“Evaluation of R. B. Tone XT for the safety, efficacy, tolerability and pregnancy outcomes in the management of pregnancy anemia.”

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Abstract:

Objective: The objective of the study was to evaluate the clinical benefits associated with R. B. Tone XT tablet (Medley pharmaceutical, Mumbai) containing ferrous ascorbate equivalent to elemental iron 100 mg + folic acid 1.5 mg + elemental zinc 22.5 mg, in pregnancy anemia in India.

Material and Methods: The post marketing surveillance study was an open label and non-comparative study. The drug R. B. Tone XT was administered to 15 anemic pregnant women in the age range of 22-32 years. Drug was administered from 13th week of pregnancy until delivery. Baseline haemogram was evaluated at 13th week of gestation before starting iron supplementation. Another haemogram was evaluated at one week prior to the predictable date of delivery to estimate increase in levels. Study included birth weight, gestational age and increase in haemoglobin level as therapeutic outcomes. Efficacy & tolerability was evaluated by the investigator. The subjective improvement of the clinical symptoms like fatigue, and breathlessness were evaluated on a predefined scale of Fatigue Severity Scale (FSS) and Breathless Severity Scale (BSS), respectively.

Results: All the patients completed the study. Haemoglobin level was increased by 10.80% from the base line. Mean birth weight of infants was found to be 2.93 ±0.07 kg. Mean gestational age at the time of delivery was 38.92 ± 0.38 weeks. Not a single case of preterm delivery was reported during the study. Efficacy and tolerability was rated by the investigator as excellent in 53.33% and good 26.66% of the patients. The study drug showed excellent GI tolerability with few (13.33%) incidence of gastritis & constipation. Patients reported with significant improvements in fatigue and breathlessness on FSS and BSS scale, respectively.

Conclusion: R. B. Tone XT has excellent efficacy, tolerability, & safety in pregnancy anemia with an excellent pregnancy outcome in terms of gestational age and birth weight.

Keywords: Pregnancy anaemia,ascorbate,gestational age.

Introduction:

Maternal mortality continues to be a major health problem in the developing world. Nearly 600,000 women die each year as a result of complications of pregnancy and childbirth; most of these deaths could be prevented with attainable resources and skills.¹ Iron deficiency anemia (IDA) remains the commonest medical disorder in pregnancy in the developing world ¹², with the burden of disease impacting on both the mother and the newborn.

Anaemia ranges from mild, moderate to severe and the World Health Organization (WHO) pegs the haemoglobin level for each of these types of anaemia in pregnancy (Table 1).³
Table 1: WHO haemoglobin levels used to define pregnancy anemia.

<table>
<thead>
<tr>
<th>Pregnancy anemia</th>
<th>Hb threshold (g/dl)</th>
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<tr>
<td>Mild Anemia</td>
<td>10-10.9</td>
</tr>
<tr>
<td>Moderate Anemia</td>
<td>7-9.9</td>
</tr>
<tr>
<td>Severe Anemia</td>
<td>&lt;7</td>
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</table>

Anaemia affects an estimated 50 per cent of the Indian population.\(^4\) In India the National Nutritional Anaemia Control Programme (NNACP) was initiated in 1970 to provide free iron-folic acid (IFA) supplementation to all pregnant women commencing from the second trimester until 3 months of lactation. Following nearly 20 years of the IFA program the National Family Health Survey (NFHS) reported that the prevalence of IDA had dropped from the previous estimated 80-90\% to 49.7\%.\(^5\)

The Indian Council for Medical Research (ICMR)’s district nutrition survey data also reported similar anemia prevalence of 84.2\%, with 13.1\% being in the severe anemia category.\(^6\) In another survey, a total of 84 per cent pregnant and 92.2 per cent lactating women were anemic with severe anaemia in 9.2 and 7.3 per cent respectively.\(^4\)

A pregnant woman requires about 2 to 4.8 mg iron every day. To have it from the dietary sources, one must consume 20-48 mg of dietary iron. This is practically impossible in India because of average vegetarian diet does not contain more than 10-15 mg of iron and the phytate content in it further reduces iron absorption. Moreover majority of Indian women enter pregnancy already with iron depleted condition. The iron store is markedly diminished when there is fall in Hb values. Therefore in India there is a need for routine iron supplementation to all pregnant women.\(^7\)

Taking into account the above aspect, the study was undertaken to evaluate the clinical benefits associated with R. B. Tone XT administration (Combination of ferrous ascorbate, Folic acid, Zinc) in pregnancy anemia.

**MATERIALS AND METHODS**

**Subjects:**

The post marketing surveillance study was an open label and non-comparative study. Study drug R. B. Tone XT tablet, (Medley pharmaceutical, Mumbai) containing ferrous ascorbate equivalent to elemental iron 100 mg + folic acid 1.5 mg + elemental zinc 22.5 mg was prescribed once daily to all pregnant women from 13\(^{th}\) week of gestation until delivery. Informed consent was obtained from the patients & the post marketing surveillance was in accordance with the clinical principles laid down in declaration of Helsinki. Fifteen pregnant women with anemia (Hb < 11 g/ dL as per WHO) were enrolled in the study. The patients were in the age range of 22- 32 years.

**Parameters evaluated:**

The patients were monitored for haemoglobin improvement by taking blood samples and subjective improvement of symptoms were evaluated by FSS and BSS scale.

1. **Haemogram**

   Baseline & the end of therapy haemogram were done.
2. Pregnancy outcomes:
For more information on the functional consequences of iron supplementation during pregnancy, birth weight and gestational age as outcomes of the study were included.

3. Global assessment of efficacy and tolerability:
Investigator was asked for the assessment of efficacy and tolerability. Efficacy and tolerability were assessed on predefined characteristics of Poor, Good, and Excellent.

4. Assessment of fatigue and breathlessness:
Using established principles, a scale measuring key symptoms of fatigue and breathless was constructed.

   Fatigue Severity Scale (FSS):
   Efficacy of treatment in improving the fatigue was assessed by the investigator on a 10 point Fatigue Severity Scale (FSS); in which “0” marked as “none” and “10” marked as “severe”.

   Breathless Severity Scale (BSS):
   Severities of breathlessness was recorded on Breathless Severity Scale (BSS) scores 0 to 5 (0= only during exercise and 5= too breathless to leave home).

5. Adverse events:
Each subject was carefully monitored for adverse events. All the adverse events either reported by patients or observed by the investigator were recorded with information about severity, action taken and outcome of the action. Severities of adverse events were recorded on a scale of scores 1= resolved, 2=improved, 3=unchanged, 4=worsened).

Analysis of data:
Data analysis on various patient outcome measures was performed using graph pad prism 5. Comparison between the baseline values with the value at the end of the study was made, by applying paired student t-test. The values were expressed as Mean ± SEM (Standard Error Mean).

RESULTS
All the patients enrolled in this study, completed the study. Average age was 27.93 ± 0.81 years.

1. Haemoglobin
The effects of R. B. Tone XT on the haemograms are mentioned in table 2. It was observed that with the use of R. B. Tone XT, there were significant improvements in the Haemoglobin (Hb) levels (p<0.001), RBC count (p<0.05) and Packed Cell Volume (PCV) (p<0.001) from the baseline. Moreover, administration of R. B. Tone XT resulted in 10.80 % & 5.42% increase in baseline Hb & RBC values, respectively.

Figure 1: Effect of R. B. Tone XT on Haemoglobin levels. (**p<0.001).
Table 2: Effect of R. B. Tone XT on haemogram.

<table>
<thead>
<tr>
<th>Biochemical Findings</th>
<th>Baseline</th>
<th>End of Study</th>
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<tr>
<td></td>
<td>Hb (g/dL)</td>
<td>9.44±0.255</td>
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<tr>
<td></td>
<td>RBC (million/µL/mm³)</td>
<td>4.06 ± 0.11</td>
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<tr>
<td></td>
<td>PCV (%)</td>
<td>31.1±0.65</td>
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<tr>
<td></td>
<td>MCV (%)</td>
<td>76.7±2.63</td>
</tr>
<tr>
<td></td>
<td>MCH (Pg)</td>
<td>23.3±0.93</td>
</tr>
<tr>
<td></td>
<td>MCHC (g/L)</td>
<td>28.4±1.82</td>
</tr>
<tr>
<td></td>
<td>Reticulocyte Count (10⁶/mm³)</td>
<td>15.9 ± 0.39</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM (Standard Error Mean)
*p<0.05, **p<0.01, ***p<0.001
PCV: Packed Cell Volume; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RBC: Red Blood Cell;

2. Pregnancy outcomes:
Till the completion of study, not a single case of preterm delivery and low birth weight were reported. Mean birth weight of infants was found to be 2.93 ±0.07 kg. Mean gestational age at the time of delivery was 38.92 ± 0.38 weeks.

3. Assessment of efficacy and tolerability:
On the predefined scale of efficacy & tolerability, R. B. Tone XT was effective and has excellent tolerability as assessed by the investigator. From the 15 (100%) treated patients, the 53.33 % patients were assessed excellent ratings and 46.66 % patients were assessed good ratings for efficacy as well as tolerability by the investigator (figure 2).

Figure 2: Assessment of efficacy & tolerability with R. B. Tone XT.
4. Assessments of fatigue and breathlessness:
All the 15 patients (100%), who were enrolled in the study showed fatigue on FSS scale. After completion of R. B. Tone XT therapy there was significant (p<0.001) improvement in the FSS scores from baseline (3.27±0.37) to the end of the study (1.13±0.29) as shown in figure 3 (a).
All the 15 patients (100%), who were enrolled in the study showed difficulty in breathing on BSS scale. After completion of R. B. Tone XT therapy there was significant (p<0.001) improvement in the BSS scores from baseline (1.93±0.26) to the end of the study (0.67±0.16) as shown in figure 3 (b).

Figure 3: Clinical assessment of patients for the effects of R. B. Tone on fatigue (a), and breathlessness (b) based on FSS & BSS scale, respectively. (**p<0.001)
Values are expressed as Mean ± SEM (Standard Error Mean).
*p<0.05, **p<0.01, ***p<0.001

5. Adverse Events:
The study drug showed excellent GI tolerability with few incidences (13.33%) of gastritis & constipation. All the adverse events were mild to moderate in origin and resolved with adequate treatment.

DISCUSSION:
Despite viable ways to treat iron deficiency anemia, the disease is still the most prevalent nutritional deficiency in the world. While giving iron supplements to pregnant women is part of most public health regimens, there has been little success in decreasing high rates of iron deficiency anemia.8

There are two general types of iron supplements which contain either the ferrous or ferric form of iron. In India, there are many marketed brands of liquid iron preparations available which contain iron salts/complexes like ferrous sulphate, ferrous fumarate, ferrous gluconate, ferric ammonium citrate, colloidal iron, ferrous ascorbate, and ferric hydroxide polymaltose complex (also called Iron Polymaltose Complex or IPC).
In case of ferrous compounds [Fe(II) salts], at alkaline pH, Fe(II) is rapidly oxidized, resulting in the formation of large, non-absorbable ferric hydroxide polymers, which will attack the gut wall and produce a range of gastrointestinal symptoms and discomfort. Addition of ascorbic acid converts the ferric form to ferrous form thus making it absorbable from duodenum and upper jejunum, resulting in considerable enhancement of the absorption of iron. It has been demonstrated that Fe(II) ascorbate is less easily oxidized than Fe(II) in ferrous sulphate. Absorption of ferrous ascorbate averaged 52% higher than ferrous sulphate in subjects with iron deficiency. Thus when administered as ferrous ascorbate, Fe(II) salt is more resistant to oxidation at alkaline pH, delivers maximum amount of ferrous iron to the duodenal brush border and at the same time produces minimum GI adverse effects.

Adequate folate intake during the periconception period, the time right before and just after a woman becomes pregnant, helps protect against a number of congenital malformations, including neural tube defects. Folate deficiency during pregnancy may also increase the risk of preterm delivery, infant low birth weight and fetal growth retardation, as well as increasing homocysteine level in the blood, which may lead to spontaneous abortion and pregnancy complications, such as placental abruption and pre-eclampsia.

Zinc, an essential trace element, plays a critical role in normal growth and development, cellular integrity and many biological functions, including protein synthesis and nucleic acid metabolism. Since all these are involved in cell division and growth, zinc is believed to be important for fetal growth and development. Zinc requirement is increased during pregnancy but the lack of a valid indicator precludes a true estimate of zinc deficiency in pregnancy even in developed countries. Preliminary human data suggest a beneficial effect of prenatal zinc supplementation trials in particular on infant's neurobehavioral development.

Zinc supplementation improves pregnancy and infant outcome.

Results from this study show that there are improvements in hematological parameters as well as pregnancy outcomes. The data presented in table 2 and figure 1-3 indicates the effectiveness of R. B. Tone XT in various pregnancy related outcomes. Oral therapy of R. B. Tone XT showed 10.80% increase in hemoglobin and 5.42% increase in RBC count. Compliance is inevitably an issue for any long-term treatment regimen, but the high rate of gastrointestinal adverse events is likely to be an additional barrier. However, throughout the study R. B. Tone XT was assessed safe based on the less adverse event recorded. Not a single incidence of preterm delivery and low birth weight was observed at the end of the study. The subjective improvement of the clinical symptoms is equally important, thus, we evaluated the major clinical symptoms like fatigue, and breathlessness on a predefined scale of FSS and BSS, respectively. At the end of study all the clinical symptoms score significantly reduced from baseline. In addition to this common side effects like gastritis and constipation of
mild to moderate severity were reported which were
resolved with adequate treatment.
Thus the study proves that R. B. Tone XT is
efficacious and safe in anemia associated with
pregnancy.
CONCLUSION:
The fixed dose combination of Ferrous ascorbate
(equivalent to elemental iron 100 mg), Folic acid
(1500 mcg) and elemental Zinc (22.5 mg) (R. B. Tone
XT) therapy achieves a better outcome for the
management of iron deficiency anemia in pregnancy
with excellent efficacy, tolerability & safety. R. B.
Tone XT also improves pregnancy outcomes in terms
of gestational age at the time of delivery and birth
weight.

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