Original Article

Effect of iron and folic acid tablet versus capsule formulation on treatment compliance and iron status among pregnant women: A randomized controlled trial

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Abstract

Background: Iron supplementation during pregnancy in programmatic settings has failed to produce desired results. Formulation of iron supplementation may have a role in compliance and hematological parameters. **Objective:** We did this study to compare the compliance to iron supplementation, change in mean hemoglobin and serum ferritin level after iron supplementation in capsule form and tablet form during pregnancy. **Materials and Methods:** In this single-blinded (investigator blinded), active comparator, randomized controlled trial we enrolled pregnant women (aged ≥18 years) from May to November 2014 during second trimester to receive iron supplementation either as capsule (ferrous fumarate) or tablet (ferrous sulphate) during entire pregnancy. The outcome was compliance (good compliance ≥ 90%) to iron supplementation assessed by pill count and change in mean hemoglobin and serum ferritin. Statistical significance was tested using Chi-square test and Student's *t* test. **Results:** We enrolled and randomized 204 pregnant women for iron supplementation; capsule form ($n = 100$) and tablet form ($n = 104$). Out of which 52 (25.5%) women (23 in capsule arm and 29 in tablet arm) were lost to follow up. As compared to tablet arm, the capsule arm had higher good compliance (22% vs 16.8%), increase in mean hemoglobin (0.79 vs 0.44 gm/dL) and increase in mean serum ferritin (2.50 vs -2.14 ng/mL), but the difference was not statistically significant. **Conclusion:** Pregnant women who received either of the formulation reported a low compliance. Iron supplementation in capsule formulation resulted in more increase in blood hemoglobin level, though clinically insignificant.

Keywords: Compliance, ferritin, hemoglobin, pregnancy

Introduction

Nutritional anemia, a major public health problem in India, is primarily due to iron deficiency.[1] Pregnant women are most susceptible to develop iron deficiency anemia which is associated with maternal and fetal complication.[2-4] Despite large-scale health interventions, the prevalence of iron deficiency anemia in India has not declined satisfactorily. In India, fourth round of National Family Health Survey (NFHS-IV) conducted in year 2015–16 report prevalence of anemia among pregnant women to be 50.3%, a reduction of nearly 8% from the previous round of 2005–06.[5,6]

In a nationally representative survey in 2002, only 15% of pregnant women had consumed more than 70% of the recommended dietary allowance of Iron.[7] Government of India guideline recommends iron and folic acid supplementation for minimum 100 days during ante natal period. Apart from many other factors, compliance to oral iron supplementation during

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Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_339_18

How to cite this article: Srivastava R, Kant S, Singh AK, Saxena R, Yadav K, Pandav CS. Effect of iron and folic acid tablet versus capsule formulation on treatment compliance and iron status among pregnant women: A randomized controlled trial. J Family Med Prim Care 2019;8:378-84.

pregnancy is poor due to side effects and lack of perceived benefit of iron intake.[8] Coverage evaluation Survey by UNICEF in year 2009 reported a compliance of 30% to 100 days of oral iron supplementation in India.[9] Maternal iron indicators such as hemoglobin and serum ferritin level are dependent on proportion of prescribed tablets consumed during pregnancy. Various studies have postulated that compliance to oral iron therapy is dependent on formulation of oral iron.[10,11] Iron supplementation in capsule formulation instead of tablet is postulated to increase the bioavailability of iron and decrease the side effects due to minimal interference from gastric secretion.[12] Therefore, iron supplementation delivered in capsule formulation is hypothesized to enhance the overall compliance and thereby larger increase in hemoglobin and other body iron status indicators compared to oral formulation. This assumption however has not been documented in field settings in India. The primary objective of this study was to test whether the compliance to capsule formulation would be better than tablet formulation for oral iron supplementation among pregnant Indian women. The secondary objective was to compare the change in mean hemoglobin and serum ferritin level following oral iron supplementation. We hoped that the findings of this study would help policy makers in revisiting the strategy of anemia control during pregnancy.

Materials and Methods

Study design and participants

We did this single-blinded, active Comparator, simple Randomized, Controlled Trial (RCT) to compare the compliance to same dose of iron supplementation in capsule (intervention) with tablet formulation (control) among pregnant women.

This study was done in a subdistrict hospital in district Faridabad. The recruitment of participants was done from May to November 2014. The clientele for antenatal and natal services were mostly from nearby urban, periurban area. The hospital had ante natal clinics on 3 days in a week and provided comprehensive antenatal care including specialist consultation, essential diagnostic services, free drugs, and ultrasonography facility. The hospital provided 24 × 7 delivery services including both essential and emergency obstetric services. Study participants were pregnant women aged ≥18 years with gestational age >12 weeks, attending the antenatal clinic of hospital and who had not consumed any iron supplement prior to enrollment in the study. Exclusion criteria were any known hematological disorder or severe anemia (hemoglobin ≤7 gm/dL). Eligible pregnant women were recruited in the study after obtaining written informed consent. The study was approved by the Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi and the clinical trial protocol is registered with Clinical Trial Registry of India (Reference number: CTRI/2018/04/013361).

Sample size calculation

Sample size was calculated for the primary outcome, i.e., compliance to oral iron supplementation. We assumed the compliance in control arm (tablet) as 43%, based on the report of latest Coverage Evaluation Survey.[9] We wanted to detect an absolute increase of 20% in the intervention arm at 5% significance level, and 80% power. Assuming an attrition rate of 15% the estimated required sample size was 112 in each arm with 1:1 ratio.

Baseline assessment, randomization, and blinding

All consecutive eligible pregnant women consenting to participate were randomly assigned through random number generation in a 1:1 ratio to receive iron and folic acid supplementation in either capsule formulation (intervention) or tablet formulation (active control). Recruited women were administered an interview schedule to elicit the baseline information regarding sociodemographic, obstetric, and dietary history. Socioeconomic status was assessed using modified Kuppusamy's scale.[13] A total of 4 mL of venous blood sample was drawn through venipuncture of the cubital vein under strict aseptic precaution to estimate blood hemoglobin and serum ferritin level. Blood sample was immediately centrifuged and kept at -20°C. Sera was transported under cold chain to a central laboratory for analysis. Blood hemoglobin was measured using a point of care test based on absorbance measurement of whole blood at an Hb/HbO2 isobestic point (HemoCue Hb 301 system manufactured by HemoCue AB, Ängelholm Sweden). Quality control was achieved with built in self-test using liquid controls as per the manufacturer's instructions. This method is reported to have high correlation ($r = 0.995$) with hemoglobin estimated by cyanmethemoglobin method.[14] Serum ferritin was estimated at an accredited laboratory using a commercial ELISA kit (ORG5FE, ORGenTec, Mainz, Germany). All tests were performed by trained laboratory personnel.

Randomization was done after baseline assessment to ensure that the investigators and laboratory staff were blinded to treatment allocation. A pharmacist did the randomization using random numbers which were generated by St. Johns Research Institute (funding agency) and were directly communicated to the pharmacist. The funding agency and the pharmacist had no role in any other aspect of study, such as analysis, baseline, or outcome assessment.

Intervention

Pregnant women received iron supplementation either in the form of capsule or tablet at the time of enrolment, as per their treatment allocation**.** Active ingredient of capsule was ferrous fumarate, whereas the tablet had ferrous sulphate. Both the formulations are reported to have similar bioavailability and side effects.[15,16] Both capsule and tablet each had 100 mg of elemental iron and 500 mcg of folic acid. Ferrous sulphate tablet (Generic) was provided routinely through the government supply chain. Ferrous fumarate capsule (Autrin®, Wyeth limited) was procured from open market. Since, it was a pragmatic trial; no attempt was made to estimate the actual iron content of the formulations. Following national guidelines, 100 mg/day

of elemental iron was provided to women with hemoglobin level >11 gm/dL, whereas 200 mg/day of elemental iron was provided to women with hemoglobin level ≤11 gm/dL at the time of initial assessment. Blister pack containing 30 tablet or capsule was provided during recruitment. Replenishment was provided either during the monthly hospital visit by pregnant women or during house visit by the study team, if the woman had missed her scheduled monthly hospital visit. Study team collected empty blister pack provided during the previous visit to estimate the numbers of tablet/capsule consumed. Iron supplementation continued for three months, or till the termination of the pregnancy or loss to follow up, whichever was earlier. Hemoglobin estimation was repeated monthly if hemoglobin level was ≤11 gm/dL; and 3 monthly if the last measured hemoglobin level was >11 gm/dL, as per the national guidelines. Dosage of iron supplementation was adjusted based on the last measured hemoglobin level.

Outcome

The primary outcome of the study was compliance to oral iron supplementation. The secondary objective was the change in mean hemoglobin and serum ferritin level following iron supplementation. Compliance was assessed by pill count. We counted the number of empty blisters in the returned pack. Consumption of ≥90% of the prescribed pills was categorized as good compliance, whereas <90% was categorized as poor compliance.[17]

Statistical analysis

The analysis plan was to test superiority of capsule formulation over tablet formulation for absolute increase of 20% in compliance. We set *a priori* the clinically meaningful increase in the mean increase of hemoglobin level as 1 gm/dL. Chi-square test was done to ascertain the statistical significance of the increase in compliance. Student's and paired *T* test was done to compare the change in mean hemoglobin level between the two groups.

Results

We recruited 204 eligible pregnant women in the study and randomly assigned them to receive iron supplementation in capsule formulation (n = 100) or tablet formulation (n = 104). A total of 52 (25.5%) women, of which 23 (23%) were in capsule group and 29 (27.9%) in tablet group were lost to follow-up [Figure 1]. Following local custom, pregnant women often shifted residence to their family of origin particularly during their first pregnancy. This was the most common cause for loss to follow-up.

The mean age of the pregnant women recruited in study was similar in both the groups (23.8 years in capsule group and 23.5 years in tablet group). Baseline characteristics are presented in Table 1.

Compliance

Proportion of women with good compliance (>90%) at the end of 3 months was 16.8% in control arm and 22.0% in intervention arm. The difference was statistically not significant. A total of 159 women (control arm = 78, and intervention arm = 81) provided information on reasons for nonconsumption of oral iron supplementation. Almost half (46%) in intervention arm and even higher (60%) in control arm cited forgetfulness as a reason for not consuming oral iron supplement. Gastrointestinal symptom was the reported cause for not consuming oral iron supplementation in 48.1% in intervention arm and 37.2% in control arm. The difference was statistically not significant.

Mean change in hemoglobin level

The mean (SD) net gain in hemoglobin level for control and intervention arm during the intervening period between recruitment and end of the study was 0.44 (1.50) gm/dL and 0.79 (1.21) gm/dL, respectively [Table 2]. Thus, the excess net

Table 1: Sociodemographic and obstetric history of the study participants

Variable	Category	Control arm (n=104) n (%)	Intervention arm (n=100) n (%)
Age (in years)	Mean (SD)	23.5 (3.6)	23.8 (3.3)
Place of residence	Urban	88 (84.6)	87 (87.0)
	Rural	16 (15.4)	13 (13.0)
Socioeconomic status	Upper	38 (36.5)	36 (36.0)
	Middle	34 (32.7)	35 (35.0)
	Lower	32 (30.8)	29 (29.0)
Occupation	Employed	1 (1.0)	3 (3.0)
	Unemployed	103 (99.0)	97 (97.0)
Education	Graduate	10 (9.6)	18 (18.0)
	Inter and high school	32 (30.8)	28 (28.0)
	Middle and primary school	40 (38.5)	37 (37.0)
	Illiterate	22 (21.1)	17 (18.0)
Menstrual cycle	Regular	99 (95.2)	89 (89.0)
	Irregular	5 (4.8)	11 (11.0)
Gravida	Median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)
Parity	Median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-1.0)
Abortion	Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Live births	Median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)

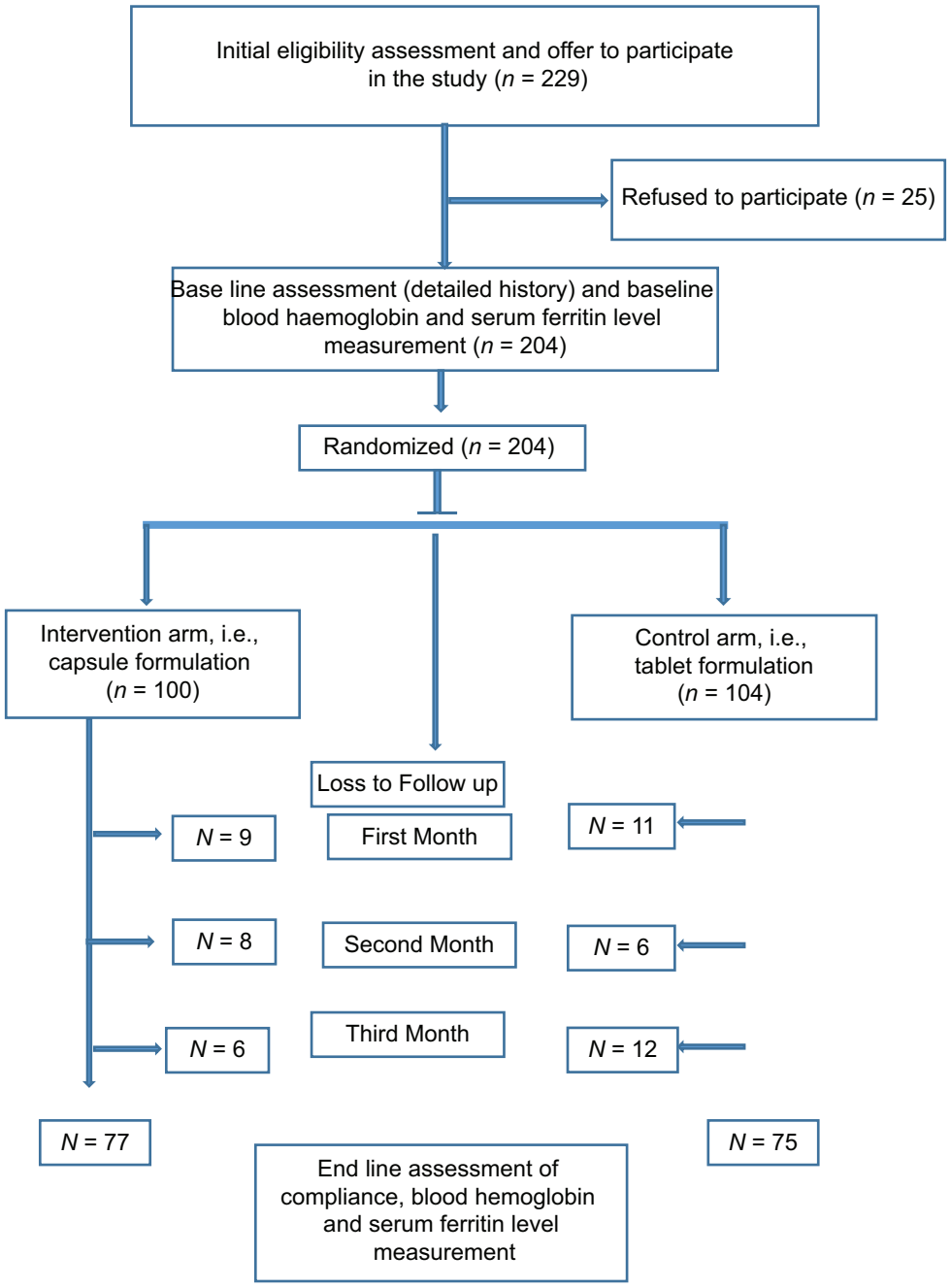

Figure 1: Flow of participants

Table 2: Mean change in hemoglobin and serum ferritin level in two arms of the study

Variable	Arm	Mean (±SD)	*P* (independent *t* test)
All Pregnant Women			
Mean change in haemoglobin (gm/dL)	Control (*n*=75)	0.44 (1.50)	0.112
	Intervention (*n*=77)	0.79 (1.21)	
Mean change in serum ferritin (ng/mL)	Control (*n*=75)	−1.14 (30.80)	0.933
	Intervention (*n*=77)	-0.80 (19.20)	
Pregnant Women with good compliance (> 90%)			
Mean change in haemoglobin (gm/dL)	Control (*n*=16)	0.83 (1.37)	0.409
	Intervention (*n*=20)	1.19 (1.01)	
Mean change in serum ferritin (ng/mL)	Control (*n*=16)	−2.14 (6.93)	0.420
	Intervention (*n*=20)	2.50 (20.18)	

mean hemoglobin gain after oral iron supplementation in the intervention arm over control arm was 0.35 gm/dL, which was statistically not significant ($P = 0.11$).

We also attempted similar analysis that was restricted to only those pregnant women that had good compliance (>90%) to oral iron supplementation. In this subgroup analysis, the mean (SD) increase in hemoglobin in control arm was 0.83 (±1.37) gm/dL compared to 1.19 (±1.01) gm/dL in intervention arm. The difference was statistically not significant ($P = 0.41$).

Mean change in serum ferritin level

The mean serum ferritin level at the end of the study was lower than the baseline level despite oral iron supplementation prescribed as per the national guidelines. Among pregnant women that completed the trial, the mean (SD) serum ferritin level compared to baseline declined by 1.14 (30.8) ng/mL in control arm and 0.80 (19.2) ng/mL in intervention arm. The difference between the two arms was statistically not significant (*P* value 0.93). When the analysis was restricted to those pregnant women who had good compliance to oral iron supplementation, the serum ferritin level at the end of trial in control arm declined by 2.14 (±6.93) ng/mL. In the intervention arm there was slight statistically nonsignificant increase in mean (SD) serum ferritin level of 2.50 (±20.18) ng/mL ($P = 0.42$).

Discussion

Study background

Many factors including formulation and mode of delivery affect the bioavailability of iron. Anecdotal evidence suggested that capsule formulation was perceived by the patients to be more effective than the tablet formulation. A study among pregnant women in India showed that capsule and syrup formulation had better bioavailability and fewer side effects than tablet formulation.[18] However, it is not clear whether supplementation of oral iron as capsule formulation will lead to much more improvement in hematological parameters than iron tablets. We hypothesized that capsule supplementation will have better compliance and resulting in higher increase of hemoglobin and serum ferritin. If the hypothesis was found to be correct then it would have major public health significance for pregnant Indian women most of whom suffer from anemia. However, in this study, we found that compliance was almost similar in both the groups resulting in nonsignificant difference in hemoglobin and serum ferritin from recruitment to the end line as well as change in hemoglobin and serum ferritin was not significantly affected by the type of iron formulation.

Comparison of capsule and tablet as iron supplementation

To the best of our knowledge, there is no head-to-head RCT comparing compliance and hematological parameters with iron supplementation as capsule and tablet formulation during pregnancy. In a prospective study in which iron supplementation was given based on physician prescription, pregnant women had similar side effect profile and response to iron indicators irrespective of whether supplementation was ferrous sulphate or ferrous fumarate.[16] However, there are few RCTs which have compared different other formulations. In an RCT done in India among pregnant women, iron polymaltose complex (IPC) had almost similar increase in hemoglobin as compared to ferrous sulphate.[19,20] Another RCT found that oral IPC as compared to ferrous sulphate tablets had a significantly more increase in hematocrit and serum ferritin level without any significant increase in hemoglobin after 90 days of follow-up (6.62 ± 2.04% vs 5.81 ± 2.4%, $P = 0.07$; and 64 ± 40 ng/mL vs 41 ± 28 ng/mL, $P = 0.004$, respectively). Although adverse events occurred significantly more frequently in the ferrous sulfate group.[21] Even in children, it has been shown previously that composition of iron does not have any significant difference in either the compliance or hematological parameter.[22] Thus, evidence regarding effect of iron formulation, i.e., either capsule or tablet on either compliance or hematological indicators remains inconclusive.

We also noted that the compliance to oral iron supplementation was overall poor (less than 25%), irrespective of the type of oral iron formulation. Two important reasons reported here were forgetfulness and side effects particularly gastrointestinal side effects. So, it appears that the pregnant women did not perceive that oral iron in capsule formulation was any better compared to tablet formulation. However, in a previous study from India, less side effects were reported after supplementation as capsule rather than tablet.[18] Since amount of iron in both formulations was same, it is reasonable to expect similar rate of gastrointestinal side effects. Thus, similar poor compliance in both arms of the study is along the expected line.

The mean hemoglobin rise after oral iron supplementation was small and clinically not meaningful (0.44 and 0.79 gm/dL in control and intervention arms, respectively). This finding is not surprising considering that the compliance was poor irrespective of oral iron formulation. Therefore, continuing with the existing national policy for prevention and control of anemia in pregnant women in India is unlikely to achieve its goal in real life situation.

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We also did a subgroup analysis for comparison of hematological parameters with respect to level of compliance. Even in pregnant women with good compliance, the mean (SD) increase in hemoglobin in control arm was 0.83 (±1.37) gm/dL compared to 1.19 (±1.01) gm/dL in intervention arm. The difference was statistically not significant ($P = 0.409$). We realize that the number of pregnant women included in the analysis was small. However, the important message is that even if the compliance to oral iron supplementation were to improve, the rise in hemoglobin level is likely to be of borderline clinical significance. This was true irrespective of formulation used for supplementation. Equivalence in biochemical parameter is understandable because the iron content in both the formulations were same. Therefore, the consequences in terms of change in biochemical parameters would be expected to be similar.

The mean serum ferritin level at the end of the study was lower than the baseline value for both arms. This suggests that despite oral iron supplementation the body iron reserve had declined. The oral iron supplementation, irrespective of compliance status, had failed to replenish body iron reserve.

Strengths and limitations

To the best of our knowledge, this is the first study to do head-to-head RCT comparing compliance and hematological parameters with iron supplementation as capsule and tablet formulation during pregnancy with a sample size of more than 200. Thus, this study has important pragmatic implications in treatment and control of anemia during pregnancy. However, 25% loss to follow-up was higher than anticipated. However, there was no differential loss to follow-up across the treatment arms. Reduced sample size could adversely impact the power of the study. We looked at the 95% confidence interval range which appeared reasonably narrow. Hence, we believe that the loss to follow-up did not adversely affect the validity of the findings. Also, we did not collect information regarding self-medication or medication prescribed by a private practitioner and thus could not conduct per protocol analysis.

Frequent visits/contacts of the study staff with pregnant women could have altered the behavior in a positive direction. Therefore, the observed compliance could be an overestimate of what actually occurs in real life situation. However, this effect is expected to be similar for both arms of the study. Therefore, the difference in compliance rate between the two arms would remain unaffected.

The least count of serum ferritin estimation was 10 ng/mL. Therefore, even if the serum ferritin level was below 10 ng/mL it was recorded as 10 ng/mL. This could have resulted in overestimate of mean serum ferritin level. We had not measured other markers of the iron status such as Total Iron Binding Capacity (TIBC), and serum iron which would have enhanced our ability to interpret the results.

Presence of chronic infection could lead to artificially raised serum ferritin level. C reactive protein (CRP) is a surrogate marker of chronic infection. We had not measured CRP. If some of the pregnant women also had chronic infection, not an unreasonable assumption, then the mean serum ferritin was likely to be an overestimate. Thus, the true status of body iron reserve was probably worse than what was apparent by the study finding.

Conclusion and Future Directions

Thus, we conclude that the compliance to oral iron supplementation among pregnant Indian women, irrespective of formulation, was poor. Oral iron supplementation as ferrous fumarate in capsule formulation resulted in clinically insignificant increase in blood hemoglobin level; and actual decline in body iron reserve as indicated by serum ferritin level as compared to supplementation as ferrous sulphate tablets. This study did not give a conclusive evidence if iron status and compliance can increase just by changing the iron formulation. Thus, it is important to do qualitative study to develop hypothesis regarding poor compliance followed by quantitative study so as to improve the compliance

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

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