MASSIVE IRON THERAPY IN ANAEMIA*

by

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Anaemia is one of the commonest complications encountered in women in our part of the world. It is still a major problem and takes a heavy toll of maternal and foetal life. The treatment of mild and moderate anaemia is not difficult but the real problem is to treat severe anaemia of pregnancy. Such anaemic patients die during or a few days after labour. A rapid and successful treatment has to be instituted to avoid the accident during this period. Attempts have been made in recent years to treat such patients by intravenous iron or exchange transfusion of packed blood cells. An assessment of the treatment of severe anaemia with intravenous iron and dextran complex (Imferon) has been made in this paper. Patients of congestive heart failure and of kidney and liver damage were excluded.

The following investigations were carried out in the anaemic patients in order to ascertain the type and severity of anaemia: — blood haemoglobin estimation, peripheral blood smear, leucocyte lobe average, bone marrow smear, serum iron level, serum protein level, estimation of mean corpuscular haemoglobin, estimation of mean corpuscular haemoglobin concentration, reticulocyte count, and routine examination of stool and urine.

On the basis of the above investigations the patients of iron deficiency anaemia were treated with the total dose infusion of iron dextran complex and those of dimorphic anaemia were treated with the same drug supplemented by oral or parenteral folic acid, according to the severity of the condition. Protein was, however, given as a routine to all patients.

The total dosage of iron dextran complex was calculated according to the following formula:

$$\frac{0.3 \times W \times (100 - \text{Haemoglobin}\%)}{50} = \text{ccs. of Imferon.}$$

(W stands for weight of the patient in lbs.).

Precautions were taken before infusion in order to avoid reaction and wastage. Anti-allergic drugs were in-

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jected and blood pressure and pulse were recorded before infusion. A test dose consisting of three drops of iron dextran complex mixed with two ml. of 5% glucose solution was then slowly injected by the intravenous route. The total calculated dose was now added to a pint of the diluent in order to avoid high concentration which will cause toxic reactions and thrombophlebitis. In practice only 25 ml. of iron dextran complex was added to a pint (540 ml.) of the diluent. This made a 5% solution of iron-dextran complex volume per volume in 5% glucose solution. If the total calculated dose of iron dextran complex exceeded 25 ml., the extra dose was added to another bottle, but the strength of iron dextran complex in 5% glucose solution remained the same. Hundred mg. of hydrocortisone hemisuccinate and 10 ml. of 10% calcium gluconate solution were added to the infusion. The infusion was administered at the rate of 20 drops per minute for half an hour and 40 drops per minute thereafter.

It appears from literature that iron of the iron dextran complex is removed from circulation by the Kupffer cells of the liver and the dextran is metabolized or excreted. Iron is bound up with the protein moieties to form ferritin, haemosiderin and transferrin. The iron is now in such a form that it can be readily utilised by the body for formation of haemoglobin and for replenishing the various iron depots. No iron is excreted and nearly all is utilised by the body.

The response to the therapy was judged by estimating the serum iron level 24 hours after the infusion and at weekly intervals thereafter. The increase in haemoglobin was estimated at weekly intervals for four weeks and reticulocytosis was assessed by taking the reticulocyte count on every alternate day for 14 days.

Results

Forty-two obstetrical (including 12 puerperal) and 18 gynaecological patients were subjected to the treatment. Of the 42 obstetrical patients two had pre-eclampsia and two others had postpartum eclampsia; 40 of these patients had dimorphic anaemia and only two had iron deficiency anaemia. All the 18 gynaecological patients, however, had iron deficiency anaemia.

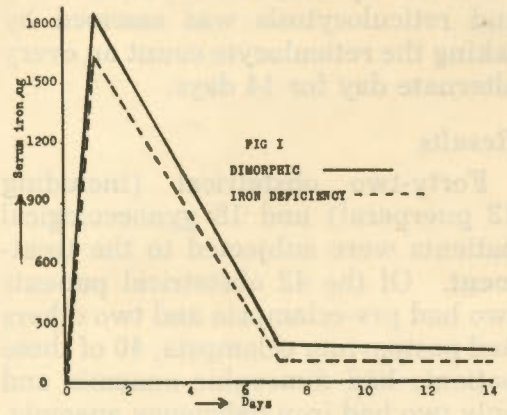
Mobilization of serum iron

In the 40 patients of dimorphic anaemia the initial serum iron level was in the range of 30-80 μg/100 ccs. of blood. The total dosage of iron infused varied between 2100 mg. to 3000 mg. The level of serum iron 24 hours after infusion varied between 700 μg-3000 μg/100 ccs. of blood. The serum iron sharply fell to the range of 80-300 μg/100 ccs. in one week and to 80-250 μg/100 ccs. in two weeks.

In the 20 patients of iron deficiency anaemia the initial serum iron level was in the range of 20-80 μg/100 ccs. The total dose of iron infused was 1000 to 2500 mg. The level of serum iron after 24 hours was in the range of 750-2500 μg/100 ccs. Thereafter the serum iron sharply fell to the level of 75-160 μg/100 ccs. in one week and to 60-160 μg/100 ccs. in two weeks.

The trend in the rise and fall in the serum iron level in the dimorphic and iron deficiency anaemia was

about the same as graphically illustrated in Fig. I.



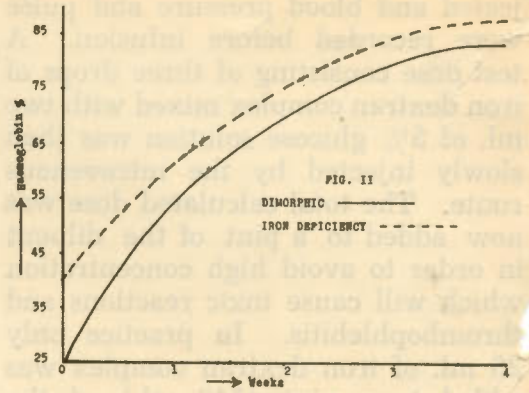
Increase in haemoglobin level

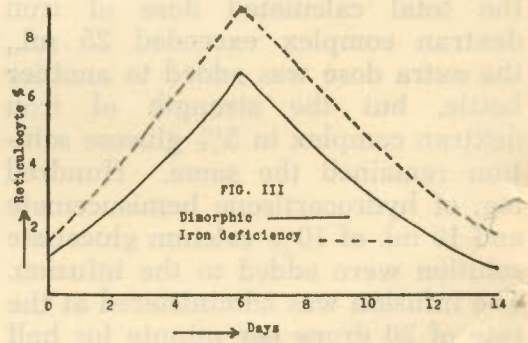
In the 40 patients with dimorphic anaemia the initial haemoglobin level was in the range of 20-30%. The rise in the first week varied between 20 to 30%, in the second week, between 15 to 20% and in the third week between 10 to 15%. There was no significant increase in the haemoglobin level in the fourth week.

In the 20 patients with iron deficiency anaemia the initial haemoglobin level was in the range of 20-60%. The increase in the haemoglobin level was 15 to 20% in the first week, between 10 to 15% in the second week and 7 to 8% in the third week. The trend in the rise and fall in the haemoglobin level has been graphically illustrated in Fig. II.

Reticulocytosis

As regards reticulocytosis, the initial reticulocyte count varied between 0 to 0.5% in the dimorphic anaemia and between 0 to 1% in iron deficiency anaemia. The reticulocytosis was more marked in iron deficiency than in dimorphic anaemia as graphically illustrated in Fig. III.





General condition

Twenty of the 30 pregnant patients had anasarca and the remaining 10 pregnant and the 12 puerperal patients had oedema of the feet. The oedema started subsiding on the third day and completely disappeared in 10 days. Their colour gradually returned and many of them looked completely changed. They regained strength rapidly.

Among the 30 pregnant patients the duration of pregnancy in 14 patients varied between 28 to 32 weeks, in 12 patients between 32 to 36 weeks and the remaining 4 were at term. Two of the 14 patients went

into labour prematurely four days after infusion. There was, however, no post-partum haemorrhage. The premature babies did not appear to have any adverse effect of the iron dextran infusion. Among the 12 patients in the next group five went into labour two days after infusion at the 34th week and had uneventful delivery. One patient, however, also at the 34th week of pregnancy went into labour only 24 hours after infusion and died on the fourth day of delivery. The death was not attributable to iron infusion. The remaining patients who survived continued to improve despite premature labour.

There were two patients of pre-eclampsia. Their blood pressure was 140/100 and 160/100 mm Hg. respectively. They were being treated with chlorpromazine tablets. There was a temporary fall in their blood pressure due to the treatment and the blood pressure had the tendency to go up again to the original level. When these patients were subjected to the iron dextran complex therapy there was a sustained fall in their blood pressure to 130/80 and 140/90 mm Hg. respectively. With disappearance of oedema and improvement in anaemia, their blood pressure came down to 120/80 mm Hg. and was maintained at that level during the rest of the pregnancy.

Two patients who had been admitted with postpartum eclampsia were treated for the condition. Though the fits had ceased the blood pressure remained high (150/100 and 160/90 mm Hg. respectively). Ten days after the cessation of fits they were subjected to intravenous iron therapy. The blood pressure came down to 120/90 and 140/80 mm Hg. respectively 48 hours after the infusion and remained normal thereafter.

One of the 18 gynaecological patients had blood pressure of 160/100 mm Hg. at the start of infusion. She had not received any hypotensive drug. The blood pressure came down to 140/90 mm Hg. in the morning following the infusion. The blood pressure remained 140/90 mm Hg. for four days but it again rose to 160/100 mm Hg. She was a patient of chronic hypertension.

Side-effects

Ten patients complained of rigor. Headache, nausea and vomiting occurred in 10 other patients. The patients with postpartum eclampsia complained of pain in the joints and muscles. In one case there was dyspnoea and feeling of compression in the chest and as soon as the reaction occurred the infusion was discontinued.

Discussion

Nissim (1947) introduced saccharated iron oxide (the first intravenous iron therapy) in the treatment of severe anaemia, but as there were toxic reactions in dosages exceeding 250 mgs. the drug fell into disrepute. One year later Anger *et al* (1948) introduced an improved preparation, dextriferron (iron dextrin) for intravenous use and it was claimed that as much as 500 mgs. of the new preparation could be injected safely without any reaction. More recently Anklesaria and Thakore (1966) have tried intravenous saccharated iron oxide in iron deficiency anaemia without adverse effect. A new com-

pound, iron dextran complex, was also found to be effective when given intramuscularly (Baird and Podmore, 1954). Intramuscular use of iron was abandoned for a time for fear of sarcoma which was produced in animal experiments. As the fear of sarcoma in the human being was unfounded, intramuscular injection came into use again during the last six years. During this period many workers, such as, Basu (1963, 1965), Bonnar (1964), Chatterjee *et al* (1965), Frampton (1965), Gartlan (1964), Lane (1963), Marchasin and Wallerstein (1964) and Pathak (1966) have used iron dextran complex intravenouly and have found encouraging results.

As one pint of blood raises the haemoglobin by only 6%, several pints of blood would be required to raise the haemoglobin of such patients to a satisfactory level. The method is costly. Procuring so much of blood is also not often possible. Moreover, blood transfusion has its attendent reactions. For these reasons the total dose iron therapy is a better alternative and can completely replace blood transfusion in such patients. In addition to the iron supplied through infusion of iron dextran complex it is necessary to supply protein to almost all patients on account of the associated hypoproteinaemia. Moreover, it is also necessary to supply the R.B.C. regenerative constitutents like folic acid and vitamin B_{12} where indicated.

A rapid haematological response occurred in the patients in the first week, and the lower the initial haemoglobin level the quicker was the rise in the haemoglobin level. The rapid increase in the haemoglobin level became a life-saving measure. The increase in haemoglobin continued steadily though at a slower rate and in the fourth week the haemoglobin level had reached the acceptable mark (70 to 80%). The reticulocyte response was more marked in iron deficiency anaemia than in the dimorphic anaemia. As regards serum iron there was a sharp rise within 24 hours of the infusion and thereafter the serum iron level started falling off rapidly. It took two weeks for the serum iron to come to normal. According to Marchasin and Wallerstein (1964) serum iron level reached a peak of 95,000 μg/100 ccs. in 10 minutes and then declined to 150 to 200 μg/100 ccs. in 2 to 4 weeks. This would indicate that mobilization of serum iron to the body depots begins to take place immediately after infussion and in 24 hours much of the iron might have gone to the body depots already.

Toxaemia of pregnancy is considered to be a contra-indication to intravenous iron therapy by some workers. In the present series four patients with toxaemia (two of pre-eclampsia and two of postpartum eclampsia) were treated with the total dose iron therapy without any adverse effect. The effect of intravenous iron therapy on blood pressure has not been analysed in human beings. Goldberg (1958) observed a drastic fall in blood pressure after a rapid intravenous iron dextran infusion in experimental animals. We noted a fall in blood pressure in two patients with pre-eclampsia and two of postpartum eclampsia. We feel that hypertension in pre-eclamptic toxaemia is no contra-indication and

that with the cure of anaemia, the placental ischaemia is relieved, resulting in restoration of blood pressure to the normal range. The fall may also be attributed to diuresis which in turn causes reduction in the interstitial fluid tension.

In one gynaecological patient suffering from chronic hypertension the fall in the blood pressure could not be maintained. The effect of iron dextran complex on the blood pressure of human beings, however, remains an open question to be answered after closer examination.

Reactions to iron dextran infusion have been variously described as mild to severe by different workers. Thus Clay et al (1965) noted moderately severe reactions including nausea, vomiting, faintness, tinnitus, stiffness, flushing, pallor and clamminess of hands in 6 of his patients but he remarked that the reactions subsided on reassurance and infusion could be completed without incident. Basu (1965) who used 8% solution of iron-dextran had one case of severe thrombophlebitis and three other mild cases of phlebitis. In the present series pain in the joints and muscles was complained of by two patients with postpartum eclampsia. One patient had severe reaction, with dysponea and a feeling of compression in the chest and to avoid any untoward effect the infusion had to be discontinued. Rigor, headache, nausea, vomiting including slight temperature were noted in 20 patients after a pint or so of the fluid had been infused. However, after discontinuing infusion for half an hour these reactions had subsided and the infusion could be completed thereafter without any incident.

In conclusion, it may be remarked that intravenous iron dextran complex is effective, economical and safe for rapid restoration of the haemoglobin level in severely anaemic pregnant and non-pregnant women.

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