THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (July–August 2015) 65(4):230–235
DOI 10.1007/s13224-014-0588-2

ORIGINAL ARTICLE

An Observational Study on the Use of IV Iron Sucrose Among Anaemic Pregnant Women in Government Healthcare Facilities from Two States of India

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Received: 16 May 2014 / Accepted: 17 June 2014 / Published online: 10 July 2014
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Abstract

Background/Purpose of the Study In India oral iron tablets for anaemia have been distributed through the health system since many years, but there has been no significant change in the burden of anaemia. The objective of the present study was to capture the existing practices on the use of intravenous iron sucrose (an alternative treatment for anaemia) in the public health system in two states of India (Tamil Nadu and Uttar Pradesh).

Methods An observational study in the form of a registry was maintained for 3 months at purposively chosen public health facilities in the above-mentioned states of India.

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Anaemic pregnant women ($n = 764$) who were given intravenous iron sucrose during the antenatal or post-partum period were included in the registry. Information was collected on severity of anaemia at which intravenous iron sucrose therapy was initiated, the dose and schedule given and any adverse events noted during and immediate post-infusion period.

Results 99 % of the infusions were given as slow infusion over a mean duration of 30 min, diluted with 0.9 % sodium chloride. The mean haemoglobin level at the time of start of intravenous therapy was 8.3 gm/dl. In Uttar Pradesh, 46 % of women received only one dose of iron sucrose in contrast with 15 % in Tamil Nadu.

Conclusions Although intravenous iron sucrose is commonly used in pregnant anaemic women, standard protocols and guidelines for its usage are lacking. These need to be formulated before scaling it up across public health facilities in India.

Keywords Anaemia · Haemoglobin · Iron sucrose · Oral iron · Pregnancy

Introduction

Anaemia is one of the commonest medical illnesses during pregnancy. In India, every second pregnant woman suffers from anaemia [1]. The prevalence of severe anaemia ranges from 2 to 20 % as estimated by National surveys and several observational studies [2–4] The risk of maternal death and morbidity increases with increasing severity of anaemia [5–7] The most common cause of anaemia in India is nutritional, followed by infections [8, 9]. The treatment of anaemia among pregnant women in the public health care system is mainly through oral supplementation of iron [10]. Due to poor compliance and late reporting of women for antenatal care (ANC), many have low haemoglobin (Hb) levels at the time of delivery. Besides poor maternal iron stores have shown to affect neonatal outcomes and early child development [11].

Studies have shown that intravenous iron sucrose (IS) is effective in raising haemoglobin faster and in replenishing the iron stores [12–16] However, these studies are very small and safety data are not very well established among pregnant women. In India, this preparation has been in use in private and public health facilities in some states for the past few years. There is, however, very little data from the health care system about the number of women who receive IS, the level of anaemia at which it is administered, the personnel administering the drug and the occurrence of any adverse effects during or after administration.

In order to capture the patterns of use and administration of the drug, a registry was proposed to be set up in Tamil Nadu (TN) and Uttar Pradesh (UP) for a period of three months. The aim of the registry was to gather information on the level of anaemia at which IS therapy was initiated, the average total dose of IS administered, the dosage schedule, type of health care professional administering the infusion, method and duration of infusion (slow/bolus) and proportion of women developing major and/or minor adverse reaction during and after administration of IS.

Materials and Methods

The study was undertaken in various public health facilities in two states of India, TN and UP. In TN, the drug is made available through public health facilities by Tamil Nadu Medical Services Corporation (TNMSC) and is in use for the past 4 years. In UP, this medication is obtained from local purchase and is not available in routine hospital supply by the government.

In TN, a total of 84 centres from the two districts of Tiruvallur and Vellore were chosen for the study by their respective Deputy Director of Health Services (DDHS) of the district, which included Block PHCs (Primary Health Centres), Upgraded Additional PHCs, Additional PHCs and District Hospital. The choice of the districts was purposive as suggested by the TN health department. Medical Colleges were not chosen as there was no supply of intravenous IS. From UP, Queen Mary's hospital, Chatrapati Shahuji Maharaj Medical University, Lucknow and Barabanki women's district hospital were purposively chosen as they were using intravenous IS. Based on prior information that around 4–5 women receive intravenous IS per week at block and additional PHC level in TN, it was decided to maintain this registry for 3 months in both the states. We anticipated obtaining treatment information from at least 1,000 pregnant anaemic women. All pregnant women attending the antenatal clinic or post-partum women who were given intravenous IS for anaemia were to be included in this study. Ministry of Health and Family Welfare, Delhi and State Health departments granted permission for the conduct of the registry for both the states. Ethics Committee of the Institute granted ethical clearance for the registry.

A data collection tool was developed to capture information from pregnant woman on age, period of gestation, Hb before the start of treatment, mode of administration, amount of intravenous iron given and any immediate and late adverse events. The treating physician recorded information on immediate non-fatal adverse events like chest compression, elevated blood pressure (BP), hypotension (BP <90/60 mmHg), bradycardia, syncope, rashes, anaphylactic reaction, admission to hospital and late adverse events like thrombophlebitis, back pain, gastritis,

nausea, vomiting, diarrhoea, metallic taste, headache, fever, arthralgia, myalgia, admission to hospital. The treating medical officer, resident doctor or the nurse at the sites were responsible to record the information of all consenting pregnant women who were given intravenous IS. The decision to initiate intravenous IS therapy was entirely the decision of the care provider as a part of their usual care. Training of all the participating centres was conducted before the actual data collection. Doctors and nurses from different centres were oriented towards the need for the registry and on data collection procedures. A written consent was obtained from the pregnant women for collection of data from the hospital records and during the administration of intravenous IS. For the women who were part of the registry, Hb was measured again if the last report was beyond 2 weeks from the time of initiation of the treatment. All Hb measurements were done by Sahli's method as this was the only method available. The name and personal details of the registry participants were not divulged in the data extraction form and anonymity was maintained.

Results

Data were collected from September 2011 to December 2011. Out of the 84 chosen centres in TN, only 37 centres (21 from Vellore and 16 from Tiruvallur) actively contributed to the registry. In total, data from 626 patients from TN and 138 patients from UP were included in the analysis after excluding those forms ($n = 14$) which had gross missing information. Majority of the data in TN were obtained from additional PHCs (76 %) and in UP from the district hospital (60 %).

More than 80 % of personnel administering the iron preparation were nurses in TN, but in UP the proportion was nearly equal for doctors and nurses. It is important to note that in TN around 5 % of the infusions were administered by auxiliary nurse midwifes (ANMs).

The mean age (SD) of the pregnant women was 23.7 years (3.2) and gestational age was 27.8 (5.1) weeks. A majority of women were in the third trimester when the first dose was given (61.3 % from TN and 55.9 % from UP). Primigravidae constituted a bulk of the women receiving IS (Table 1). All infusions were given during ante natal period in TN whereas in UP around 30 % of the infusions were given during the post-natal period (Table 2).

The mean (SD) Hb of the pregnant women was 8.3 g % (0.8) at the start of the infusion. The mean Hb was lower in UP (7.6 g %) with a wider variation (range 2.6–10.3) due to smaller sample size. Nine women had a Hb level of below 5 g % in UP. However, in TN the lowest Hb recorded before the start of the treatment was 6 g %. (Table 2).

As far as administration of the medication is concerned, nearly 3 % (36 out of 1,274) of infusions were by bolus in TN whereas in UP only one infusion out of a total of 246 was by bolus. The rest of them were given as slow infusion with 0.9 % NaCl. One dose of IS is equivalent to 100 gms of elemental iron. The total amount of elemental iron from intravenous IS for each woman varied from 30 to 600 g in TN and from 200 to 1,000 g in UP. In TN, 387 (61.8 %) women received two doses of IS and in UP, 45 (32.6 %) patients received two doses. The median duration of infusion was 30 min (25–40) in both the states. The median gap between 2 doses was 3 days in TN and 2 days in UP. However, 46 (5.81 %) women in total received two successive doses just after 1 day (Table 3).

A total of 20 episodes (1.2 %) of immediate non-fatal adverse events (like hypotension, nausea, vomiting, rashes, feeling of chest compression) were reported out of 1,545 infusions (Table 4). As per the records received, two (0.13 %) patients experienced suspected anaphylactic reaction during infusion. The infusion was stopped immediately following the reaction and anti-histamine and dexamethasone injections were given. No deaths were reported.

Discussion

This study was an effort to obtain information about the use and safety of intravenous IS in government setups from two states of India. Data from 764 women showed that majority of the women receiving intravenous IS had mild to moderate anaemia. Around 99 % of them received slow infusion and minor adverse effects were observed in 1.3 % of the infusions.

The gestational age of women who received the medication varied from 17 to 38 weeks of pregnancy which is similar to the period reported by Perewusnyk [13] (mean gestational period was 31.5 weeks ranging from 20 to 38 weeks). The mean gestational age reported in clinical trials conducted in India and abroad was around 22–23 weeks [14–16].

The mean Hb before start of the treatment was 8.3 g % in our study. This is consistent with the findings from other experimental studies in which the mean Hb varied from 7 to 11 [14, 15, 17, 18]. Experience from Zurich suggests that intravenous IS was indicated in pregnancy when there was a failure of response to treatment to oral iron as measured by the increase in reticulocyte count or Hb [13]. In our study, 2.6 g% was the lowest Hb level recorded. A survey of practitioners from India stated that the drug was prescribed by more than 50 % of them for cases of severe

Table 1 Characteristics of participants who were a part of the registry

Characteristics	Tamil Nadu	Uttar Pradesh	Overall
Proportion of women enrolled from each hospital type (%)	(*N* = 626)	(*N* = 138)	(*N* = 764)
Medical college	–	55 (39.9)	55 (7.2)
District hospital	1 (0.2)	83 (60.1)	84 (11)
Upgraded block PHC	62 (9.9)	–	62 (8.1)
Additional PHC	474 (75.7)	–	474 (62.1)
Block PHC	36 (5.7)	–	36 (4.7)
Upgraded PHC	53 (8.5)		53 (6.9)
Personnel administering/ total infusions (%)	(*N* = 1,285)	(*N* = 248)	(*N* = 1,533)
Medical officer	172 (13.4)	128 (51.6)	300 (19.6)
Consultant	3 (0.2)	1 (0.4)	4 (0.3)
Nurse	1,042 (81.1)	119 (48.0)	1,161 (75.7)
ANM	68 (5.3)	–	68 (4.4)
Mean age of the pregnant women (SD) (Range)	(*N* = 620)	(*N* = 138)	(*N* = 758)
	23.4 (3.1)	25.1 (3.6)	23.7 (3.2)
	(17–40)	(18–35)	(17–40)
Mean gestational age at first dose (SD) (Range)	(*N* = 592)	(*N* = 93)	(*N* = 685)
	27.8 (5.2)	27.8 (4.9)	27.8 (5.1)
	(12–38)	(17–38)	(12–38)
Gestational age (in weeks)	(*N* = 592)	(*N* = 93)	(*N* = 685)
First trimester (<12 weeks)	4 (0.7)	–	4 (0.6)
Second trimester (13–27 weeks)	225 (38)	41 (44.1)	266 (38.8)
Third trimester (28–42 weeks)	363 (61.3)	52 (55.9)	415 (60.6)
Gravidity	(*N* = 623)	(*N* = 138)	(*N* = 761)
Primi	261 (41.9)	93 (67.4)	354 (46.5)
Multi	362 (58.1)	45 (32.6)	407 (53.5)

Table 2 Level of haemoglobin of women enrolled in the study

Characteristics	Tamil Nadu	Uttar Pradesh	Overall
Mean Hb (in g %) at start of therapy (SD) (Range)	(*N* = 620)	(*N* = 137)	(*N* = 757)
	8.4 (0.6)	7.6 (1.3)	8.3 (0.8)
	(6.0 - 10)	(2.6 - 10.3)	(2.6–10.3)
Severity of anaemia (in g %)	(*N* = 620)	(*N* = 137)	(*N* = 757)
>9 g %	73 (11.7)	6 (4.4)	79 (10.4)
7.1–9 g %	533 (86)	108 (78.8)	641 (84.7)
5.1–7 g %	14 (2.3)	14 (10.2)	28 (3.7)
<5 g %	–	9 (6.6)	9 (1.2)
IV Iron given during (%)	(*N* = 626)	(*N* = 138)	(*N* = 764)
Ante-natal period	626 (100)	96 (69.6)	722 (94.5)
Post-natal period	–	42 (30.4)	42 (5.5)

anaemia though the lower limit of severe anaemia was not specified [19].

Our study reports that majority of the infusions were slow infusions after diluting 200 mg of the drug in 200 ml of saline and the median duration of infusions was 30 min. The administration of intravenous IS has shown some variations across studies. In one study, 200 mg of IS was diluted in 10 ml of 0.9 % saline and administered over 10–15 min [16]. A study from India reported giving a maximum dose of 200 mg diluted in 200 ml of saline for duration of 30 min as outpatient basis [14]. Another study reported that the drug was administered over 30 min for short infusions in in-patients and over 5–10 min bolus injection for outpatients [13]. Bayoumeu et al. [15] reported that a maximum of 200 mg was administered over 5 min per ampoule, where in for the first injection, the first 25 mgs was injected very slowly. If the dose exceeded 200 mg per injection, iron was administered by slow infusion with each 100 mg diluted in 100 ml of saline. Bhandal [17] reported giving it as slow infusion in 250 ml of saline over more than 30 min in post-natal women.

The occurrence of minor side effects was observed in 1.2 % of infusions. The observation study from Zurich reported rashes and flush as the common side effects from 0.36 % of infusions [13]. Other studies have reported unpleasant metallic taste and flushing during transfusion, vomiting, cough, pruritus and muscle pain as side effects [12, 14–18] There were two reports of non-fatal anaphylactic reactions in the current study. None of the above studies reported serious reactions. Broche reported one case of anaphylactoid shock and one case of phlebitis in his study on 43 post-natal women who recovered favourably after symptomatic treatment.

The data obtained from the participating centres were not adequate in terms of numbers and quality which could help to definitively draw conclusions about the safety or the implementation aspect of this medication. In TN, the number registered was below the expected number, due to reasons like shortage or no supply of intravenous IS, delayed communication about the registry activity, and forms not made available to the study sites in time from their respective authorities. In UP, the participating medical college hospital had five units in the obstetrics and gynaecology department. However, only one unit was advocating the use of intravenous IS and due to the busy schedule of the resident doctors we could not obtain the information as to how many of the anaemic women attending the antenatal or post-natal clinics received this therapy. So, we are not sure if the patients who were not part of this registry were different from those included. Though we visited the registry sites after one month of the

Table 3 Key findings on the administration of the drug

Characteristics	Tamil Nadu	Uttar Pradesh	Overall
Method of infusion (%)	($N = 1,274$)	($N = 246$)	($N = 1,520$)
Bolus	36 (1.3)	1 (0.4)	37 (0.9)
Slow infusion	1,238 (98.7)	245 (99.6)	1,483 (99.1)
Mean total dose of intravenous IS infused in gms (SD) (Range) per woman	($N = 625$)	($N = 137$)	($N = 762$)
	397 (133)	361 (181)	391 (144)
	(30–600)	(200–1,000)	(30–1,000)
Median duration of infusion in minutes (IQR) (Range)	($N = 1,300$)	($N = 245$)	($N = 1,545$)
	29.27 (25, 30)	30.15 (15, 40)	30 (25, 40)
	(0–210)	(13–50)	(5–120)
Number of doses of intravenous IS per patient (%)	($N = 626$)	($N = 138$)	($N = 764$)
One	94 (15)	64 (46.3)	158 (20.7)
Two	387 (61.8)	45 (32.6)	432 (56.6)
Three	145 (23.5)	24 (17.4)	169 (22.2)
Four	–	3 (2.2)	3 (0.4)
Five	–	2 (1.5)	2 (0.3)
Median gap in days between two doses (IQR) (Range)	($N = 681$)	($N = 111$)	($N = 792$)
	3 (3, 5)	2 (1, 3)	3 (2, 4)
	(1–74)	(1–32)	(1–74)
Gap between two doses (in days)	($N = 681$)	($N = 111$)	($N = 792$)
<2	135 (19.8)	73 (65.8)	208 (26.3)
3–4	371 (54.5)	30 (27)	401 (50.6)
>5	175 (25.7)	8 (7.2)	183 (23.1)

initiation of the registry, we could not verify all the data provided with the source data.

The representativeness of the study data could be affected due to two reasons. First, not all women receiving the drug during the three month period were included in the registry. 60 % of the data from UP were contributed from the district hospital. So, the representativeness of the women who have been included in the study is unclear and it may be incorrect to conclude that more women attending the district hospital received intravenous IS than pregnant women attending the medical college hospital.

The use of intravenous IS in primary health care facilities in TN and the personnel administering the medication deserves special mention. Majority of the infusions were given by doctors/nurses. However, nearly 4 % were administered by Auxiliary Nurse Midwife (ANMs) in TN. All infusions in TN were given as outpatient procedure unlike in UP where majority were given as inpatients. This could be because one-third of the women were post-natal cases.

Table 4 Immediate adverse events recorded during intravenous IS infusion

Adverse event	Frequency (%)/infusions ($N = 1,545$)
Immediate (during infusion)	
Feeling of Chest compression	2 (0.13)
Elevated BP	1 (0.06)
Hypotension (BP 90/60 mm Hg)	5 (0.32)
Syncope	1 (0.06)
Nausea	4 (0.25)
Vomiting	3 (0.19)
Rashes	2 (0.13)
Anaphylactic reaction	2 (0.13)

The only baseline haematological investigation done before administration of intravenous IS was Hb using Sahli's method. This was measured in haematology laboratory of the hospital and no standardization procedure was undertaken across labs. Actual increase in the level of Hb could not be obtained since follow up of patients after the infusion was not advised routinely or even if they were recorded there was lot of missing information. Despite the inherent limitations of the study, it has provided useful insights on current IS use.

The use of Intravenous IS therapy as a treatment of anaemia for pregnant and post-natal women seems promising. However, the facilities where this treatment modality is in use or will be implemented soon should maintain proper registries, have basic lab facilities for investigation and should have appropriate mechanisms for adverse events reporting and management. Although intravenous IS is widely used across world including India, evidence on safety in pregnant women needs to be established, especially before inclusion in the public health system as a means of addressing the problem of anaemia in pregnancy. Also, there is not enough evidence to show that administration of intravenous IS improves clinical outcomes of the mother and the infant [20]. It is thus imperative to conduct a large scale randomized controlled trial to prove its safety and effectiveness.

Acknowledgments The authors wish to acknowledge World Health Organisation, India for providing financial support for the conduct of the study. The authors also like to thank all the study participants for their contribution to the research. At last the authors like to acknowledge the contribution of Late Dr P Padmanaban during the conduct of the study.

Compliance with ethical requirements and Conflict of interest All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Written informed consent was obtained from all patients for being included in the study. Niveditha Devasenapathy,

Ranjana Singh, Premjeeth Moodbidri, Himanshu Bhushan, Sanjay Zodpey and Sutapa Neogi declare that they have no conflict of interest. Dr Sunanda Gupta was working with the funding organization when the present work was done. However, the findings and conclusions of the study are not biased.

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