cost of the preparation and its delivery.

In a previous study (Sood *et al.* 1975) it was observed that even after 10–12 weeks of daily oral supplementation with 120–240 mg iron together with pteroylmonoglutamic acid and cyanocobalamin, a substantial proportion of pregnant women had a haemoglobin concentration of less than 110 g/l; a serum Fe below 600 μg/l and transferrin saturation below 15% suggesting persisting Fe deficiency. It was suspected that this may have been due to an inadequate absorption of Fe. The present investigation was therefore undertaken to compare the effects of oral and parenteral Fe supplementation.

MATERIALS AND METHODS

As in the previous studies (Sood *et al.* 1975; Mathan *et al.* 1979), this trial was also conducted in both Delhi in northern India and Vellore in southern India. Pregnant women who agreed to collaborate in the study were admitted to the trial at 26±2 weeks of gestation. Women with chronic illnesses, with haemoglobin concentration less than 50 g/l, and those who had received haematinics during the last 6 months were excluded. The participating women were divided into one of the three strata according to their haemoglobin concentration (50–79; 80–109; 110 or above). Within each stratum subjects were allocated at random to one of the following treatment groups: (1) oral ferrous sulphate (Fersolate; Glaxo Laboratories, India, Ltd) providing 120 mg elemental Fe, given once per day 6 d/week; (2) Fe dextran complex (Imferon; Tata Fison, India, Ltd) providing 100 mg Fe given intramuscularly twice per week; (3) Fe as in group 1+pteroylmonoglutamic acid (5 mg/d, 6 d/week)+cyanocobalamin (100 μg intramuscularly once per 14 d); (4) Fe intramuscularly as in group 2+pteroylmonoglutamic acid+cyanocobalamin as in group 3; (5) Fe

* Present address: Faculty of Medicine, University of Garyounis, P.O. Box 1451, Benghazi, Libya.
† Present address: Department of Medicine, St Boniface Hospital, Winnipeg, Manitoba, Canada.

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Table 1. *Mean initial and final haemoglobin and packed cell volume values in five groups of pregnant Indian women given different treatments*

Treatment group	Treatment	No. of women	Haemoglobin (g/l)					Packed cell volume				
			Mean		Mean of individual differences	SE of mean of differences	Statistical significance of difference: *P* (paired *t* test)	Mean		Mean of individual differences	SE of mean of differences	Statistical significance of difference: *P* (paired *t* test)
			Initial	Final				Initial	Final			
1	Oral Fe	24	103·2	114·4	11·2	2·143	< 0·001	33·33	36·00	2·67	0·5635	< 0·001
2	Intramuscular Fe	30	100·5	120·7	20·2	2·539	< 0·001	32·66	32·73	5·13	0·5637	< 0·001
3	Oral Fe+PGA+ cyanocobalamin	35	109·9	120·5	10·6	2·698	< 0·001	34·83	37·54	2·71	0·6649	< 0·001
4	Intramuscular Fe+PGA+ cyanocobalamin	30	103·9	121·8	17·9	2·537	< 0·001	32·93	37·60	4·67	0·7676	< 0·001
5	Intravenous Fe +PGA+ cyanocobalamin	32	97·2	108·8	11·6	2·638	< 0·001	32·65	36·15	3·50	0·6091	< 0·001
Total		151	103·1	117·4	14·3			33·31	36·39	3·08		

PGA, Pteroylmonoglutamic acid.

Table 2. *Comparison of regression lines: haemoglobin concentration after therapy* (y) v. *initial haemoglobin concentration* (x) *for five groups of pregnant Indian women given different treatments*

Source of variation ...		df	$\Sigma(x-\bar{x})^2$	$\Sigma(x-\bar{x})(y-\bar{y})$	$\Sigma(y-\bar{y})^2$	Regression coefficient	Deviation from regression		
							df	SS	MS
Within treatment group:									
Treatment group	Treatments								
1	Oral Fe	23	3617	1771	2459	0·4896	22	1592	72·36
2	Intramuscular Fe	29	5017	2047	4687	0·4080	28	3852	137·57
3	Oral Fe+PGA+ cyanocobalamin	34	6531	2322	6711	0·3555	33	5885	178·33
4	Intramuscular Fe+PGA+ cyanocobalamin	29	5093	1305	2758	0·2562	28	2424	86·57
5	Intravenous Fe+PGA+ cyanocobalamin	31	4124	938	2302	0·2274	30	2089	69·63
							141	15842	112·35
Pooled within treatment groups		146	24383	8383	18917	0·3438	145	16035	110·59
						Differences between slopes	4	193	48·25
						Over-all comparison between slopes $F < 1$ (df 4141) not significant			
Total		150	27312	10565	22744	0·3868	149	18657	125·12
						Comparison between regression lines F 3·133 (df 8141) $P < 0·01$			

PGA, Pteroylmonoglutamic acid; SS, sum of squares; MS, mean square.

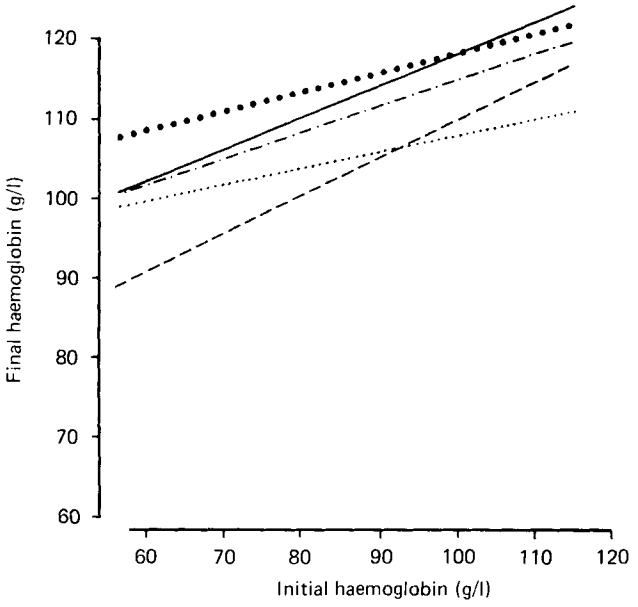

Fig. 1. Regression lines of final haemoglobin concentration (g/l) *v.* initial haemoglobin concentration (g/l) for the five groups of pregnant Indian women given different treatments. – – –, Group 1 given oral iron; ——, group 2 given intramuscular iron; – · –, group 3 given oral iron, pteroylmonoglutamic acid and cyanocobalamin; . . ., group 4 given intramuscular iron, pteroylmonoglutamic acid and cyanocobalamin; ....., group 5 given intravenous iron, pteroylmonoglutamic acid and cyanocobalamin.

dextran complex (mg) given intravenously as a single total dose infusion according to the formula (15 – patient's haemoglobin (g/dl)) × (body-weight (kg) × 3) + pteroylmonoglutamic acid + cyanocobalamin as in group 3.

Treatment was continued for 10–12 weeks. Ingestion of tablets was supervised by public health nurses. No extraneous Fe or vitamin supplements were received by these women. The total dose infusion was given under medical supervision in hospital. A test dose was first given and then if no adverse effects occurred, the calculated dose was given by slow infusion over a period of 4–6 h.

Venous blood samples were taken before treatment was started and at least 48 h after the last injection or tablet was given. Haemoglobin was estimated by the cyanmethaemoglobin method (Dacie, 1956) checked at regular intervals with an international reference standard (provided by Dr S. M. Lewis). Packed cell volume was determined by the microhaematocrit method.

Ethical considerations. All women were aware that they were participating in a therapeutic trial and were free to withdraw from the study at any point without detriment to the antenatal care offered to participants.

RESULTS

Initial (26 weeks) and final (36–38 weeks) mean haemoglobin concentration, mean packed cell volume, mean of individual differences of the two values and their standard errors, in each of the groups, are shown in Table 1. In each group the mean haemoglobin concentration and mean packed cell volume showed a significant rise. The increase was more marked in the groups receiving intramuscular Fe.

Table 3. *Estimated regression function and expected mean haemoglobin concentration (g/l) after therapy* (y) v. *initial haemoglobin concentration* (x) *for five groups of pregnant Indian women given different treatments*

Treatment group	Treatment	Estimated regression function	Expected mean haemoglobin (g/l) after therapy with initial haemoglobin of: 60	70	80	90	100	110
1	Oral Fe	$y = 63{\cdot}870 + 4{\cdot}896\ x$	93·2	98·1	103·0	107·9	112·8	117·7
2	Intramuscular Fe	$y = 79{\cdot}695 + 4{\cdot}080\ x$	104·2	108·3	112·3	116·4	120·5	124·6
3	Oral Fe + PGA + cyanocobalamin	$y = 81{\cdot}427 + 3{\cdot}555\ x$	102·8	106·3	109·9	113·4	117·0	120·5
4	Intramuscular Fe + PGA + cyanocobalamin	$y = 95{\cdot}177 + 2{\cdot}562\ x$	110·5	113·1	115·7	118·2	120·8	123·4
5	Intravenous Fe + PGA + cyanocobalamin	$y = 86{\cdot}686 + 2{\cdot}274\ x$	100·3	102·6	104·9	107·2	107·4	111·7

PGA, Pteroylmonoglutamic acid.

In each of the groups the magnitude of the rise in haemoglobin concentration after therapy was inversely related to the initial haemoglobin concentration, and the regression of the final haemoglobin values *v.* initial haemoglobin values in different groups appeared heterogeneous. Even though the slopes of regression did not reveal a difference, the regression lines were found to be significantly different from each other ($P < 0.01$). The results are presented in Table 2 and Fig. 1. In view of this, separate regression functions for each of the treatment groups were estimated and on the basis of initial haemoglobin concentration the expected haemoglobin concentration after therapy was calculated (Table 3). The analysis allows for the differences in the initial haemoglobin concentration of the groups, and clearly demonstrates the differences in the effectiveness of the various therapeutic regimens. Thus a woman who started with a pretreatment haemoglobin concentration of 70 g/l was likely to show a rise of approximately 28·1 g/l with oral Fe. Addition of pteroylmonoglutamic acid and cyanocobalamin further enhanced this beneficial effect and the expected rise in haemoglobin with an initial haemoglobin concentration of 70 g/l was 36·3 g/l. Fe administered by the intravenous route together with cyanocobalamin and pteroylmonoglutamic acid produced a similar rise in haemoglobin concentration. Intramuscular Fe produced a greater increase in haemoglobin concentration as compared to oral or intravenous Fe, the expected value in haemoglobin concentration with an initial haemoglobin of 70 g/l being 43·1 g/l.

The percentage of women with persisting anaemia (haemoglobin less than 110 g/l) at the end of the period of supplementation in groups 1–5 was 33·3, 16·7, 20·0, 6·7 and 50·0 respectively.

The mean cell haemoglobin concentration did not change significantly except in group 4 where the mean initial value of 31·42 increased to the mean final value of 32·22 ($P < 0.001$).

No adverse reactions were seen in the groups receiving intramuscular Fe, but two of the women in the group receiving intravenous Fe developed severe delayed allergic reaction several hours after the end of the infusion. Both women recovered, but the second reaction was so severe that it was judged unethical to continue this portion of the study.

DISCUSSION

This study confirms the previous findings that there is a high prevalence of anaemia in pregnant women in India (Sood & Ramalingaswami, 1968; Yusufji *et al.*, 1973); that Fe supplementation raises the mean haemoglobin concentration (Basu *et al.* 1973; Sood *et al.* 1975; Mathan *et al.* 1979), and the addition of pteroylmonoglutamic acid and cyanocobalamin to Fe supplement produces a greater rise in haemoglobin concentration than Fe alone (Sood *et al.* 1975; Mathan *et al.* 1979).

In the present study the mean rise in haemoglobin concentration in the women in group 1 given oral Fe was 11·2 g/l over a period of 10–12 weeks. If 3·7 g/l, the expected mean decrease in haemoglobin which would have occurred if no Fe had been given (Sood *et al.* 1975), is added to the value for the mean rise (11·2 g/l), the total mean rise in haemoglobin concentration occurring during this period was 14·9 g/l. Assuming a blood volume of 5 l, this equals a daily haemoglobin rise of 0·19 g/l, a daily Fe utilization of 3·24 mg and an Fe absorption of approximately 2·7% from a daily intake of 120 mg. Similar calculations for the women in group 2 who received intramuscular Fe indicate a considerably greater mean daily haemoglobin rise of 0·31 g/l and a daily Fe utilization of 5·18 mg.

The great majority of investigators have shown that the rise in haemoglobin concentration in Fe-deficient subjects, including pregnant women, is identical whether the Fe is given orally or parenterally (Pritchard & Hunt, 1958; Sturgeon, 1959; McCurdy, 1965; DeLeeuw, *et al.* 1966). However, Cope *et al.* (1956), while finding no difference between the two routes of administration in post-natal women, obtained a better response in twenty-one pregnant women given intramuscular Fe than in 133 pregnant women given oral Fe (an average

daily percentage increase in haemoglobin of 1·2 *v.* 0·9). Unfortunately Cope *et al.* (1956) give no statistical analysis of their results, nor the data to enable this to be done, therefore the significance of their finding is not clear. The greater rise in mean haemoglobin concentration obtained with intramuscular Fe, in the present study, indicates that the unsatisfactory response to oral Fe therapy is attributable to the insufficient absorption of orally administered Fe to meet the body's needs in the available period of time. A similar conclusion was also reached in a previous study in this series and the possible reasons for this poor absorption were discussed (Sood *et al.* 1975).

It is usually thought that the response to parenteral Fe is the same whether it is given intramuscularly or intravenously (Will & Groden, 1968). The greater rise in the mean haemoglobin concentration in groups 2 and 4 (given Fe dextran by intramuscular route) as compared to group 5 (given Fe dextran by total dose infusion) was therefore surprising. The total dose given intramuscularly was approximately 2000 mg Fe as compared to approximately 1000 mg Fe by the intravenous route. However, it is difficult to explain the difference in the rise in the mean haemoglobin concentration just on the basis of the difference in the total dose. Even if 0·50 of the Fe administered intravenously had been available, approximately 150 g haemoglobin should have been synthesized during this period which would have produced a rise in haemoglobin concentration similar to that seen in the women receiving Fe intramuscularly. It has been observed that the clearance of Fe dextran administered by the intravenous route is much faster than when given by the intramuscular route (Will, 1968; Will & Groden, 1968; McCurdy, 1970). This is apparently due to a slow uptake of Fe from the site of intramuscular injection. However, after its appearance in the circulation, the subsequent processing of Fe dextran is identical in both instances. It has been demonstrated that a proportion of Fe dextran administered intravenously is sequestered in the reticulo-endothelial system (RES) and becomes unavailable for haemoglobin synthesis despite continued Fe deficiency (Henderson & Hillman, 1969). This effect seems to be dose and time dependent. The larger the dose, the greater the amount of Fe dextran that remains in the RES, and the longer it stays there, the less available it becomes for haemoglobin synthesis. As the intramuscular Fe dextran is given in small and repeated doses and is released at a much slower rate, it is likely that its period of retention in the RES is shorter and its availability to the erythron is greater. This may explain the difference in the rise in haemoglobin between the two groups.

This study highlights the difficulty of providing adequate amounts of supplemental oral Fe during the course of pregnancy to women who start pregnancy with severe degrees of Fe deficiency. There is an urgent need for the development of a cheap oral Fe preparation which will provide larger amounts of available Fe without increasing the prevalence of side effects. Clearly, the relatively high cost of the preparation and delivery of intramuscular Fe and the prevalence of adverse and even fatal side effects of Fe dextran (Becker *et al.* 1966; Jacobs, 1969; Morrow, 1973) make it unsuitable for public health use. However, a safe, cheap parenteral preparation which could provide 1 g available Fe in one injection could have an important role in the treatment and prophylaxis of anaemia of pregnancy. The recently-available Fe poly(sorbitol-gluconic acid) complex (Fielding, 1977) (Ferastral) which, given intramuscularly in two sites, can provide up to 500 mg Fe at one treatment, may be an improvement on previously-available preparations although experience with its use in field situations is still limited.

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