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Correlation between pregnyl response and blood groups in infertile men

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Abstract
Pharmacogenetics is one of the factors that effect on drug response and for the important of this subject, the study researched the correlation between the blood group and therapeutic response in infertile patients who are treated by pregnyl.
Forty patients of different blood groups subdivide to four groups each one composed of ten patients of the same blood type as follow ten patients of blood group A, ten of B, ten of AB and ten of blood group O. From each patient collected two seminal samples one before treatment and the other after three months of treatment and analyze the seminal fluid to detect sperm concentration.
Result: the paper show the patients of blood group O are more response (increase sperm concentration) compare with other blood groups while those of group AB not significantly response, patients with blood group A are significantly response ($p<0.05$) (increase sperm concentration) and those with blood group B are also significant ($p<0.05$) but by lesser degree than group A. There is relationship between blood group and treatment response.
Keywords: Spermatogenesis, Male infertility, Pregnyl, Blood group, Pharmacogenetics.

Introduction:

1.1: Spermatogenesis

spermatogenesis (sperm production) is a very orchestrated and complex biological process occur in epithelium of seminiferous tubule which is testicular functional unit, that produces in a human male at puberty higher than 100 million of sperms in each day[(1)].

Spermatogenesis take place in the testicles as a series of harmonized steps[(2)]. Spermatogonial germ cells situated on the basal membrane of seminiferous tubules which suffer either self-regeneration or mitotic divide to produce primary sperm cell and these cells suffer first meiotic divide to produce secondary spermatocytes, and then undergo a second meiotic divide to give four haploid, round shaped spermatids. Development and elongate will be occur during the spermiogenesis to form a mature spermatozoa. During the spermiogenesis, the acrosome is forming at one of poles of spermatid to compose sperm head, and flagellum extends from the other pole and, after that, elongates to compose the tail[(2)].

1.1.1 Hormonal control of spermatogenesis

Spermatogenesis process take place under the control of stromal cell and steroidal hormones. The types of somatic cell which play supporting role in spermatogenesis are Leydig cells and Sertoli cells. Sertoli cells located on basal membrane which are important for germ cell to get the hormones, nutrients and other molecules which are essential to sperm maturation. While Leydig cells located between seminiferous tubules, these cells release androgen steroidal hormones[(1,3)].

While the hormonal regulation occur by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which are secreted by the pituitary under the effect of gonadotropin releasing hormone which are secreted by the hypothalamus, also controlled by estradiol-17β and testosterone that formed locally by testis which are important in regulation (feedback loop), in axis of hypothalamic-pituitary-testicular [(4)].

Follicle-stimulating hormone practiced its influences on cells of Sertoli to cause stimulation, maturation and maintain of spermatogenesis by follicle-stimulating hormone receptors which are limited to the cells of Sertoli

in the mammals[5]. While luteinizing hormone binds to its receptors found in cells of Leydig to produce of testosterone, that is the main hormone supporting adult spermatogenesis[3,6-9].

1.2: Blood group

A complete blood type would describe a full set of 30 substances on the surface of RBCs, and an individual's blood type is one of many possible combinations of blood group antigens[10]. Almost always, the person's retains the same blood group lifetime, but very rarely an individual's blood type changes[11,12]. One of the most common cause in blood type change is a bone marrow transplant for treatment some disease for example in leukemia. If a person receives bone marrow from someone who is a different ABO type (e.g., a type A patient receives a type O bone marrow), the patient's blood type will eventually converted to the donor's type.

A blood group is a classification of blood depend on the presence or absence of inherited antigenic materials on the surface of red blood cells (RBCs). These antigens may be proteins, carbohydrates, glycoproteins, or glycolipids. Several of these antigens can stem from one allele (or an alternative version of a gene) and collectively form a blood group system[13]. Blood types are inherited and represent contributions from both parents. A total of 33 human blood group systems are now recognized by the International Society of Blood Transfusion (ISBT) [14]. The most important two are ABO and the RhD antigen; they determine someone's blood type (A, B, AB and O, with +, − or Null denoting RhD status).

The ABO system is the most important blood-group system in human-blood transfusion. According to this system blood groups divided to A,B, AB and O.

The immune system forms antibodies against whichever ABO blood group antigens are not found on the individual's RBCs. Thus, a group A individual will have anti-B antibodies and a group B individual will have anti-A antibodies. Blood group AB is the least common, and these individuals will have neither anti-A nor anti-B in their serum. Blood group O is common, and individuals with this blood type will have both anti-A and anti-B in their serum[15].

The Rhesus system (Rh) is the 2nd most significant blood-group system in human-blood transfusion with currently 50 antigens. The most important Rh antigen is the D antigen, due to it is the most likely to stimulate an immune system response of the five main Rh antigens. It is common for D-negative persons not to have any anti-D IgG or IgM antibodies, due to anti D antibodies are not usually produced by sensitization against environmental materials. However, D-negative persons can produce IgG anti-D antibodies after a sensitizing event: possibly a fetomaternal transfusion of blood from embryo in pregnancy or occasionally a blood transfusion with D positive RBCs [16]. The presence or absence of the Rh(D) antigen is signified by the + or − sign, so that for example the A− group is ABO type A and does not have the Rh (D) antigen.

1.3: Pregnyl

Is a trade name of Human chorionic gonadotropin (hCG) which is a glycoprotein produced at high concentrations by the trophoblasts of the placenta[17].

HCG consisting of an α and β subunits. The α subunit belongs to the glycoproteins hormone (GPH) family that also includes luteinizing hormone (LH) and follicle stimulating hormone (FSH)[18]. The β subunit is unique to each glycoprotein and bestows the specificity of the hormone [19].

HCG and LH give the same activity, that is, they motivate the production of testosterone in the testicles of males and progesterone and estradiol in the female ovaries[20]. HCG is utilized as a treatment for male infertility. hCG stimulates the Leydig cells of the testes by binding to the LH/CG receptors producing testosterone and triggering sperm production. The LH receptor is also present in a large number of tissues other than the ovary and thus hCG (and LH) may have hitherto unknown functions[21,22].

Material and Method

2.1: patients

Forty patients divided to four groups depending on their blood group (ABO), (10 patients of A, 10 = B , 10 = AB, 10 = O) after the investigation test to sure the blood group by pull of two mL of blood from the antecubital vein with antiseptic measures of each subject in a disposable syringe, and transferred immediately to a tube containing ethylene diamine tetra acetic acid (EDTA). Blood grouping (ABO) and Rhesus factors (Rh) was done by the antigen antibody agglutination test.

2.2: Seminal fluid analysis (SFA)

Samples were obtained from 40 male patients of 20 - 45 years of age attending fertility center in AL-sader medical city(both primary and secondary infertility cases). All specimens were collected into clean, dry, sterile plastic containers by masturbation after an abstinence period of 3-5 days and were analyzed within 1h of collection. After allowing at least 30 min for liquefaction to occur, semen analysis was performed to measure sperm concentration, normal sperm morphology and percentage sperm motility. The container labeled with the necessary information including name and age, file number, abstinence period and time of sample collection. Macroscopic and microscopic examinations were performed according to WHO methodology mentioned in details in WHO manual[23]. The SFA down before start the treatment and after three months of treatment.

Results

The response of the patients to the therapy appear variable depend on the blood group of the patient and as seen in the table (1) and figure (1) the average of sperm concentration (million/ml) in blood group O is markedly increased after three month of treatment ($P < 0.002$ compared with before: t-test). Patients, with blood group A shown a relatively less increase in sperm concentration compared with group O but it significant ($p < 0.039$).

While those with blood group B also appear significant rise ($p< 0.046$). Only the patients of blood group AB give simplest alteration in sperm concentration by the pregnyl used in the study which is non-significant.

From table (2) and figures (2,3,4 and 5) there is correlation between blood groups and the response infertile male to pregnyl where vary from very good response to blood group O for good response to group A and then group B and the last one is blood group AB.

Discussion

The difference in blood group associated with variation of percentage of occurrence the disease among the persons as for example, The persons of blood group A are more susceptible for cardio-vascular diseases, atherosclerosis, peripheral vascular diseases and many other cardio vascular diseases compared to non A types, especially the O types. Other example, The infertility is more distributed in persons of blood type O followed by B then A[24]. Also this difference in blood group may be associated with difference in pharmacogenetics.

During the last years, begin speak about the role and the effect of pharmacogenetics in medication response and appear the adverse effects. Where there are individual differences between one person and another. Worked large number of studies to cover this field and these research studied the input of genetic factor in contrast between the patients in both safety and efficacy of the drug. Example of pharmacogenetics, During second World War, was noticed the antimalarial medication (primaquine) was accompanied by acute hemolytic crises especially in Afro-American army, and is rarely at Caucasian army. After period, it was found that this occur by a genetically determined lack of glucose-6-phosphate dehydrogenase, which altered red blood cells metabolism[25,26]. That's what encouraged me to study the relationship between response to therapy and blood group in infertile patient. As show in this study the infertile males of blood group AB non-significant respond to pregnyl in standard regimen while patients with blood group O are significantly respond to treatment where there is good increase in sperm concentration from 7760000 to 12650000 (million/ml) as average ($p<0.05$; $N=10$) while the patients with blood group A in the second place in therapeutic response and those with blood group B are also significantly respond but by lesser degree. From these results can be suggest there is correlation between blood group and drug response.

This relationship between treatment response and blood group genetically may be mostly come from two different ways, either from genetic factors influence on pharmacokinetic of the drug especially on the metabolism by increase it and this lead to decrease drug plasma level, result in weak or no effect, and that may we need to increase the dose to resolve this problem and give good effect or use alternative drug.

The metabolism of certain drugs is depend on the amount and kind of functional alleles for some genes which are carries by a person. These genes more common encoded the cytochrome-P enzymes. The metabolizer type can be divided to poor metabolizers (applied to describe the persons with slight or without functional activity of a selected cytochrome-P enzyme), intermediate metabolizers, extensive metabolizers and ultrarapid metabolizers. according to the kind of cytochrome-P variation existent, the therapeutic medication response is predominatingly variable. For example, poor metabolizers mean are failure to metabolize some drugs worthily, result in accumulation of the drug in the body and reach to toxic level. while in case of ultrarapid, the active drug convert to inactive quickly, lead to less treatment response[27].

FSH receptor (FSHR), which is present exclusively on the membrane of granulosa cells, plays an essential role in mediating FSH action, thereby inducing folliculogenesis[28, 29]. It has been observed that reduced presence of this receptor on granulosa cells may account for poor influence on ovarian response to FSH in female undergoing IVF treatment. The findings suggest that increasing the dose of exogenous FSH does not get better oocyte development probably due to insufficiency of receptor expression on granulosa cells[30]. A number of normally occurring inactivate mutations in the receptor gene it has been reported in subjects with infertility. The phenotype of the infertile subjects has been well correlated with the extent of FSHR inactivation [28, 31]. Besides inactivating mutations, several single-nucleotide polymorphisms was diagnosed in the receptor coding region. where a significant relation between FSHR gene polymorphisms and ovarian response has been reported in subjects undergoing IVF treatment[32, 33].

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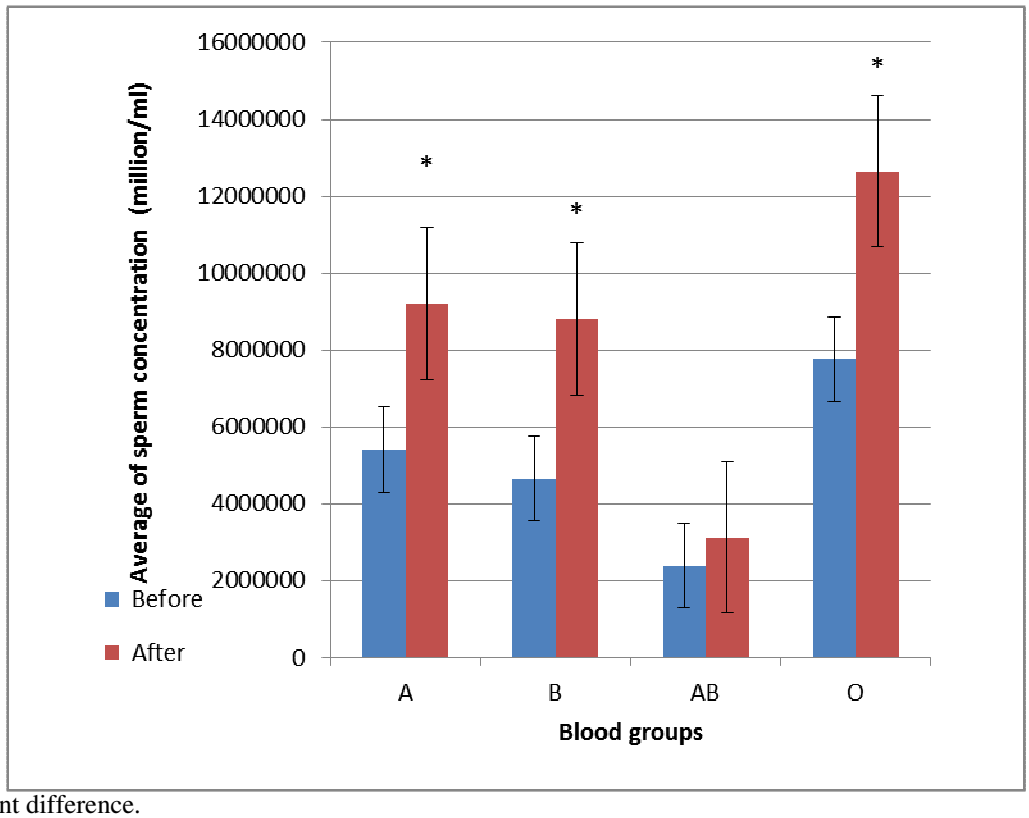
Table-1 : Comparison of drug effect on sperm concentration between different blood groups.

Groups	Samples No.	Sperm concentration Mean ± S.E.M	Significant
Before A After A	10 10	5400000.00 ± 2228352.66 9200000.00 ± 3534119.41	0.039*
Before B After B	10 10	4650000.00 ± 1621127.87 8800000.00 ± 2841361.18	0.046*
Before AB After AB	10 10	2390000.00 ± 763682.60 3120000.00 ± 901825.31	0.233
Before O After O	10 10	7760000.00 ± 2690691.77 12650000.00 ± 3476947.90	0.002*

(*):Significant difference.

Table-2 : Correlation between drug response and blood groups. (Paired Samples Correlations).

Pairs		Samples No.	Correlation	Significant
Pair 1	Before A & After A	10	0.950	0.000
Pair 2	Before B & After B	10	0.813	0.004
Pair 3	Before AB & After AB	10	0.777	0.008
Pair 4	Before O & After O	10	0.959	0.000



(*):Significant difference.

Figure-1: Variation in pregnyl response of average of sperm concentration among blood groups.

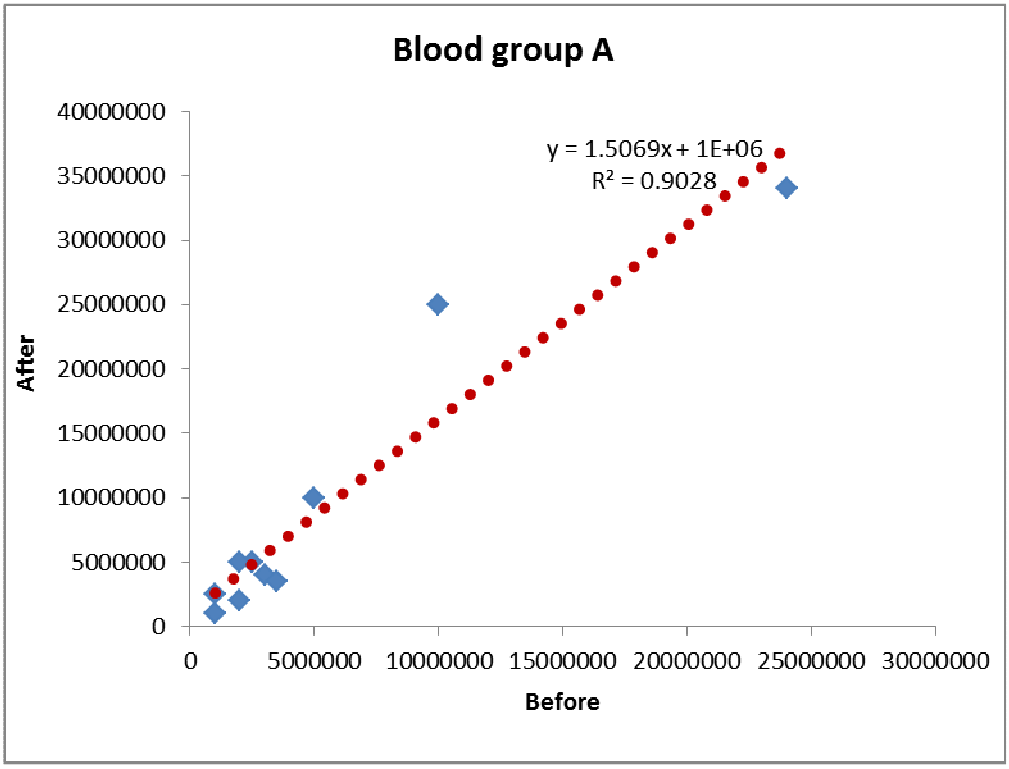


Figure-2 : Correlation between drug response and blood group A.

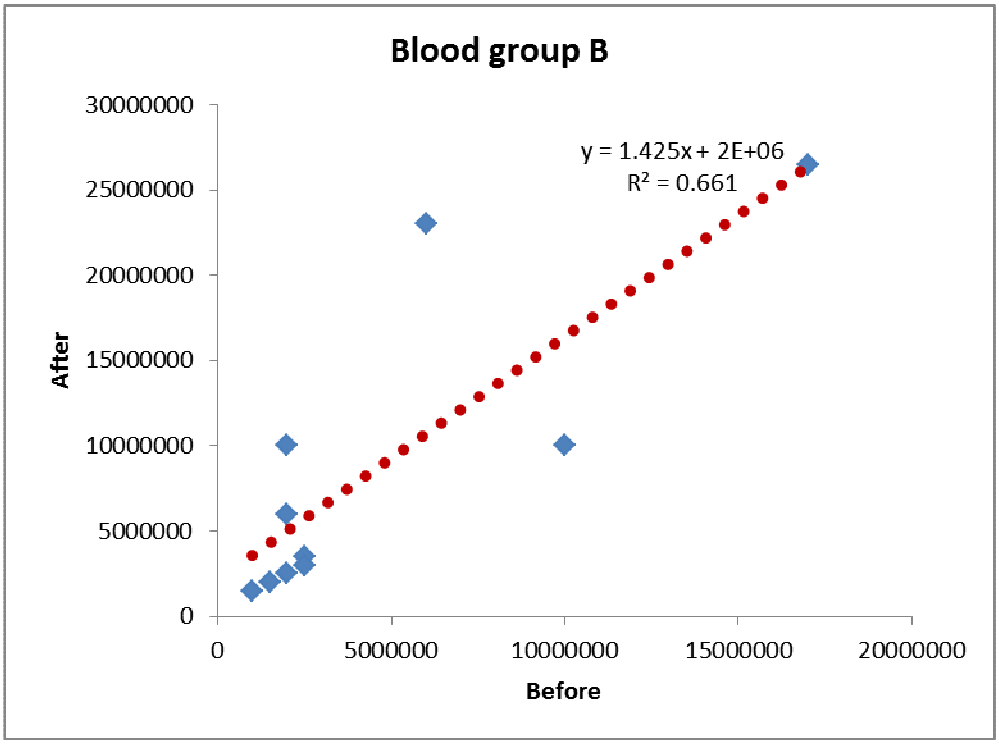


Figure-3 : The relationship between the drug influence and blood group B.

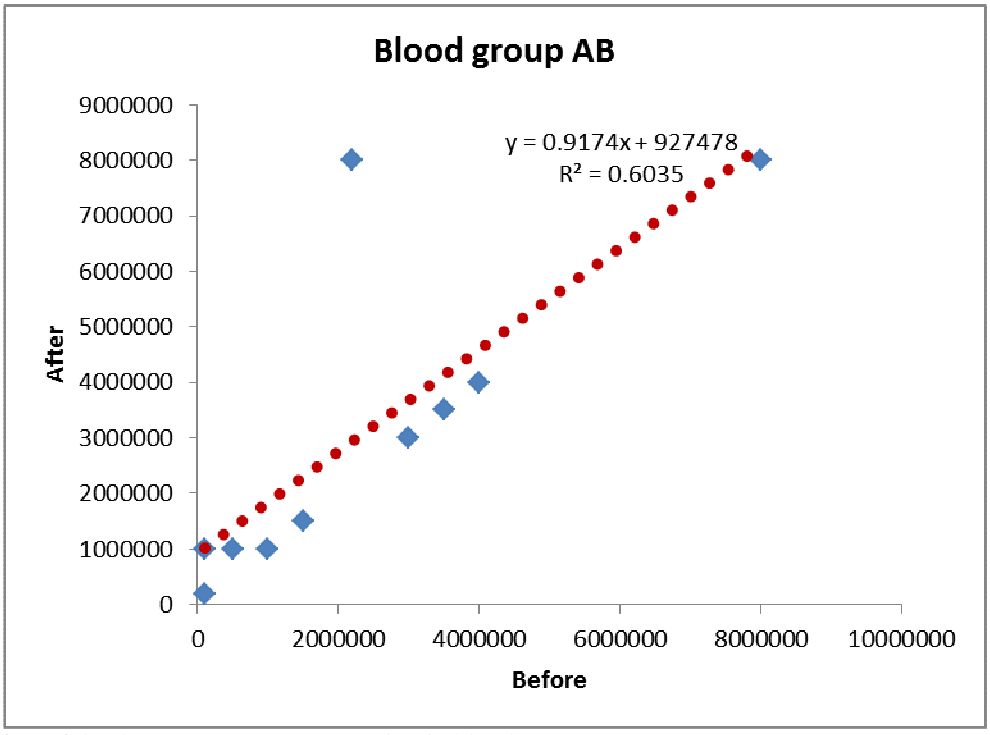


Figure-4 : Effect of the drug on sperm concentration in blood group AB.

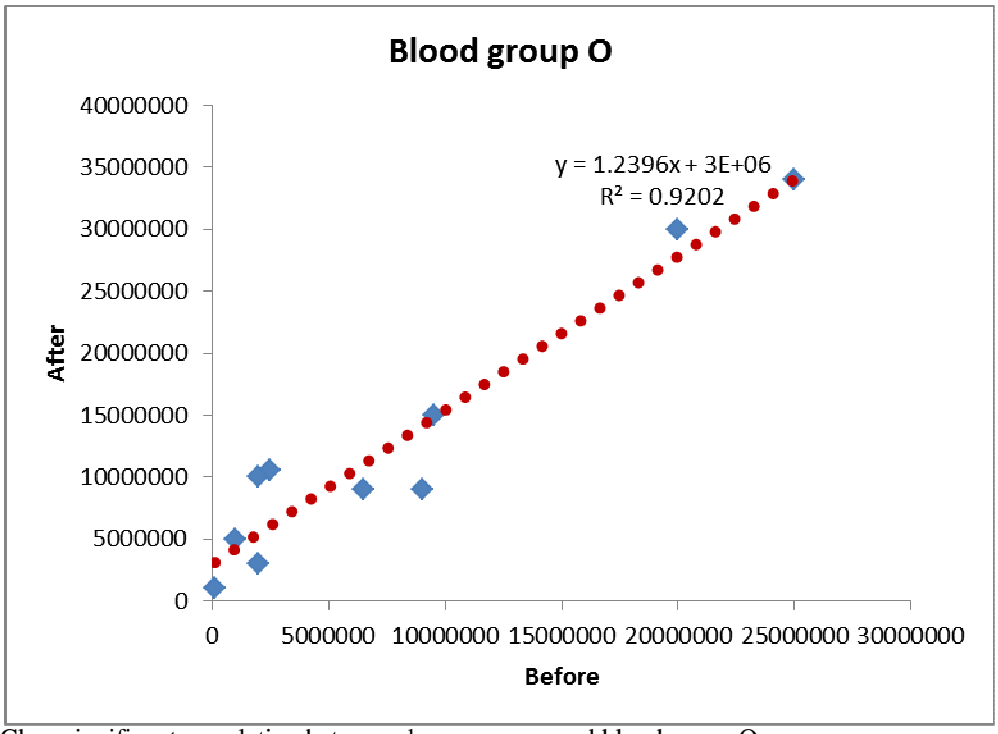


Figure-5: Clear significant correlation between drug response and blood group O.

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