Cost-effectiveness of Parenteral Iron Therapy for First-line Management of Iron Deficiency Anemia among Pregnant Women in a Natural Programme Setting in Gujarat

Outcome Report

2020-21

Regional Resource Centre for Health Technology Assessment (HTA-RRC)

Indian Institute of Public Health Gandhinagar (IIPHG)

Research Team

Principal Investigator

Dr. Somen Saha	Associate Professor, Indian Institute of Public Health Gandhinagar

Co- Investigators

Dr. Apurvakumar Pandya	Economic Evaluation Specialist, Indian Institute of Public Health Gandhinagar
Dr. Komal Shah	Assistant Professor, Indian Institute of Public Health Gandhinagar
Ms. Yogini Kandre	Programme Associate, Indian Institute of Public Health Gandhinagar
Mr. Devang Raval	Programme Associate, Indian Institute of Public Health Gandhinagar

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List of abbreviations

ADR	Adverse Drug Reaction
ANC	Antenatal care
CHC	Community Health Centre
FCM	Ferric Carboxymaltose
GDP	Gross Domestic Product
GOI	Government of India
Hb	Haemoglobin
HRQoL	health-related quality of life
ICER	Incremental Cost-effectiveness Ratio
IDA	Iron-Deficiency Anemia
I-NIPI	Intensified National Iron Plus Initiative
INR	Indian Rupee
IV	Intravenous
IVIS	Intravenous Iron Sucrose
MoHFW	Ministry of Health and Family Welfare
OI	Oral Iron
PHC	Primary Health Center
QALYs	Quality Adjusted Life Years
USD	United State Dollar
VAS	Visual Analog Scale

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Executive Summary

Maternal anemia is a major public health issue in India. The government of India recommends parenteral iron to manage moderate and severe grades of anemia. In contrast to its clinical efficacy, the cost-effectiveness of Intravenous Iron Sucrose (IVIS) and Ferric Carboxymaltose (FCM) is not yet established. This paper illustrates the protocol of health technology assessment of intravenous therapy to improve haemoglobin concentration over oral therapy. The study is being conducted in two districts of Gujarat state. The study participants were selected by a proportionate sampling method from the district. The districts were divided into four settings, i.e., rural, tribal, desert, and coastal, based on the previous year's registered pregnancy. Baseline data were collected on key outcome indicators using a mixed-method approach. The study reported a change in mean Hb level across intervention and control arms. An incremental mean change in Hb was noted in the FCM group (11.80 g/dl from 6.7 g/dl) followed by IVIS (11.45 g/dl from 8.2 g/dl) at the time of the fourth follow-up. The mean Hb was reduced from the baseline (9.55 g/dl from 9.99 g/dl) in control arm. Per beneficiary (undiscounted) cost for IVIS was INR 7,260, INR 7,185 for FCM, and INR 4,038 for OI group. We did not include FCM for cost-effectiveness analysis considerinal marginal sample size. IV iron sucrose was found to be costly but more effective than the oral therapy for the treatment of moderate and severe anaemia. The ICER was calculated at INR 783.11 which is 0.049% of the country's per capita GDP (INR 1,61,458). Further, IVIS was well tolerated as side effects are less compared to that of oral iron. Study findings on clinical efficacy remains inconclusive due to multifactorial clinical outcomes. Considering the limited sample size and lack of blinding, larger studies are needed to validate the results findings. Future studies on clinical efficacy would be critical in establishing effect of rise in hemoglobin level on maternal and birth outcomes.

Keywords: maternal anemia, oral iron therapy, IV iron sucrose, cost-effectiveness, health technology assessment, India

Introduction

Maternal anemia is a major public health issue in India. Specifically, iron-deficiency anemia (IDA) during pregnancy is a significant public health concern because of its association with perinatal mortality, preterm

birth, neonatal low-birth-weight, and maternal mortality and morbidity.[1] Moreover, in Gujarat, iron deficiency is higher (65%) among anemic women. [2] Conventionally, the first line of treatment for IDA in pregnant women is oral supplements of iron. However, oral iron (OI) therapy is associated with numerous side effects, chiefly constipation, vomiting, and epigastric discomfort, and hence the compliance to this mode of treatment is minimal. [3] Also, OI is not sufficient for the treatment of moderate and severe IDA detected during the late stage of pregnancy.[4] Through intravenous iron sucrose (IVIS) administration, parenteral therapy has emerged as an effective alternative to oral treatments in pregnant women.[5] Apart from its quick absorption, intravenous (IV) mode is also known to impart a lesser incidence of hypersensitive reactions. [6] Recently ferric carboxy maltose (FCM) has also emerged as an effective treatment for IDA during pregnancy and the postpartum periods. [7,8] Table 1 shows national guidelines for IDA treatment among pregnant women.

Table 1. Intensified National Iron Plus Initiative (I-NIPI) Operational Guidelines for management of Iron Deficiency Anemia among pregnant women

For Mild (10-10.9 g/dl) and Moderate (7-9.9 g/dl) anemia	Two tablets of Iron and Folic Acid tablet, i.e., OI (60 mg* elemental Iron and 500 mcg Folic Acid) daily, orally given by the health provider during the ANC contact Parenteral iron (intravenous iron sucrose (IVIS) or ferric carboxymaltose (FCM) may be considered as the first line of management in pregnant women who are detected to be anemic late in pregnancy or in whom compliance is likely to be low (high chance of lost to follow-up)
For Severe (5-6.9 g/dl) anemia	The treatment will be done using IVIS or FCM by the medical officer Immediate hospitalization recommended in the third trimester of pregnancy at a health facility where round-the-clock specialist care is available

Source: I-NIPI Guideline (MoHFW, GOI 2018) *100mg elemental iron is being supplied by the government, and hence it is being used instead of 60 mg

POSHAN Abhiyan (Prime Minister's Overarching Scheme for Holistic Nourishment Campaign) was launched in March 2018 in India to reduce the burden of anemia.[9] Complying with the overarching objective of POSHAN Abhiyaan to reduce malnutrition, Anemia Mukt Bharat (Anemia Free India)

strategy is designed to achieve the ambitious target of 50% reduction of anemia among women of reproductive age by 2025.[10] Moreover, digital methods for testing and point-of-care treatment are recommended to fulfill this target.

Program theory

The study was carried out in Banaskantha and Devbhumi Dwarka. Banaskantha has dominant tribal and desert areas while Dev bhumi Dwarka has coastal and rural areas. Pre-dominantly both districts have rural areas hence our study was in rural setting.

The data was collected from the Primary Health Centres (PHCs) – those PHCs offering IVIS or FCM as Intervention and those PHCs offering conventional oral iron therapy alone. The State procures IVIS and FCM; however, due to delay in procurements, districts selected for the study procured IVIS at district levels whereas FCM was procured by Medical Officer based on the requirement. Out of total 6 PHCs, 3 PHCs (2 in Banaskantha and 1 in Devbhumi Dwarka) were considered respectively as Intervention arm and conrol arm.

In routine practice, pregnant women with moderate anemia (<10 g/dl) receive OI therapy where as patients with severe and moderate anemia (Hb>7 g/dl and <10 g/dl) with very low compliance or high chance of loss-to-follow-up are provided IVIS. Patients with severe anemia (Hb>7 g/dl) with high risk conditions (such in last trimester or other complications), FCM is preferred. All these decisions are taken by Medical Officer after examination. All patients either in IVIS or FCM are continued with half dose of OI supplements (180 tablets instead of 360 tablets during pregnancy period).

Evidence Synthesis

It is evidenced that with an increase in each 1 g/dl mean Hb level, the risk of maternal mortality falls by 25%.[11] Evidence indicates that the Hb level in the range between 5 to 12 g/dL is significantly associated with reducing maternal mortality.[12] Therefore, an aggressive approach for treating moderate and severe anaemia among pregnant women is justified. OI therapy is indicated in a patient diagnosed with moderate anaemia in pregnancy unless the patient presents late in pregnancy or those whose compliance is likely to be low (high chance of loss-to-follow up). In these patients, parenteral iron therapy is indicated. A systemic review conducted by Qassim et al. in 2018 [8] concluded that different IV iron preparations (ferric carboxymaltose / iron polymaltose /iron sucrose) were similar in terms of safety and efficacy. They documented that cost and convenience of administration mainly influence the selection of specific parenteral iron preparation. However, evidence on the effect of parenteral iron therapy on improvements in critical maternal or perinatal outcomes lacked in the available literature. Some randomized controlled trials [11–13] have shown promising results with IVIS and FCM. However, under programmatic conditions, there are no studies that compare the cost-effectiveness of IVIS and FCM with the OI for improvement of haemoglobin level. Unfortunately, no studies from Indian settings had performed comprehensive cost (including cost incurred by health system) evaluation of oral and parenteral iron therapy. [13] One cost-effectiveness study conducted in Uttar Pradesh between oral vs. injectable iron therapy was primarily hospital-based, and health system cost was not included. [13] Similarly, other studies conducted by Jose et al. [14] and Mahey et al. [15] had also excluded health system cost in cost-effectiveness analysis. In conclusion, the present study is conducted at Peripheral Health Institutes in a natural programme setting using a health system and societal perspective. Therefore, it has a huge scope of generating evidence for policy-makers.

Policy Implications and Novelty

- IVIS is indicated in the national guideline (I-NIPI) for the treatment of moderate and severe anemia. However, there is no evidence on cost-effectiveness of IVIS in local context.
- Present study aligns with I-NIPI guideline and generates evidence on IVIS for treatment of maternal anemia in natural program setting.
- The study outcomes has pontial in contributin to the the Anaemia Mukt Bharat (Anaemia Free India) strategy to achieve the ambitious target of 50% reduction of anaemia among women of reproductive age by 2025.

Aim of the study

The study aims to compare clinical efficacy and cost-effectiveness of the IVIS and FCM therapy with oral iron therapy among pregnant women with IDA in a programmatic setting at Banaskantha and Devbhoomi Dwarka district of Gujarat, India

Objectives of the study

Primary objective of the study is to measure change in mean hemoglobin level from baseline

Secondary objectives:

- To measure treatment compliance
- To measure incidence of morbidity and mortality associated with iron deficiency anemia
- To measure health-related quality of life (HRQoL) using EQ-5D tool

Methodology

Study population

The observational study was undertaken prospectively at Banaskantha and Devbhoomi Dwarka districts of Gujarat during 2020-21. All registered pregnant women between 14-18 weeks' gestation period were enrolled from both districts for seven to eight months in the study. During the study period, patients with moderate and severe anemia were recruited. The study followed a natural program setting without manipulating the study environment. Classification and treatment of IDA among pregnant women was as per national guidelines. (Table 1)

Complying the Government guidelines[16], the medical officer at the health care facility determined the appropriate iron therapy assignment based on the participant's status of anemia as their routine practice.

Patients with mild and moderate anemia received OI, while patients with severer anemia and moderate anemia with very low compliance or high chance of loss-to-follow-up was provided parenteral iron therapy. Patients who received a blood transfusion in the last 120 days or required a blood transfusion at any stage of the intervention were excluded from the study. Apart from these, patients with haemoglobinopathy, other red cell disorders, or any chronic infections such as hepatitis, HIV, and showing any history of an allergic reaction to intravenous iron infusion were also be excluded from the study.

Sample size

From an earlier study [12] where the mean Hb increased from 9.75 g/dl to 11.06 g/dl with a standard deviation of 0.72 after taking OI, while mean Hb increased from 9.18 g/dl to 11.24 g/dl with a standard deviation of 0.82 after administrating IVIS, the 0.75 g/dl change in haemoglobin between these two arms was considered to calculate the sample size. Thus, by considering alpha error 5% and the power of the study as 95%, the estimated sample size was 26 per group. By assuming a loss-to-follow up of 20%, the expected sample size was 32. Hence the study's total calculated sample size was 128; 32 patients from each arm in two districts. Inj. FCM was not started in all PHCs in Banaskantha and Devbhoomi Dwarka districts. Therefore, a third group (Inj. FCM) was limited. We have enrolled 193 patients and 144 patients were followed-up until post-partum phase.

Study procedures

The study was conducted in a natural program setting and the study unit was Primary Health Center (PHC) and Community Health Centre (CHC). The blocks were selected by proportionate sampling method from the four divided regions of the district, i.e., rural, tribal, desert, and coastal based on the previous year's registered pregnancy. The PHCs Banaskantha and CHC in Devbhumi Dwarka were selected randomly from the proportionately selected blocks. Patients with moderate anaemia who were exclusively on OI supplement was recruited as the control population. Women were asked to bring back empty packs and were asked about the intake of tablets and the stools' color to ensure the consumption of the tablets. Patients with indicated IVIS or FCM by the medical officer was taken under the intervention arm. Iron requirements was calculated using modified Ganzoni's formula as follow. [17]

$$\text{Iron requirement(mg): Total iron deficit[mg]}$$
$$= \text{Bodyweight [kg]} \times (\text{target Hb} - \text{actual Hb}) \left[\frac{\text{g}}{\text{dl}}\right] \times 0.24$$
$$+ \textit{storage iron}\ (500)[mg]$$

At the baseline, information regarding sociodemographic profile, obstetric history, pre-intervention assessment (includes height, weight, Hb), and history of intervention were recorded. All pregnant women were followed up to 6 weeks following delivery. Hb levels were measured at the end of each month after baseline and at the 42nd day of the post-natal period. Haemoglobin estimation was carried out by a digital haemoglobinometer (HemoCue Hb 201^{+} System recommended by the Ministry of Health and Family Welfare) [10] through a laboratory technician available at the facility before treatment and during each follow-up visit.

Valuing of Health outcomes

Health-related quality of life (HRQoL) was assessed using the EQ-5D-5L tool at baseline and first follow-up. The tool has five domains, namely mobility, self-care, usual activities, pain/discomfort, anxiety/depression, was considered. Given score range from 1 to 5, with 1 being the worst and 5 the best. The EQ-5D self-reported questionnaire also includes a visual analog scale (VAS), which records the respondent's self-rated health status on a graduated (0–100) scale, with higher scores for higher HRQoL. The VAS provides a direct valuation of the respondent's current state of health, whereas the descriptive system was used as a health profile or converted into an index score representing a von Neumann-Morgenstern utility value for current health.[18] The level of problem reported on each of the EQ-5D dimensions determines a unique health state. Health states were converted into a weighted health state index by applying scores from the EQ-5D preference weights elicited from general population samples using the Crosswalk Index calculator. [19] These weights lie on a scale on which full health has a value of 1 and dead a value of 0. For this study, Thailand population weights were used to convert to an EQ-5D index score.

Measuring the cost of care

The per beneficiary cost of therapy was estimated from a societal perspective. Cost under various heads such as cost of therapy, consumables, healthcare resources (shared human resource, beds, etc.), out-of-pocket expenses, and wage loss was collected from financial records and field interviews. Cost of therapy by OI, IVIS, and FCM was obtained from both government rate contracts and local bulk procurement. Details of consumables, including materials and supplies issued, consumed, quantity used per test, and price per unit was collected from the respective facility. Financial and administrative records, including procurement and consumables records was reviewed. Healthcare facility-related costs such as time and bed occupied during IVIS or FCM administration was calculated, whereas research costs such as costs associated with additional testing of sampled cases using digital haemoglobinometer was excluded from

the analysis. Out-of-pocket expenditure in terms of traveling cost and wage loss (of a patient and accompanying person) due to referral or follow-up was gathered from field records. The costs was presented as average values across interventions viz – OI, IVIS or FCM.

Measuring the cost-effectiveness

The Incremental Cost-Effectiveness Ratio (ICER) was calculated by combining costs and outcomes. The CEA results was expressed in cost per QALY gained. Time horizon of the study was one year and 3% discounting was applied. One-way sensitivity analysis was carried out by varying model parameters to estimate uncertainty in all parameters. A tornado chart is presented using ICER values to depict changes in selected variables that influence the results.

Data storage and security

Data was stored in encrypted and password protected computer sytem at the institution. Hard copy of the records was stored in a locked cupboard in a secure location at the Institute. Access to records and study data was restricted to study personnel. Further study data was de-identified and is stored separately from the data.

Ethical approval

The ethics approval for the study has been obtained by the Institutional Ethics Committee on 25th May 2019 wide letter no., TRC-IEC No: 11/2019-20 and the protocol was approved by Technical Advisory Committee of Department of Health Research in 2019.

Results

Enrolment in the study

Total 193 patients enrolled; IVIS group had 82; FCM 5 and OI group reported 106 enrollments. Table 2 presents district-wise patient enrolments in the intervention and control arm.

Table 2: Patients enrolled in the Study (N=193)

Districts	**Intervention Arm**		**Control Arm**	**Total**
	IVIS	**FCM**	**OI**	
Banaskantha	50 (60.9)	5 (100)	75 (70.7)	130 (67.4)
Devbhoomi Dwarka	32(39.1)	0	31 (29.3)	63 (32.6)
Total	**82 (42.5)**	**5 (2.6)**	**106 (54.9)**	**193 (100)**

The study included 5 follow-ups. Up to 2nd follow-up, all patients were tracked; however, a total of 186 (96.4%) patients was followed during the 3rd visit and 171 (88.6%) during the 4th visit. The 5th follow-up during the post-partum period witnessed reduction in follow-up of patients to nearly half 144 (51.8%). The primary reasons for fewer follow-up visits were migration, and taking service from private providers. Table 3 presents follow-up data.

Table 3: Patient follow-up (N)

Baseline and follow-up	**Intervention Arm**		**Control Arm**	**Total**
	IVIS	**FCM**	**OI**	
Baseline	82	5	106	193
1st follow-up	82	5	106	193
2nd follow-up	82	5	106	193
3rd follow-up	81	5	102	186
4th follow-up	80	5	90	171
Post-partum follow-up	76	2	66	144

Sociodemographic characteristics of study participants

Sociodemographic characteristics of the patients in the intervention and control arm are presented in Table 4.

Table 4: Baseline sociodemographic characteristics of the study participants

Variables	**Intervention Arm**		**Control Arm**	**Total**
	IVIS	**FCM**	**OI**	
Age				
Up to 20 Years	13 (15.8)	0	18 (17.0)	31 (16)
21 to 30 Years	66 (80.5)	04 (80)	81 (76.4)	151 (78.2)
31 Years and above	03 (3.7)	01 (20)	07 (6.6)	11 (5.8)
Age in Mean Years	25.02 ± 3.55	28.2 ± 4.3	24.8 ± 4.04	25.0 ± 3.8
Mean Height (cm)	153.32 ± 8.5	152.4 ± 1.81	151.5 ± 6.3	152.3 ±7.28
Religion				
Hindu	43 (52.4)	02 (40)	68 (64.2)	116 (60.1)
Muslim	39 (47.6)	03 (60)	38 (35.8)	77 (39.9)
Education				
Up to Elementary	12 (14.6)	0	19 (17.9)	31 (16.1)
Up to Primary	15 (18.3)	0	26 (24.5)	41 (21.2)
Secondary & Higher Secondary	13 (15.9)	03 (60)	21(19.8)	37 (19.2)
Graduation	08 (9.8)	0	07 (6.6)	15 (7.8)
Illiterate	34 (41.5)	02 (40)	33 (31.1)	69 (35.8)

Baseline characteristics of the study participants

Below table 5 highlights baseline characteristics of patients in intervention and control arms.

Table 5: Baseline characteristics of the study participants (Mean)

Variables	Intervention Arm		Control Arm
	IVIS	FCM	OI
Gestational period	16	16.15	16
BMI (kg/m^2)	20.5	17.8	20.5
Hb (g/dL)	8.13	6.72	9.99
Travel cost	42.5	44	22.7
Wage loss	331.7	280	200

Baseline Mean difference in Sahli's and Digital Hemoglobinometer

Haemoglobin estimation was carried out by Sahli's method and a digital haemoglobinometer (HemoCue Hb 201$^+$ System recommended by the Ministry of Health and Family Welfare) through a laboratory technician available at the facility before treatment. The mean percentage change (0.59) was recorded in each arm (Figure 1). During each follow-up, Hb estimation was carried out using a digital haemoglobinometer.

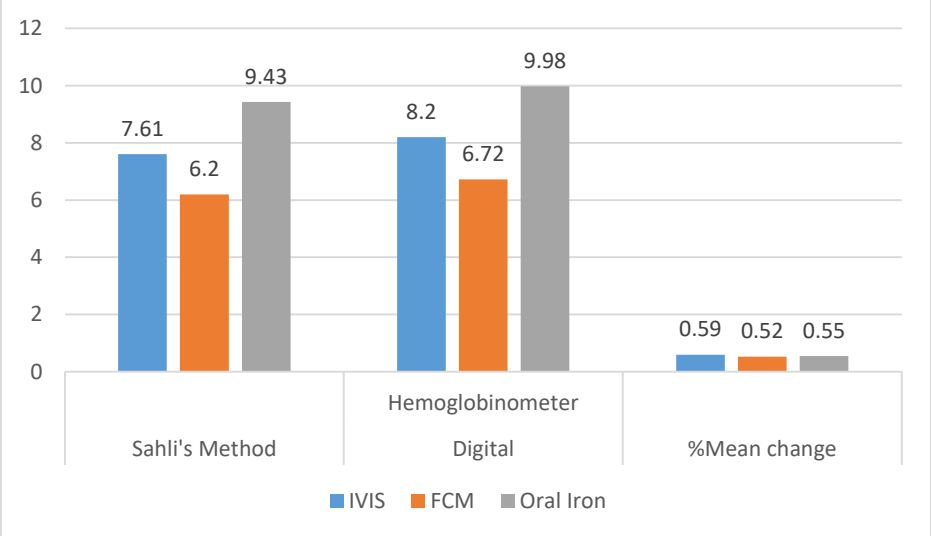

Figure 1. Baseline Mean difference in Sahli's and Digital Hemoglobinometer

Outcome measurments

Change in mean hemoglobin level from baseline in intervention and control arm

The study reported a change in mean Hb level across intervention and control arms. An incremental mean change in Hb was noted in the FCM group (11.80 g/dL from 6.7 g/dL) followed by IVIS (11.45 g/dL from 8.2 g/dL) at the time of the fourth follow-up – 16 week from the baseline (Figure 2). In the control arm, mean Hb was reduced to 9.55 g/dL at the forth follow-up from the baseline (9.99 g/dL). Figure 2 depicts the change in mean Hb levels across three interventions.

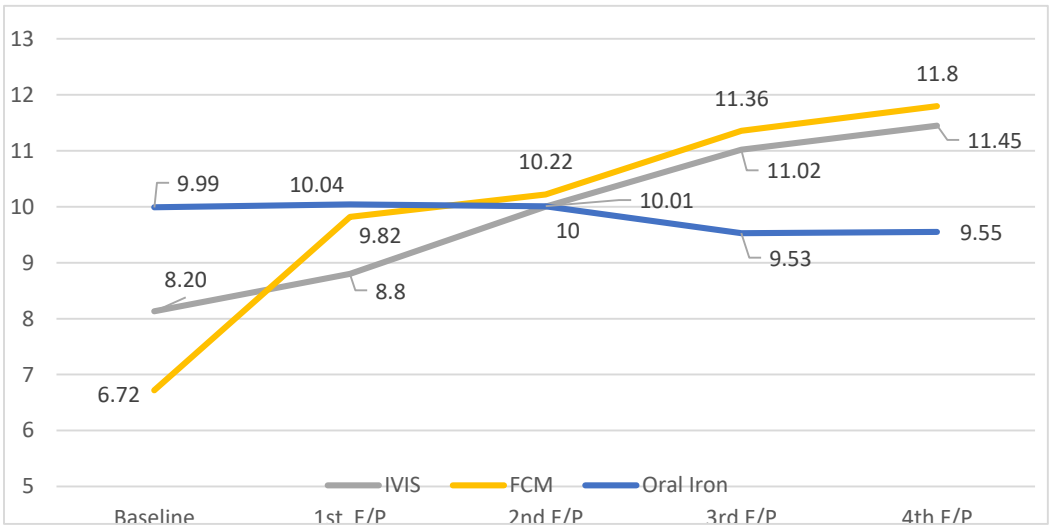

Figure 2. Percentage mean change across intervention and control arms

Side effects in intervention and control arm

No major side effects were reported. As shown in Table 6, side effects were reported more (60%) in the control arm than the intervention arm. About 60.4% patients enrolled in OI (n=64/106) reported side effects while only 10.9% of patients (n=9/82) in IVIS and 20% in FCM group (n=1).

Table 6: Side effects across interventions (frequency/%)

Intervention	Intervention Arm		Control Arm
	IVIS	FCM	Oral Iron
Side effects	9 (10%)	1(20%)	64 (60%)
Types of side effects reported [n(*f*)]			
Nausea	0	0	20 (31.3)
Diarrhea	0	0	13 (20.3)
Vomiting	0	0	12 (18.8)
Burning Sensation	0	0	10 (15.6)

Constipation	0	0	4 (6.3)
Gastritis	0	0	4 (6.3)
Abdominal pain	0	0	1 (1.6)
Pain at site of injection	7 (77.7)	1 (100)	0
Muscle spasm	2 (22.3)	0	0

In the intervention arm, side effects were limited to pain at the injection site (n=7) and muscle spasm (n=2) among the IVIS group and only one patient reported pain at the injection site as side effects. There was no adverse drug reaction (ADR) in both arms. All side effects in intervention arm were managed at PHC whereas 36% side effects were managed in OI group.

Treatment compliance

Intervention arm reported 100% compliance in IVIS and FCM group within intervention arm. All participants completed the treatment whereas 73% compliance was noted in control arm (i.e. OI therapy group). Major reason for discontinuing was side effects, migration, and accessing private providers.

Key outcomes

We assessed outcomes of IVIS in intervention arm as FCM group had only 5 patients and OI from control arm. We could gather data of delivery outcomes of 76 (out of 82) from intervention arm and 66 (out of 106) of women in control arm due to COVID-19 pandemic context. All health staff were engaged in COVID-19 related activities.

About 93% participants in Intervention arm had institutional delivery and rest 7% were recorded home delivery. Out of total institutional delivery, 85% were normal delivery which was higher compared to control arm and slightly lower incidence of c-section delivery (15% and 24% respectively in intervention and control arms). Table 7 depicts detail of key outcomes.

Table 7: Key outcomes in interventions and control arm(frequency/%)

Place of Delivery	**IVIS**	**OI**
Institutional	72 (93)	58 (88.9)
Home	4 (7)	8 (12.1)
Total	76 (100)	66 (100)
Type of delivery		
Institutional delivery	**n=72**	**n=58**
Normal	61 (85)	44 (76)
C-section	11 (15)	14 (24)
Home delivery	**n=4**	**n=8**

Normal	4 (100)	8 (100)
Normal Delivery	**n=64**	**n=58**
Pre-term birth	7 (11)	9 (16)
Live-birth	57 (89)	46 (79)
Still birth	(0)	3 (5)
Cesarian Section Delivery	**n=11**	**n=14**
Pre-term birth	4 (36)	4 (29)
Live-birth	6 (55)	6 (43)
Still birth	1 (9)	4 (29)
ND_Pre-term birth	**n=7**	**n=9**
Low birth weight	1 (14)	2 (22)
Normal birth weight	6 (86)	7 (78)
ND_Live birth	**n=57**	**n=46**
Low birth weight	5 (9)	5 (11)
Normal birth weight	52 (91)	41 (89)
C-S D_Pre-term birth	**n=4**	**n=4**
Low birth weight	1 (25)	2 (50)
Normal birth weight	3 (75)	2 (50)
C-S D_ Live birth	**n=6**	**n=6**
Low birth weight	1 (17)	2 (33)
Normal birth weight	5 (83)	4 (67)

We could not gather data on complications such as post-partum haemorrage (PPH), requirement of blood units during delivery, maternal mortality due to PPH, early neonatal mortality as all staff were engaged in COVID-19 related duties. Therefore, we restricted our analysis to low birth weight and normal birth weight as final outcomes and QALY as model outcomes.

Health related Quality of Life (HQoL)

Health Related Quality of Life of patients were assessed using EQ5D5L & EQ-VAS tool. Baseline and Forth follow-up (16 weeks following basline) data show mean difference in EQ5D5L score. Improvement in the mean score is observed in both arms; however, intervention arm (IVIS and FCM group) noted more improvements in 5D & 5L and EQ-VAS. Table 8 shows EQ5D5L & EQ-VAS.

Table 8: Baseline and Endline EQ5D5L mean score

Int	Baseline						5th follow-up (Post-partum)					
	Mobility	Self-care	Usual activity	Pain / Discomfort	Anxiety/ Depression	Health as per EQ-VAS	Mobility	Self-care	Usual activity	Pain / Discomfort	Anxiety/ Depression	Health as per EQ-VAS
IVIS	4	4	1	3	4	81± 7.88	2	2	2	1	4	93.6 ± 4.5
FCM	4	3	5	3	4	77± 7.69	4	4	3	2	2	90.1 ± 4.5
Oral Iron	4	4	3	4	4	83.9± 7.56	3	4	2	4	5	89 ± 3.8

We used EuroQol's Crosswalk value sets of Thailand using EQ5D5L profile. Table 8 presnts EQ5D5L profile and corresponding utility index value for both baseline and endline in intervention and control arms.

Table 9: EQ5D5L Index Value in intervention and control arm

Index	Baseline			Endline (5th follow-up - Post-partum)		
	IVIS	**FCM**	**OI**	**IVIS**	**FCM**	**OI**
Corresponding utility index value	0.273	0.134	0.139	0.412	0.321	0.104

EQ5D5L utility index value was reported lower in the control group than intervention arm values and baseline value. Similar patterns were seen for the visual analog scale (VAS). Following Table 9 depicts the EQ5D5L utility value index as per Thailand norm and EQ-VAS mean score. We further calculated EQ5D5L utility index value for normal delivery and c-section delivery for cost-effective analysis (Figure 10).

Table 10: EQ5D5L profile and utility index value based on type of delivery in intervention and control arm

Type of Delivery	IVIS		OI	
	EQ5D5L profile	**Utility Index Value**	**EQ5D5L profile**	**Utility Index Value**
Normal delivery	24221	0.409	34345	0.092
C-Section delivery	32242	0.321	32255	0.071

Incremental costs of intervention and control arm

The study gathered cost data. Table 11 presents the undiscounted base case/mean cost of both arms.

Table 11: Base Case Cost data for the study (in INR)

Program costs	Base case/ Mean	Min	Max	Source
Cost of IV per dose	30	24	36	Primary
Cost of FCM injection per patient	1400	1120	1680	Primary
Cost of IFA tablet/dose (total 360 tablets)	0.098	0	0	Primary
Cost of management of complications for IVIS	30	24	36	Primary
Cost of management of complications for OI	30	24	36	Primary
Cost of management of complications for FCM	30	24	36	Primary
Cost of antenatal care per patient	649	519	779	Prinja et al. 2017
Cost of postnatal care per patient	705.7	565	847	Prinja et al. 2017
Cost of bed per patient at PHC/CHC	583.5	467	700	Prinja et al. 2017 (1556)
Cost of normal delivery in hospital	1650	1320	1980	Primary
Cost of caesrean section	2500	2000	3000	Primary/Cheeranjeevi Yojna
Cost of treatment of complications in delivery for normal delivery	1556	1245	1867	Prinja et al. 2020
Cost of treatment of complications in delivery for c-section delivery	3112	2490	3734	2 days hospital stay (converted from 3.5 days of stay reported by Ray et al 2021)
Cost of shared HR				
ASHA	150	120	180	INR 3000 monthly remuneration divided by 26 days, divided 8 hours. Then two hours cost of ASHA was calculated
ANM	3.45	3	4	INR 30000 monthly salary divided by 26 working days, 30 minutes per patient per day
Lab Technician	5.9	5	7	INR 17000 monthly salary divided by 26 days, devided by 8 hours. And then 10 minutes cost was culculated
Medical Officer	13.5	11	16	INR 60000 monthly salary divided by 26 days and 8 hours a day. Then 15 minutes per patienttome was
User cost				
Cost of travel (IVIS)	445.4	356	534	

Cost of travel (FCM)	290	232	348	Primary (from baseline to endline)
Cost of travel (OI)	136.2	109	163	
Wage loss (IVIS)	2957	2365	3548	
Wage loss (FCM)	1860	1488	2232	
Wage loss (OI)	1273.5	1019	1528	
Cost of home delivery	200	0	200	Primary

Overall cost towards intervention was calculated. Table 11 provides cost details.

Table 12: Overall Cost from Societal Perspective for Each Arm

Cost Parameters	Intervention Arm		Control Arm	Remarks
	IVIS (n=82)	FCM (n=5)	OI (n=106)	
A. Program Cost				
Human Resource	14173.7	173	3180	IVIS: INR 172.89 unit cost of HR for IVIS / FCM multiplied into total benificiairies.
B. Service Delivery Cost				
Cost of treatment	12300	7000	3710	INR 150 treatment cost for IVIS, INR 1400 for FCM, and INR 35 for OI multiplied by benificiaries availed complete treatment
Cost of management of side effects/complications	270	30	1920	INR 30 cost of side effects multiplied by no. of benificiaries experienced side effects
Cost of bed at PHC	47847	2918	0	
Cost of Antenatal Care	53218	3245	68794	INR 649 (Prinja et al. 2017) multiplied by no. benificiaries availed full ANC
Cost of Post-natal Care	33874	1411	39519.2	INR 705.7 (Prinja et al 2017) multiplied by no. of benificiaries availed post-natal care
Cost of normal delivery in hospital	117945	1650	122067	INR 1650 cost of normal delivery at PHC multiplied by no. of benificiaries.
Cost of caesrean section	21250	6600	40500	INR 2500 (Chiranjeevi Yojana) cost of c-section multiplied by no. of benificiaries.
C. User cost (Out-of-Pocket Expenditure)				
Travel cost (Baseline till endline)	36523	1450	12249	Primary Travel cost multiplied by no. of benificiaries till 4th followed-up

Wage loss (Baseline till endline)	242433	9300	114615	Primary Wage loss multiplied by no. of benificiaries till 4th followed-up
Cost of normal delivery in hospital	10722	150	11097	Primary INR 150 per institutional delivery multiplied with number of benificiaries had normal delivery in hospital
Cost of C-section	4250	2000	8100	Primary INR 500 per c-section delivery multiplied with number of benificiaries had c-section
Cost of home delivery	480	0	2320	Primary INR 200 per home delivery multiplied with number of benificiaries had home delivery
Grand Total	5,95,285	35,927	4,28,071	
Per beneficiary cost	**7,260**	**7,185**	**4,038**	
Discounted per benificiary cost (3%)	**6,907**	**6,969**	**3,913**	
Additional costs				
Pre-term birth (for n. delivery) cost	8,816		5,594	Cost of treatment of complications in delivery for normal delivery as reported by Prinja et al 2017 (1556) was used assuming pre-term birth have experienced complications
Pre-term birth (for C-S. delivery) cost	10,372		7,150	Cost of treatment of complications during delivery for C-section delivery as reported by Ray et al 2021 (3112) was used assuming pre-term birth underwent c-section deliveries have experienced complications
Discounted pre-term (for n. delivery) cost	8,555		5,427	
Discounted Pre-term (for C-S. delivery) cost	10,065		6,936	

Total cost was INR 5,95,285; INR 35,927 and INR 4,28,071 for IVIS, FCM and OI group respectively. Undiscounted per beneficiary cost for IVIS was INR 7,260 INR 7,185 for FCM, and INR 4,038 for the OI group. Additional cost of complications in delivery for normal delivery and c-section was calculated to assess cost of pre-term birth.

Cost-effectiveness Analysis

A decision tree was parameterized on MS Excel spreadsheet to estimate change in QALYs and cost from societal perspective. Proximal outputs in terms of changes in himoglobin, place of delivery (institutional or home delivery), normal delivery, c-section delivery, pre-term birth, still birth, live birth, low-birth weight and normal birth weight were modelled to estimate QALY gained. We would like to highlight assumptions and conditions of the study.

Assumptions and Conditions

- Basically this programme was done in rural setting where IVIS was provided with taking consent from the patient. The programme was already implemented in selected districts of the PHC and we had just observed and collected data.
- Beneficiaries were from rural and tribal context, their perception may be influenced by other health conditions such as side effects of OI, or fever.
- In the programme setting, half OI supplements (180) were continued in IVIS and FCM interventions.
- Since the study was observational, we could not determine causal effects. Higher change in IVIS and FCM can be attributed to Partial OI supplements plus IVIS or FCM.
- We used clinical outcomes based on systematic review and availability of data from the field. However, we acknowledge that clinical outcomes considered in the study were multifactorial.
- The study was on anemia where anemia and mean hemoglobin change were conditions, not a disease. Hence to calculate approximate cost-effectiveness, we used clinical outcomes which are relevant to the study.
- Data on clinical indicators suh as complications during pregnancy, maternal mortality due to postpartum haemorrhage (PPH), pregnancy-related complications due to PPH, early neonatal mortality, and requirement of blood units during delivery could not be collected due to COVID-19 pandemic. We considered, pre-term birth, still birth, live birth and low birth weigh of babies and normal weight of babies as health outcomes for modelling.
- Transition probabilities were calculated from primary data. Few unit costs (costs per bed, cost of normal/c-section delivery, cost of complications during normal/c-section delivery) were derived from secondary literature.

Transition probabilities were derived from primary as well as secondary literature. Details of transition probabilities and other data used for populating the decision tree is presented below. The Table 12 shows data considered for purpose of decision analytic modelling in intervention and control arm.

Table 13: Calculation of transition probabilities for intervention and control arm

Transition from	Transition To	Transition Probabilities	%	Source
Intervention Arm				
Antenatal Women	Institutional delivery	0.970	97.0	Primary
Antenatal Women	Home delivery	0.030	3.0	Primary
Institutional delivery	Normal	0.850	85.0	Primary
Institutional delivery	C-Section	0.150	15.0	Primary
Home delivery	LBW	0.089	8.9	Primary
Home delivery	NBW	0.911	91.1	Primary
Normal delivery	Pre-term birth	0.109	10.9	Primary
Normal delivery	Live birth	0.891	89.1	Primary
Normal delivery	Still birth	0.000	0.0	Primary
Norm_del_ptb	Low-birth weight	0.140	14.0	Primary
Norm_del_ptb	Normal birth weight	0.860	86.0	Primary
Norm_del_lb	Low-birth weight	0.090	9.0	Primary
Norm_del_lb	Normal birth weight	0.910	91.0	Primary
C-Section	Pre-term birth	0.364	36.4	Primary
C-Section	Live birth	0.545	54.5	Primary
C-Section	Still birth	0.091	9.1	Primary
C-S_del_ptb	LBW	0.250	25.0	Primary
C-S_del_ptb	NBW	0.750	75.0	Primary
C-S_del_lb	LBW	0.170	17.0	Primary
C-S_del_lb	NBW	0.830	83.0	Primary
QALY (discounted)			0.400	Primary
QALY- ND (discounted)			0.397	Primary
QALY- S-C D (discounted)			0.311	Primary
Cost_Programme (ID) (discounted)			6907.4	Primary
Cost_HD (discounted)			465.6	Primary
Cost_compl. nor.del. (discounted)			8417.0	Prinja et al. 2016
Cost_compl. C-section (discounted)			9926.3	Primary
Avg. Age of Cohort			25.020	Primary
Control Arm				

Antenatal Women	Institutional delivery	0.889	88.900	Primary
Antenatal Women	Home delivery	0.111	11.100	Primary
Institutional delivery	Normal	0.760	76.000	Primary
Institutional delivery	C-Section	0.240	24.000	Primary
Home delivery	LBW	0.100	10.000	Primary
Home delivery	NBW	0.900	90.000	Primary
Norm delivery	Pre-term birth	0.155	15.520	Primary
Norm delivery	Live birth	0.793	79.310	Primary
Norm delivery	Still birth	0.052	5.170	Primary
Norm_del_ptb	Low-birth weight	0.220	22.000	Primary
Norm_del_ptb	Normal weight	0.780	78.000	Primary
Norm_del_lb	Low-birth weight	0.110	11.000	Primary
Norm_del_lb	Normal weight	0.890	89.000	Primary
C-Section	Pre-term birth	0.290	29.000	Primary
C-Section	Live birth	0.430	43.000	Primary
C-Section	Still birth	0.290	29.000	Primary
C-S_del_ptb	LBW	0.500	50.000	Primary
C-S_del_ptb	NBW	0.500	50.000	Primary
C-S_del_lb	LBW	0.330	33.000	Primary
C-S_del_lb	NBW	0.670	67.000	Primary
QALY (discounted)			0.0031	Primary
QALY- ND (discounted)			0.0028	Primary
QALY- S-C Del (discounted)			0.0021	Primary
Cost_Program (discounted)			3913.00	Primary
Cost_HD (discounted)			2218.00	Primary
Cost_compl. nor.del. (discounted)			5426.58	Primary
Cost_compl. C-section (discounted)			6935.90	Primary
Avg. Age of Cohort			24.05	Primary

Incremental Cost-Effectiveness

Cost-effective analysis was done based using the decision tree model. From societal perspective, IVIS incurs an incremental cost of INR 783.11 per QALY gained which is 0.49% of the per capita GDP of India. Thus, IVIS intervention can be concluded to be very cost-effective.

Table 14: Results of cost-effectiveness analysis between IVIS and OI therapy

Outcomes	IVIS	OI
Cost (in INR) per patient treated as per modelling	6768.28	6503.79
Incremental Cost (in INR)	286.05	
Effects	0.368	0.003
Incremental Effects	0.365	
ICER	783.11	

Figure 3 illustrates cost-effectiveness plane.Organge dot indicates ICER value which falls in the North East quadrant. It means intervention is costly than comparator but highly effective.

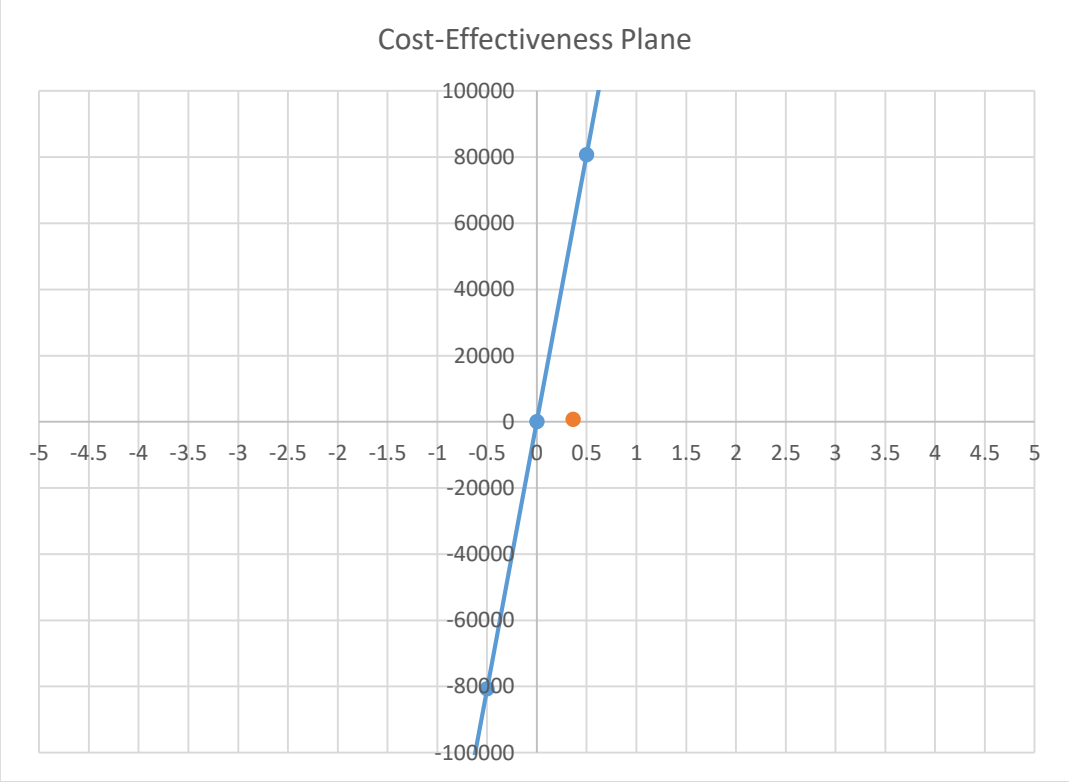

Figure 3: Cost-effectiveness plane of the study

One-way sensitivity analysis was applied. Figure 5 presents results from simulations done as part of one-way sensitivity analysis. The tornado diagram of one-way sensitivity analysis shows that ICER value is slightly changed when the input parameter is changed in multiple indicators. Program cost of intervention arm, low-birth weight and pre-term birth in control arm are key parameters that influence the model.

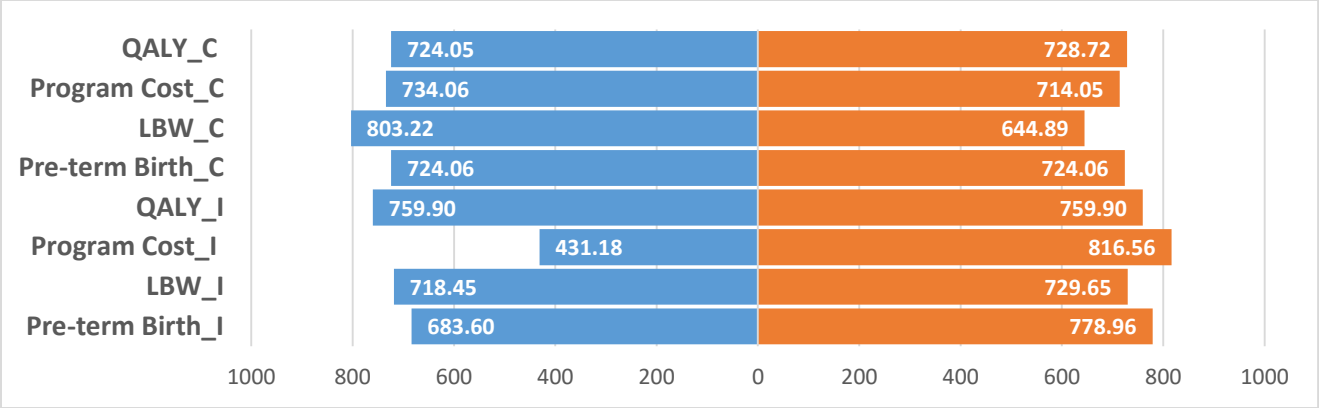

Figure 4: Tornado diagram of cost-effectiveness of IVIS and OI therapy

Budget Impact Analysis

Budget Impact Analysis (BIA) has been performed to estimate the cost for the roll-out of IVIS intervention at the State level. The BIA has been performed at 201 Prices. The Budget Impact Analysis depicts budget allocation for the five years. Table 15 shows budget impact analysis and assumptions used. Using top down approach, we have calculated eligible population and supply side costing was used to assess incremental costs of intervention to be delivered in horizontal delivery platform.

We have considered 60% coverage of the pregnant women with moderate and severe anemia in the first year, 70%, 80%, 90% and 95% in subsequent years. The state-wide scale-up for the state would cost INR 33,99,21,168 for the first year, with above costs in subsequent years. For calculation, we have not discounted the cost but we have calculated the average inflation rate (2%) and added the cost for the second year onwards, which can be found in the last row of table 15.

Table 15: Budget Impact Analysis

State Level (2021Prices)											
Sr. No.	**Budget Head**	**Budget sub-heads**	**Unit Definition**	**Units**	**Unit price**	**Annualized cost (INR)**					**Source**
						Year 1	Year 2	Year 3	Year 4	Year 5	
A	Program cost	Shared Human Resource	Medical Officer (5 days)	44,614	173	7,711,530	9,004,633	10,291,009	11,577,385	19,940	No. of PHC taken from NRHM Gujarat (https://nrhm.gujarat.gov.in/health-services.htm)
Total (A)						**7,711,530**	**9,004,633**	**10,291,009**	**11,577,385**	**19,940**	
B	Service Delivery Cost	Cost of IVIS treatment	Primary Health Centre level	44,614	150.00	6,692,100	7,807,485	8,922,840	10,038,195	10,595,873	60% coverage of all pregnant women with moderate and severe anemia in first year, 70% in second year, 80% in third year, 90% in fourth year and 95% in fifth year.
		Cost of management of side effects/complications	Individuals experiencing side effects	4,908	30	147,226	171,765	196,302	220,840	233,109	11% patients had side effects in primary study

		Cost of bed at PHC	Average four hours bed for IVIS	43,499	584	25,381,462	29,611,896	33,842,329	39,048,404	41,217,857	All patients received IVIS treatment
		Cost of Antenatal Care	ANC registered	44,614	649	28,954,486	34,072,500	42,345,936	42,345,936	44,698,687	97.5% patients received ANC
		Cost of Post-natal Care	Individuals	41,491	706	29,280,213	34,160,467	39,040,453	43,920,510	46,360,446	93% of patients received PNC in primary study
		Cost of normal delivery in hospital	Individuals	36,784	1,650	60,693,930	70,810,080	80,925,686	91,041,407	101,751,948	85% based on primary study; 90% in fifth year
		Cost of caesrean section	High risk cases managed at tertiary care level	6,491	2,500	16,228,250	18,933,000	21,637,875	24,342,600	17,129,950	15% based on primary study; 10% in fifth year
		Cost of treatment of complications in delivery for	At PHC level	1,471	1556	2,289,436	2,671,030	3,052,560.80	3,434,185.36	3,838,207	4% of total hospital delivery

		normal delivery									
		Cost of treatment of complications during delivery forC-section delivery	At Tertiary Care level	551.76	3112	1,717,077	2,003,194	2,289,436.16	2,575,615.68	1,812,486	8.5% of scesarian patients
Total (B)						**171,384,181**	**200,241,417**	**232,253,417**	**256,967,692**	**267,638,562**	
C	Out-of-Pocket Expenditure (User cost)	Travel cost (Baseline + follow-up)		44,614	445	19,871,076	23,183,070	26,495,064	29,806,613	31,462,611	
		Wage loss (Baseline + follow-up)		44,614	2,957	131,923,598	153,911,850	175,900,102	197,885,397	208,879,523	
		Cost of normal delivery in hospital		36,784	150	5,517,600.00	6,437,250	7,356,881	8,276,550	9,250,200	
		Cost of C-section		6491	500	3,245,500	3,786,500	4,327,575	4,868,500	3,426,000	

		Cost of home delivery		1338	200	267,684	312,298	356,914	401,528	423,835	3% of total AN women received IVIS treatment
Total (C)						**160,825,458**	**187,630,968**	**214,436,536**	**241,238,588**	**253,442,169**	
Grand Total (without inflation rate)						**339,921,168**	**396,877,017**	**456,980,962**	**509,783,665**	**521,100,670**	
Grand Total (with inflation rate)						**Inflation rate (2%)**	**396,956,393**	**457,072,358**	**509,885,622**	**521,204,890**	Average of last four years inflation 2.8+ 2.37+2.45+ 0.39

Discussion

We conducted the study to assess the effectiveness of IVIS and FCM over oral iron among moderately and severely anemic women in a natural program setting in Gujarat. It showed that an incremental change in mean Hb level in the IVIS group was higher compared to Oral Iron. IVIS is safe and effective in pregnancy. It improved anemia in short duration and fills iron stores better than OI. This has been the observation in other studies too.[20-27] As the rate of increase in hemoglobin is faster, IVIS is suitable for treatment of IDA with lower hemoglobin in the second trimester. There was a highly significant difference in the hemoglobin level after treatment between the two arms, which has also been observed by Neeru, Nair and Rai, [22] Neogi et al., [23] and Radhika et al.[29]

Al et al., observed that the IVIS group achieved significantly higher hemoglobin level (P value ≤ 0.001) in a shorter period (P value ≤ 0.001).[28,29] In the present study, iron supplement was provided to IVIS group in order to comply Government's guideline. Similar practice was reported in the Bayoumeu et al.'s study.[20] Iron supplement was continued after the IVIS treatment similar to the study conducted by by Neeru, Nair and Rai (2012)[22] wherein the IVIS group maintained hemoglobin with routine supplementation of OI after the treatment.

Because of the high prevalence of anemia (66.4%) in pregnant women as per the National Family Health Survey-5,[30] oral supplementation even with normal iron stores is essential in India. Unlike in the parenteral iron-treated group, once the anemia is corrected with OI, absorption slows down.[21] This is responsible for the iron stores not being replenished with OI, unlike intravenous iron.

Many Indian studies have used the intravenous route for parenteral iron and reported side-effects such as pain, staining at injection site.[31,32] In the present study, IVIS group reported few side effects compared to side effects in OI group. These side effects may caused discontinuation of OI supplementation. Present study reported 100% compliance in IVIS group compared to OI group (73%).

In terms of cost, IVIS group had higher cost compared to OI group. However, it is important to mention that cost of management of side effects, complications during normal and c-section delivery and user cost

(home delivery) was higher in the OI group. It means that IVIS certainly reduce user cost significantly and health system cost in management of complications.

Present study reported improvement in mean hemoglobin after treatment and birth weight of babies. Similar findings was reported in a study conducted in Norteast India. [33] Previous studies have studied cost-effectiveness of IVIS compared to Oral Iron therapy and found IVIS intervention promising.[29,34]
A recent cost-effectiveness study based on randomized control trial in India also found IVIS to be more costly but more effective than the OI therapy for treatment of severe anaemia. The ICER was calculated at INR 31 951 (USD 445.2) per safe delivery. Present study included pregnant women with moderate and severe anemia and found to be very cost-effective. The ICER was calculated at INR 724.06 which is 0.45% of the country's per capita GDP (INR 1,61,458).

Limitations

Several limitations for assessing the cost-effectiveness are highlight here. Initially we planned to gather data on IVIS and FCM intervention, however, considering COVID-19 context, FCM was not procured and hence FCM was not provided, only 5 patients received FCM from exisiting stack. New stock of FCM was not filled as all efforts were focused on COVID-19 prevention and management. We planned enrolment of 396 patients in the study (intervention and control arm) but we could gather only 193 antenatal women. Furthermore, we could not collect data on some clinical disorders suh as data on complications during pregnancy, maternal mortality due to postpartum haemorrhage (PPH), pregnancy-related complications due to PPH, early neonatal mortality, and requirement of blood units during delivery. Thus, we considered, pre-term birth, still birth, live birth and low birth weigh of babies and normal weight of babies as health outcomes for modelling. This study was observational study hence no blinding possible. Clinical outcomes used for the study are influenced by multiple factors which is the limitation of the study. Despite all these limitations, present study hold critical value in evidence generation on IVIS intervention and complement national strategy to support policy decisions for scale-up.

Conclusion

The study reported an incremental change in mean Hb level in the IVIS group compared to Oral Iron. IV IS was found to be cost-intensive but more effective than oral therapy for the treatment of moderate and

severe anaemia. Further, it is well tolerated as side effects are less compared to that of oral iron. Study findings on clinical efficacy remains inconclusive due to multifactorial clinical outcomes. Considering the limited sample size and lack of blinding, larger studies with robust methodologies are needed to validate the results findings. Future studies on clinical efficacy would be critical in establishing effect of rise in hemoglobin level on maternal and birth outcomes.

Acknowledgment

We thank Dr. Manish Fancy and Dr. Raj Sutharia from the Department of Health, District Panchayat, Banaskantha and Devbhumi Dwarka respectively for their support in carrying out this study.

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