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Research Article

ANAEMIA IN THE MALE HEALTHY VOLUNTEERS PARTICIPATING IN BIOEQUIVALENCE STUDIES

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ABSTRACT

Healthy male volunteers participate in bioequivalence studies conducted to establish the sameness between test and reference drugs. These studies involve loss of blood which adds to the already prevalent nutritional anemia in the volunteers. This study attempts to understand the magnitude and severity of anemia among the volunteers participating in bioequivalence studies. 100 laboratory reports of volunteers were randomly obtained and laboratory parameters were entered in case record forms. The results showed 52 % of volunteers were anemic with hemoglobin level less than 13 g/dl.

Keywords: Anaemia, healthy volunteers, bioequivalence studies.

INTRODUCTION

The number of the Pharma Industries are continuously being increased resulting in increase of the production of the generics, to get approval for marketing authorization of these generics, these drugs needs to be tested against the already approved available brands in market and thus the conduct of the clinical studies happen to compare the rate and extent of new drug is equivalent to that of the already approved marketed drug. These studies are conducted at particular sites on healthy population of the uniform age, race and gender of the humans at the Contract Research Organizations. India, being a rapidly developing and Newly Industrialized country is becoming a hub of the clinical trials and growth of the Contract Research Organizations that support and provides services on the biopharmaceutical and medical devices are being increased comparatively. The growth of the CRO's is increased by 15 % from the year 2007 and may further increase in future.[1] Currently many foreign countries are focusing on India to conduct the clinical studies because of its

- Low cost involved in conduct of the study
- Huge population
- Widely accepted Asian race of the population by different regulatory bodies.

In challenge to the conduct of the Clinical studies, these CRO's pool huge number of the volunteers who are willing to participate in the clinical trial studies by taking a Consent for participation, these volunteers are screened for the medical examination, Physical examination and Systemic examination and are compensated with certain amount as agreed and defined as per the standard set procedures and approved by the Independent ethics committee/Institutional Review board.

Selection criteria for subjects

As per the CDSCO.nic.in the studies should be normally performed on healthy adult volunteers with the aim to minimize variability and permit detection of differences between the study drugs. Subjects can be males or females; however the females are generally excluded due to the teratogenecity and other administrative and logistical problems to handle the female volunteers. These CRO's during the screening for healthy volunteers will perform a battery of Lab investigation to ensure healthy status of the volunteers like serology, Hematology, Biochemistry, Chest X-ray, ECG including LFT and RFT profiles. Central drug standard control organization issued guidelines for Bioavailability and Bioequivalence studies. In General, when the Volunteer participate in the studies the CRO's take blood sampling in single dose trails of an immediate release product at least there should be sampling points during the absorption phase, three to four at the projected T max and four points during the elimination phase. The No. of points used to calculate the terminal elimination rate constant should be preferably determined. To capture three elimination half lives and is continued for a sufficient period to ensure that the area extrapolated from the time of the last measured concentration to infinite time is only a small percentage (normally less than 20 %) of the total AUC. And is of around 250 ml - 350 ml in different periods after certain washout period depending upon the protocol to obtain plasma sample.[2] And as per the regulation of ICMR guidelines on human subjects from healthy adults and non-pregnant women who weigh normal for their age and not more than 500 ml blood is drawn in an 8 week period and frequency of collection is not more than 2 times per week.[3] Though the regulators are taking enough steps to control the volunteer cross participation by developing cross participation verification system to avoid cross participation in multiple clinical studies /CRO's. This system ensures volunteer safety and integrity of the study being conducted. In spite of the regulatory stringent actions cross participation and continued participation of volunteers in studies after each window period between studies lead to lowering of hemoglobin levels apart from the nutritional deficiencies in diet and infections contributing to anemia. There are no reports on hemoglobin levels of volunteers participating in bioequivalence studies hence the present study was conducted to understand prevalence of anemia among the healthy volunteers participating in Bioequivalence studies and severity of anemia among healthy volunteers.

MATERIALS AND METHODS

The study related data was obtained from screening records of volunteers after prior approval from the management. 100 laboratory reports of volunteers were retrieved randomly from the records section and data was entered in case record forms. The data includes age, blood group, hematological, biochemical and serological test results. The data was entered in Microsoft X cel and the data was represented as mean ± SD.

RESULTS

The mean age of the volunteers was 29.9 ± 6.14 years. The most common blood group was O^+ which was found in 43 % of volunteers. The mean Hb level of volunteers was 13.22 ± 1.39 g/dl. The Hb level of > 13 g/dl was taken as normal according to the laboratory reference range. Among 100 male volunteers 52 % had Hb < 13 g/dl; the distribution of Hb levels is shown in Figure 1. The mean values of other hematological and biochemical parameters are shown in Table 1. The most common reason for screen failure of volunteers was low Hb levels (52 %). The other reasons for screen failure were elevated ESR (42 %), abnormal RBC count (28%) and abnormal differential WBC count (13 %), pus cells in urine (8 %), abnormal LFT (4 %) and abnormal platelet count (1 %).

Table 1: Mean ± SD of the hematological and biochemical parameters of volunteers participating in BE studies

Parameter	Mean ± SD
Hemoglobin (g/dl)	13.22 ± 1.39
RBC count (mil/µl)	5.04 ± 0.53
Platelet count (Lakhs/cumm)	2.87 ± 0.55
Packed cell volume	39.74 ± 4.02
WBC count	7567 ± 1415
ESR (mm/hr)	13.89 ± 7.43
Blood Urea (mg/dl)	32.61 ± 7.83
Serum creatinine (mg/dl)	0.85 ± 0.06
Uric acid (mg/dl)	4.78 ± 0.98
Total cholesterol (mg/dl)	133.71 ± 23.84
Total bilirubin (mg/dl)	0.83 ± 0.12
Bilirubin direct (mg/dl)	0.14 ± 0.05
Alkaline phosphatase (u/l)	83.88 ± 14.32
SGOT (u/l)	26.25 ± 4.85
SGPT (u/l)	47.22 ± 6.74
Proteins total (g/dl)	7.25 ± 0.40
Serum Albumin (g/dl)	4.14 ± 0.41
RBS (mg/dl)	87.81 ± 10.34

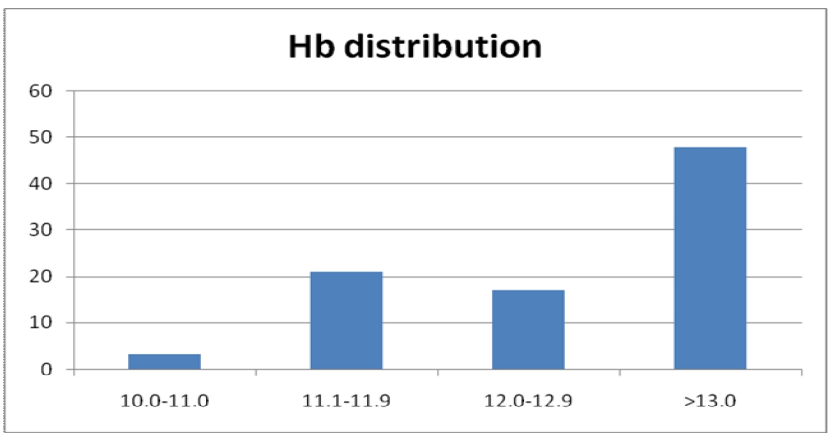

Figure 1: distribution of Hb levels in male volunteers participating in BE studies

DISCUSSION

Prevalence of anaemia in all the groups is higher in India as compared to other developing countries. In India, anaemia affects an estimated 50 % of the population. According to WHO if the prevalence of anemia at community levels is more than 40 %, it is considered as problem of high magnitude.[4] Sanjay *et al.* in a hospital based cross sectional study anemia was more common in females than males, 18 % males and 82 % females were reported anaemia of various degrees in the study period. Most of the males had mild anaemia 16 % followed by moderate 6.61 % and severe 0.77 %.[5] In National family health survey-3, anaemia in adults almost one-quarter of men (24 percent) are anaemic. Among men, 13 percent have mild anaemia, 10 percent have moderate anaemia, and 1 percent has severe anaemia.[6] Ramachandra SS *et al*, found the prevalence of anemia in males in a study group of 396 rural community residents is 17.7 %.[7] The prevalence of anaemia reported in Andhra Pradesh, India in the NFHS-3 (70.8 % in children 6–59 months; 62.9 % in females 15–49 years; 23.3 % in males 15–49 years). As the mean age of the male volunteers in present study is 29.9 years, the noted 52 % anemic is significant compared to 23.3 % in the general male population in the state. The reasons for low hemoglobin levels in the male volunteers as discussed above could be due to continuous blood loss from participation in studies and lack of check on cross participation leading to volunteers participating in studies during 3 months interval recommended between the studies. Sanjay *et.al.*[5] noted that most of the males had mild anemia followed by moderate and severe anemia in the country, similarly in the present study 32.6 %, 40.38 % and 0.05 % males had mild, moderate and severe anemia, which shows most of the males have mild to moderate anemia. The mean values of other laboratory parameters were in normal reference range. The main causes of anaemia are nutritional and infectious. With regard to infections, malaria is another major cause of anaemia: it affects 300-500 million people, and in endemic areas it may be the primary cause of half of all severe anaemia cases. Hookworm infection and in some places schistosomiasis also contribute to anaemia. Anaemia can also be due to excessive blood loss, such as gastrointestinal infections associated with diarrhoea.[4] The elevated ESR which is one of the indicator of infection was raised in 42 % of volunteers, interestingly the anemia was noted in 78.57 % of those volunteers with elevated ESR compared to 13.79 % among volunteers with

normal ESR. Hence it is recommended to take a detailed history of any infections and infestations in volunteers participating in the studies to exclude the volunteers predispose to anemia. Volunteer cross participation can be prevented by maintaining a volunteer database to cross check the participation during 3 months of interval period between the studies.

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