In vitro Effects of lithium on Human Sperm Motility

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Abstract- Lithium has a significant impact in reducing the symptoms of bipolar mania but in long periods of use with therapeutic doses can cause several disorders in various organs including the reproductive system. In this study on the sperm concentration and motility has been examined. Nowadays, infertility coming from incapability of male system, particularly from sperm disorder is very common. Some types of sperm disorders may result from the medications used by human. The main aim of this was to investigate the *in vitro* effects of lithium on human sperm motility. Different concentration of lithium was prepared and human semen samples were exposed to lithium solution and the sperm count and motility was examined using routine laboratory method. The results showed that lithium caused decreased motility of sperms with dose dependent pattern, i.e., the more concentarion of lithium applied, the more decrease in sperm motility occurred. In conclusion, lithium has a potential to impair sperm count and motility, so, this aspect of the drug should be considered in patients using lithium.

Index Terms- lithium, Human Sperm, Motility

I. INTRODUCTION

LITHIUM is a soft silver-white metallic element of the alkaline group, having an atomic number of 3. Its name originates from the Greek (lithos) meaning stone. It has a light atomic mass of 6.941 a. m.u. In nature it never exists freely, but appears in ion form in compounds. Lithium is a monovalent cation (Li+) when it loses the only electron of the second orbital. It has two stable isotopes 6Li and 7Li, the latter being more abundant in nature. Its biological significance is based on the use of its salts in handling psychiatric disease. It is used mainly as a mood stabilizer when dealing with bipolar mood disorders (BD) formerly (manic depressive psychosis), and to a lesser extent in combination with other antidepressants in treatment of major depression. [1] The modern history of lithium started in 1949 with the publication of a paper by Cade [2] after noticing its specific effect in patients with mania. The history of lithium use in psychiatry has been well described and shows varying degree of acceptance in different countries as well as some controversies [3] Yet after more than 60 years, lithium remains the first-line treatment for prevention of manic and depressive episodes of bipolar disorder (BD). In developed countries, it is used by 1 to 3 per 1000 people [4] the savings brought by lithium between 1970 and 1991 have been estimated at US$8 billion per year in the United States alone.[5] Lithium is indicated in the treatment of manic episodes of Bipolar Disorder. Bipolar Disorder, Manic (DSM-III) is equivalent to Manic Depressive illness, Manic ,in the older DSM-II terminology .Lithium is also indicated as a maintenance treatment for individuals with a diagnosis of Bipolar Disorder. Maintenance therapy reduces the frequency of manic episodes and diminishes the intensity of those episodes which may occur .Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks [6]

Spermatozoa were first described by Leeuwenhoek in the 17th century but it was not until 1928 that the sperm count was found to be associated with fertility potential [7]. The mammalian sperm cell consists of a head, a midpiece and a tail. The midpiece has a central filamentous core with many mitochondria spiralled around it, used for ATP production for the journey through the female cervix, uterus and uterine tubes. The tail or "flagellum" executes the lashing movements that propel the spermatocyte The tail or "flagellum" executes the lashing movements that propel the spermatocyte.During fertilization, the sperm provides three essential parts to the oocyte: (1) a signalling or activating factor, which causes the metabolically dormant oocyte to activate: (2) the haploid paternal genome: (3) the centrosome, which is responsible for maintaining the microtubule system. [8]. Sperm cells are carried out of the male body in a fluid known as semen Normal values of semen parameters issued by the World Health Organisation (WHO) in 1992 are generally used as reference values.(Standard tests- volume: 2.0 ml or more, pH: 7.2-8.0, sperm concentration: 20x106 spermatozoa/ml or more, total sperm count: 40x106spermatozoa per ejaculate or more, motility: 50% or more with forward progression (categories a and b) or 25% or more with rapid progression (category a) within 60 minutes of ejaculation, morphology: 30% or more with normal forms, vitality: 75% or more live,i.e.,excluding dye, white blood cells: fewer than 1x106/ml, immunobead test: fewer than 20% spermatozoa with adherent particles, MAR test: fewer than 10% spermatozoa with adherent particles).(Optional tests—Glucosidase.neutral.: 20 mU or more per ejaculate, zinc.total.: 2.4 mol or more per ejaculate, citric acid.total.: 52 mol or more per ejaculate, acid phosphatase.total.: 200 U or more per ejaculate fructose.total.: 13 mol or more per ejaculate)

Normal semen is an admixture of spermatozoa suspended in secretions from the testis and epididymus which are mixed at the time of ejaculation with secretions from the prostate, seminal vesicles, and bulbourethral glands. The final composition is a viscous fluid that comprises the ejaculate [9]. Sperm motility describes the ability of sperm to move properly through the female reproductive tract (internal fertilization) or through water (external fertilization) to reach the egg. Sperm motility can also be thought of as the quality,

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which is a factor in successful conception.Sperm movement is activated by changes in intracellular ion concentration. The changes in ion concentration that provoke motility are different among species. The change in cell volume which alters intracellular ion concentration can also contribute to the activation of sperm motility:

1) a central skeleton constructed of 11 microtubules collectively termed the axoneme and similar to the equivalent structure found in cilia
2) a thin cell membrane covering the axoneme
3) mitochondria arranged spirally around it the axoneme have classified sperm motility under two categories only:
   a. Progressive motility (PR)
   b. Non progressive motility (NP) [10]

Among male infertility factors are primary factors like disorder in sperm transport from testicles to tubes and secondary factors such as side effects of drugs, hormones and their metabolites, toxins, urinary tract infections, and some diseases like diabetes, inflammation, and some surgical operations. In the twenty-first century, environmental pollution, radioactive radiation, inappropriate nutrition, noise pollution, addiction to tobacco, alcohol, coffee, and drugs are main factors of progressive disorder in reproductive processes .[11] Preclinical studies have shown that lithium alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines, but the specific biochemical mechanism of lithium action in mania is unknown[12] In this study, the focus is on the lithium ion (+Li) among the factors affecting sperm parameters negatively and reducing male fertility. The lithium ion is the effective substance of drugs known for treating manic depression that is often used as carbonate and chloride salts and long-term use of its therapeutic doses causes certain structural and functional disorders in different body organs despite its strong effect on reduction of disease's symptoms.[13,14] The main aim of this study was to determine in vitro effects of lithium on human sperm count and motility.

II. Material And Methods

In this experimental laboratory investigation, we used lithium solution (lithium powder dissolved in serum physiologic solution) to determine the effects of lithium on sperm motility. We prepared 4 samples as following:

Group 1: 1^{cc} normal semen + 0.1mg/dl lithium
Group 2: 1^{cc} normal semen + 0.01 mg/dl lithium
Group 3: 1^{cc} normal semen + 0.001 mg/dl lithium
Group 4 (control group): 1^{cc} normal semen+ serum physiologic solution (50 lambda)

10 and 20 minutes after adding lithium to semen sperm count and motility was examined using routine laboratory method.

III. Results

In all experimental groups, sperm count 10 and 20 minutes after addition of lithium was 47.000.000/ ml. There was no significant difference between sperm count of experimental groups and control group which consist of 47.000.000/ ml sperm cell.

Table I shows the sperm motility in semen solution without added drug or serum physiologic solution. Sperm count in this solution was 47.000.000/ml.

TABLE I
SPERM COUNT IN SEMEN SOLUTION WITHOUT ADDED DRUG OR SERUM PHYSIOLOGIC SOLUTION

Groups	Motility (%)	Class B (%)	Class C (%)
Normal Semen	45	25	20

Table II shows the motility and the classes of sperms in control and experimental groups after 10 minutes

TABLE II
MOTILITY AND THE CLASSES OF SPERMS IN CONTROL AND EXPERIMENTAL GROUPS AFTER 10 MINUTES

Groups	Motility (%)	Class B(%)	Class C(%)
Control	45	25	20
0.001mg/dl lithium	50	30	20
0.01mg/dl lithium	30	10	20
0.1mg/dl lithium	0	0	0

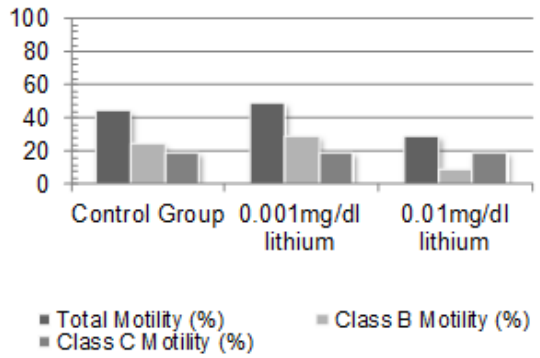
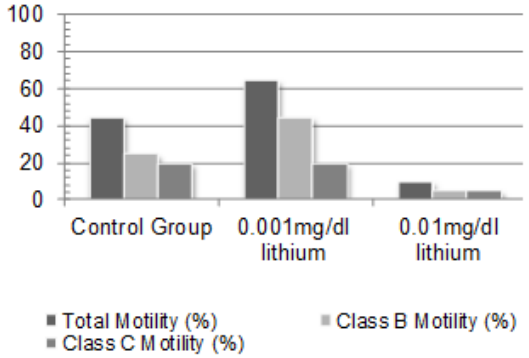


Table III shows the motility and the classes of sperms in control and experimental groups after 20 minutes

TABLE III
MOTILITY AND THE CLASSES OF SPERMS IN CONTROL AND EXPERIMENTAL GROUPS AFTER 20 MINUTES

Groups	Motility (%)	Class B(%)	Class C(%)
Control	45	25	20
0.001mg/dl lithium	65	45	20
0.01mg/dl lithium	10	5	5
0.1mg/dl lithium	0	0	0



Our findings show that lithium has inhibitory effects on sperm motility with dose dependent pattern; that is, the more concentarion of lithium applied, the more decrease in sperm motility occurred.

IV. Discussion

We have shown that lithium has inhibitory effects on sperm motility. Studies have shown that men using lithium for a long time suffer from complications such as reduced steroidogenic activity and reduced efficiency of spermatogenesis process.[15] Factors, like lithium, which change the normal shape of mitochondrial membrane disrupt mitochondrial ATP formation.[16] Furthermore, lithium is considered as a strong ATP production blocker by inhibiting GSK3 enzyme in the glycolysis pathway (main pathway for ATP production). The strong GSK3 kinase adjusts phosphorylation of glucose metabolism enzymes and its inhibitory effect on severe reduction of flagellar movements is remarkable.[17,18]. and also an excessive increase in expression of the signaling pathway of WNT/CTNNB1 in Sertoli and Leydig cells and aggregation of stable structure of the molecule CTNNB1 along with changes in gene expression of cell toward stopping cell cycle in M/G2 and apoptotic induction reduce the number of sex cells and testicular somatic cells.[19] Lithium reduces the activity of hypothalamus-pituitary-gonad axis, and spermatogenesis-stimulating hormones. It also affects testicles directly that may result in profound complications. Since the lithium ion can pass through the blood-testis barrier, it affects developing sexual cells and disrupts maturation and release of spermatozoa out of seminiferous epithelium by stopping cell differentiation and growth cycle and consequently reduces the number of the total sperm count.[14,20] The results of this study also confirm the role of lithium in number of motile sperms, and motility of sperm's tail. These properties make it an ideal candidate for development as a potential novel spermicidal agent.

V. Conclusion

We have shown that lithium inhibit sperm motility in a dose dependent manner. This property may make it a candidate for development as a potential novel spermicidal agent.

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