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Transdermal Iron Therapy in Women with Anemia: A Comparative Study of Efficacy and Tolerability Versus Oral Supplementation

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a significant health concern among adolescent girls and women, often compounded by poor adherence to oral iron therapy due to gastrointestinal side effects. Objective: To compare the efficacy, tolerability, and compliance of two transdermal iron lotion formulations with oral iron supplementation in women with confirmed IDA. Methods: A randomized controlled trial was conducted with 300 women divided into three arms: oral iron supplementation, Transdermal Lotion 1 (iron, folic acid, B12, vitamin D), and Transdermal Lotion 2 (minimal-iron comparator). Primary outcomes included hemoglobin improvement and adherence; secondary outcomes were changes in ferritin and vitamin D levels. Results: Transdermal Lotion 1 showed higher adherence (90% vs. 65%) and fewer side effects compared to oral therapy. Hemoglobin improved >1 g/dL in 60% of the oral group and 39.8% of Lotion 1 users. Notably, 56% of Lotion 1 users improved ferritin from <30 to >50 ng/mL and 67% achieved sufficient vitamin D levels—benefits not observed with oral iron or Lotion 2. Conclusion: Transdermal iron delivery, especially Lotion 1, offers a well-tolerated, moderately effective alternative for managing anemia in women with enhanced nutritional benefits.

Keywords: Iron Deficiency Anemia, Transdermal Therapy, Ferritin, Vitamin D, Women's Health, Compliance, Oral Iron Side Effects.

INTRODUCTION

Iron deficiency anemia (IDA) affects millions of adolescent girls and women globally. Iron functions as a component of a number of proteins, including enzymes and hemoglobin, the latter being important for the transport of oxygen to tissues throughout the body for metabolism. The components of iron requirement used as factors in the modeling include basal iron losses, menstrual losses, fetal requirements in pregnancy, increased requirement during growth for the expansion of blood volume, and/or increased tissue and storage iron.

Background

Micronutrients malnutrition due to deficiency of vitamins and minerals is known as "hidden hunger." About of one-third of the world's population especially those in the developing

countries suffers from hidden hunger. According to the 2021 Global Nutrition Report (GNR, 2021) released in Nov 2021, India has made no progress on anemia and childhood wasting. Over half of Indian women in the age group 15-49 years are anemic. There has been a rise in anemic Indian women from 52.6 per cent in 2016 to 53 per cent in 2020. Associations for adverse maternal, fetal and neonatal outcomes were noted with severe and moderate anemia but not mild anemia. Increases in low birth weight and very low birth weight were reported in women with severe and moderate anemia, the majority of all pregnant women [1-5].

In India, 58.5% of children (under five years) are anemic and 72% of this proportion is because of the inadequate amount of iron in the body. The iron deficiency in the body leads to insufficient levels of hemoglobin for red blood cells. In addition to iron, the body also needs folate and vitamin B-12 to produce enough healthy red blood cells. People with a diet consistently low in iron, folate, vitamin B-12, and copper are at a greater risk of anemia, which increases further in menstruating girls. Deficiencies of iron, folate and vitamin B12 especially during early childhood have also been linked with poor cognitive development in children. Micronutrient deficiencies result out of poor supplementation delivery and can cause neurodevelopmental and other serious medical conditions. Oral fortification of micronutrients has been proven to have limited efficacy. Oral fortification is restricted by multiple challenges of taste, stability, poor absorption and gastrointestinal disturbances [6].

Rationale

Oral iron therapy, though commonly prescribed, often leads to poor adherence due to side effects such as nausea, constipation, and metallic taste.

Despite the well-recognized benefits of micronutrient supplementation interventions, the benefits of conventional oral supplements have been suboptimal due to poor adherence and concerns about safety and adverse effects. There is scope for development of innovative techniques for supplementation of these essential micronutrients. An innovative intervention for prevention of micronutrient deficiencies in children involved the use of a nanotechnology platform in the form of nanosized liposomes for fortification of body oil which is traditionally used for body massage in Indian infants. The intervention of nanosized liposomal encapsulated micronutrient fortified body oil (LMF body oil) was developed as part of a proof of concept randomized controlled study conducted among rural Indian infants to evaluate the effects of such an intervention on micronutrient deficiencies and neurodevelopmental outcomes. Previous studies have shown that Nano-fortified transdermal oil increased Vitamin D levels in children compared to placebo and also decelerated the ratio of infants trending towards anemia by increasing their hemoglobin levels [7]. Transdermal drug delivery systems provide a promising alternative by bypassing the gastrointestinal tract. This study aimed to compare two transdermal formulations with oral iron supplementation in terms of compliance, efficacy, and tolerability, while also assessing changes in serum ferritin and vitamin D levels.

STUDY OBJECTIVES

Primary Objective

- To determine the ease of use of the transdermal application of micronutrient fortified lotion to alleviate the levels of iron along with other micronutrients (including folic acid, Vit B-12, Vit D) in mild to moderate anaemic girls and women.

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- To assess the safety of transdermal application of the lotion.
- To assess the compliance patterns of transdermal application of the lotion.

Secondary Objectives

- To investigate the efficacy of transdermal application of micronutrient fortified Oil/Lotion for prevention of micronutrient deficiencies in mildly/moderately anemic adolescent girls and women

METHODS

Study Design

A randomized, controlled, three-arm trial was conducted on 300 women with confirmed iron deficiency anemia. Participants were allocated into:

- **Arm 1: Oral Supplementation**
  Ferrous bisglycinate (60 mg elemental iron), zinc bisglycinate (15 mg), folic acid (1 mg), and methylcobalamin (500 mcg).
- **Arm 2: Transdermal Lotion 1**
  Ferrous bisglycinate (5 mg elemental iron), vitamin B12, vitamin D3, and folic acid.
- **Arm 3: Transdermal Lotion 2 (Placebo Comparator)**
  Transdermal base with minimal iron content.

Participants

Inclusion Criteria:

a) Adolescent girls (10-20 years) and women (20-50 years), residing in the study area.
b) Iron deficiency anemia with low hemoglobin ranging from 9-10.9 g/dL at the onset of the study (at first visit).
c) A ferritin level of < 30ng/ml (has a 92% sensitivity and 98% specificity) for diagnosing iron deficiency.
d) Must be able to provide informed consent.
e) Willing and able to comply with treatment plan, scheduled visits and laboratory tests.

Exclusion Criteria:

a) Women or girls with significant co-morbidities including hemoglobinopathies.
b) Those who have history of oral or IV iron intolerance.
c) Not residing in the study area.
d) Participants receiving/starting any other investigational agents, biological agents or other medication.

Outcome Measures

- Primary:, Ease of application, compliance, and side effects
- Secondary: Hemoglobin improvement Ferritin level improvement, vitamin D sufficiency post-treatment

Study Evaluations and Measures

Screening and Baseline Evaluations (Procedures and measurements)

- Screening test done by skin-prick method to check hemoglobin (Hb) levels during inclusion of participants.

- Physical examination: can be done to check the signs of low iron; fatigue, shortness of breath, dizziness, pale skin, slowed appetite, and cravings for non-food.
- Venous sample will be taken for hemoglobin, CBC, Vit D3, and serum ferritin, measured at baseline and then at 12 weeks after treatment.
- Hemoglobin also measured by skin-prick at 6 weeks after treatment.

Statistical Considerations

Statistical Methods:

All statistics conducted using IBM SPSS Statistics software. For descriptive statistics, mean, standard deviation (SD), minimum, median and maximum values of Hb calculated for continuous variables, and the proportion/ percentage will be computed for categorical values at 0, 6 and 12 weeks of transdermal oil application. For inferential statistics a paired samples t-test will be applied to compare two groups of dependent samples, for normally distributed data, and for non-normally distributed data, the Wilcoxon Sign-rank test performed.

Study Medication

Description, Packaging, Labeling, Dosage, Drug Accountability:

- Transdermal lotion allows delivery of micro-nutrients through skin using innovative nanotechnology. Safe nanoparticles developed by MKPPL encapsulate micronutrients and interact with the outermost layer of skin to enhance micronutrient penetration.
- Rigorously tested ingredients contain: Ferrous bisglycinate, Folate Cyanocobalamin, Cholecalciferol
- Single application per day of the transdermal lotion.
- The technology has demonstrated safety and efficacy in *in vitro* and *in vivo* animal models for transdermal delivery of nutrients at supplemental doses. The technology has also demonstrated no irritation potential during irritation patch testing in healthy human volunteers
- Have published clinical trial data indicating safety and efficacy, for use in new born infants.

Safety Management

Clinical Adverse Event Reporting:

All reports of serious adverse events (SAE)s adjudicated by pre-designated clinical experts -- when confirmed as an SAE, these quickly reported to the PI, Chief Quality Officer and to the Data Safety Monitoring Board (DSMB). All reported side–effects captured.

Informed Consent and Confidentiality:

All women who are present for screening receive education on key aspects of the trial. Written informed consent obtained from the participants after explaining that the participation in the study is entirely voluntary and confidentiality and anonymity strictly maintained.

RESULTS

Completion Rates and Adherence

Treatment Group	Completed	Lost to Follow-up	Discontinued Due to Side Effects
Oral Supplementation	85	12 (9.1%)	35 (26.5%)
Transdermal Lotion 1	104	6 (5.3%)	3 (2.7%)

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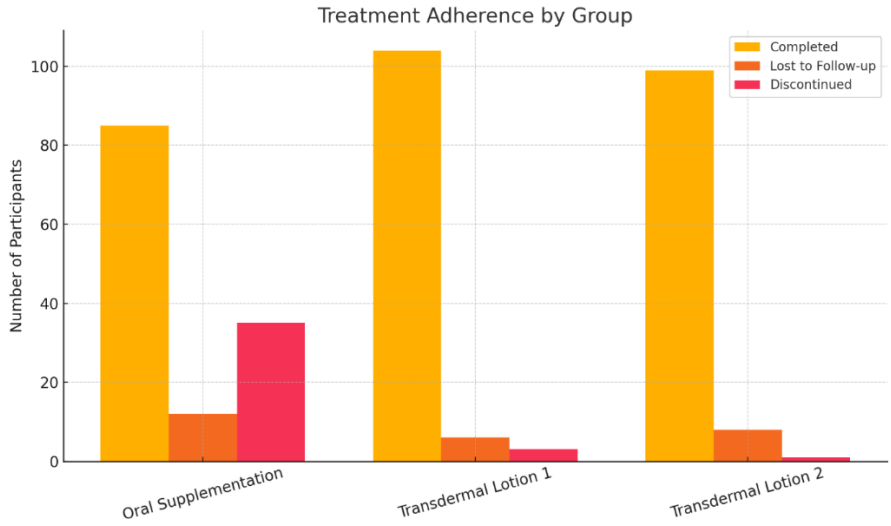
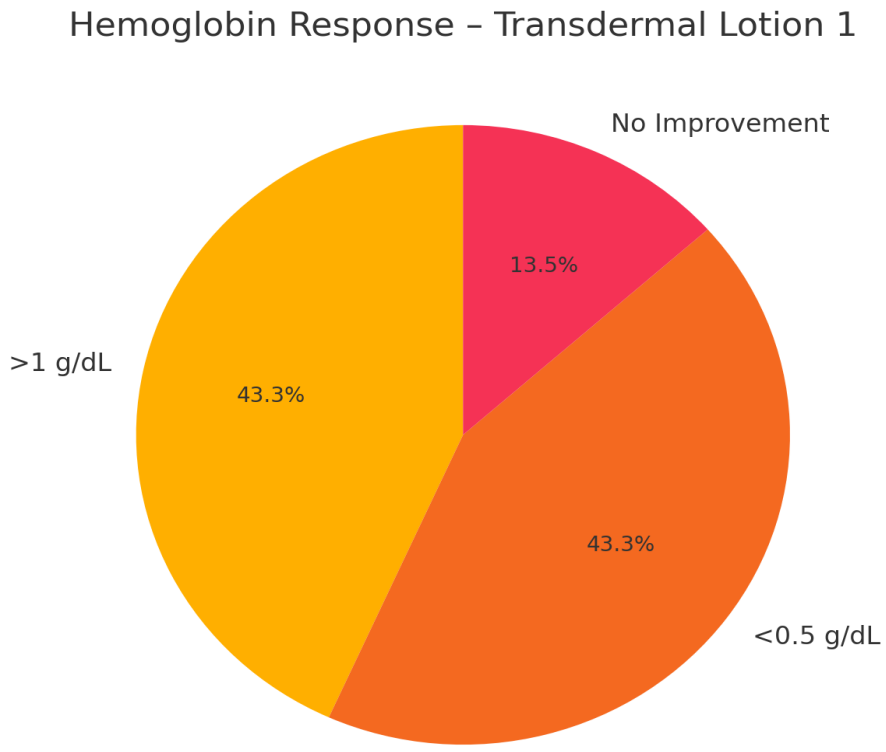
Transdermal Lotion 2	99	8 (7.4%)	1 (0.9%)



Hemoglobin Response

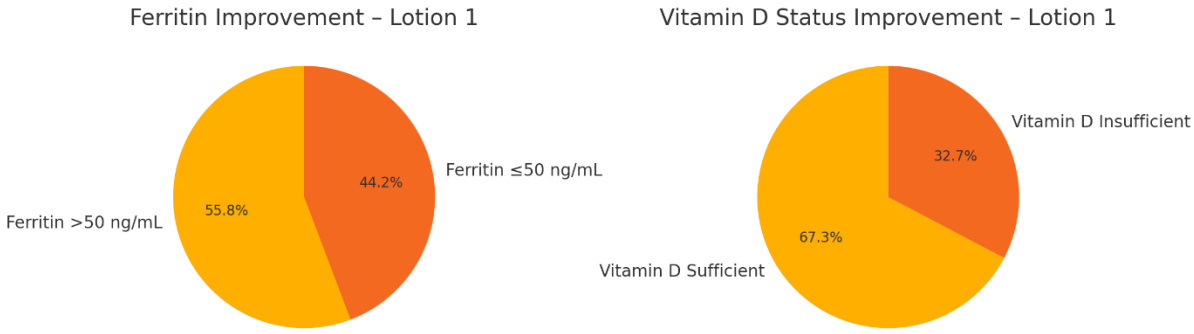
Outcome	Oral (n=85)	Lotion 1 (n=104)	Lotion 2 (n=99)
Hb improvement >1 g/dL	51 (60%)	45 (39.8%)	3 (3.0%)
Hb improvement <0.5 g/dL	34 (40%)	45 (39.8%)	25 (25.2%)
No improvement in Hb	0	14 (12.4%)	71 (71.7%)



Ferritin and Vitamin D Outcomes

Only measured in Transdermal Lotion 1 (n=104):

- **Ferritin >50 ng/mL (from <30 ng/mL)**: 58 women (56%)
- **Vitamin D: Insufficient → Sufficient**: 70 women (67%)



Side Effects and Tolerability

- **Oral Group**: High dropout due to gastrointestinal side effects (nausea, gastritis)
- **Lotion 1**: Mild complaints related to smell, no major adverse events
- **Lotion 2**: One mild skin reaction; otherwise well tolerated

DISCUSSION

This comparative study highlights several important findings:

- While **oral supplementation** showed the greatest hemoglobin improvement (>1 g/dL in 60%), **its high discontinuation rate (35%) limits its utility**.
- **Transdermal Lotion 1** had better adherence, fewer side effects, and significant ferritin and vitamin D gains, pointing to **a more holistic nutritional benefit**.
- **Transdermal Lotion 2**, a minimal-iron comparator, showed poor efficacy, reinforcing the essential role of active iron content in the formulation.

The inclusion of vitamin D and folate in Lotion 1 likely contributed to broader improvements in nutritional status, making it especially useful in populations with multiple deficiencies.

This comparative study contributes valuable insights to the growing body of evidence on alternative delivery systems for iron supplementation, particularly in populations with high prevalence of iron deficiency anemia (IDA) and poor adherence to conventional oral therapies. Our findings demonstrate that while oral supplementation resulted in a higher proportion of hemoglobin improvement (>1 g/dL in 60% of participants), this benefit was offset by a notably high dropout rate of 35%, largely attributable to gastrointestinal side effects such as nausea, gastritis, and constipation. These adverse events are widely recognized as barriers to compliance in oral iron therapy, especially in women of reproductive age [8,9].

In contrast, Transdermal Lotion 1 offered a more tolerable and compliant solution, with only 2.7% discontinuation and a completion rate of over 90%. Importantly, it delivered additional nutritional benefits beyond hematologic parameters—56% of users achieved a significant rise in serum ferritin from <30 ng/mL to >50 ng/mL, and 67% transitioned from vitamin D insufficiency to sufficiency. These outcomes are clinically relevant, as both iron and vitamin D deficiencies frequently coexist in women and contribute to fatigue, reduced productivity, and impaired immune function [10,11].

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The inclusion of folic acid and vitamin B12 further enhances the formulation's capacity to correct multiple micronutrient deficiencies concurrently. This multi-nutrient transdermal strategy may thus be more appropriate for public health programs in low- and middle-income countries (LMICs), where women often present with overlapping nutritional deficits due to poor dietary intake, recurrent infections, and limited healthcare access [12].

Lotion 2, which contained minimal iron, acted as a placebo comparator and demonstrated poor efficacy across all hematological and biochemical parameters, reaffirming that active iron content is indispensable for therapeutic benefit. This arm helped isolate the effect of the active ingredients in Lotion 1 and confirmed that transdermal delivery without sufficient iron does not yield measurable improvements.

These findings resonate with previous exploratory work on transdermal iron formulations, which have shown promising absorption profiles and bioavailability in preclinical models and pilot studies [13,14]. However, our study is among the first randomized controlled trials to directly compare transdermal iron delivery with standard oral supplementation, using not only hemoglobin as a primary endpoint but also including serum ferritin and vitamin D as secondary markers of nutritional improvement.

From a practical standpoint, the ease of application, absence of gastrointestinal irritation, and broader micronutrient correction make Transdermal Lotion 1 a strong candidate for further development and large-scale implementation. It is particularly suitable for adolescents and women with comorbid gastrointestinal conditions, menstrual irregularities, or histories of intolerance to oral iron.

Nevertheless, limitations include the single-site nature of the study and relatively short duration of follow-up. While our findings are statistically and clinically significant, longer-term studies assessing sustained efficacy, recurrence of anemia, and cost-effectiveness are warranted.

CONCLUSION

Transdermal iron therapy, particularly the first formulation, offers a **safe, tolerable, and moderately effective alternative** to oral iron. It is especially suited for women with poor tolerance to oral iron or gastrointestinal disorders. The added benefit of improved ferritin and vitamin D levels further enhances its value in addressing multiple deficiencies in at-risk populations.

RECOMMENDATIONS FOR FUTURE RESEARCH

- Larger multi center trials to validate efficacy and biochemical outcomes
- Long-term studies assessing sustained improvement and relapse rates
- Cost-benefit analyses for public health implementation

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