The use of oral pentoxifylline HCl in treatment of idiopathic male infertility.

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الخلاصة

العُقْم مشكلة تصيب ما يقارب 15 % مِنْ الأزواج المتزوجين حديثاًوربع الحالات مجهولات السبب .الكثير مِنْ العقاراتاستخدمتبشكل تجريبي لعِلاج ه ذا الن وع م ن العقم. ولان عقار البنتوكسيفيلبن أستخدمَ عمليا لتحسين نتائج التلقيح الخارجي بإضافته إلى الحيامن خ ارج الجسم,قررتجربة الاستخدام النظامي له ذا ال دواءوص ف ه ذا ال دواء ع ن طريق الف م لس تونمريضاً مص ابين بالعُقم المجهول الس بب أعطِ يَلَهم دواء بجرعة 400ملغم مرَّتين في اليوم لثلاثة شهور ، بعد ذلكأجري فحص الس ائل المن وي والذي أظهر عدم حدوث تغيرات ايجابية في نتائج التحليل المنوي لأغلبيةِ المرضى. حَصلَت بعض التغيرات الايجابية في 9% من المرضى لكن دون حَدوثَ حملَ.استنتج مِنْ هذه الدراسةِ بأنّ الاستخدام النظامي لعقار البنتوكسيفيللين عن طريق الفم غير مؤثرُ في معالجةِ العُقم المجهول السببِ.

Abstract

Infertility is a problem affecting about 15% of newly married couples. Twenty five percent of them have no identifiable etiology; idiopathic. A lot of drugs and agents have been used empirically. Pentoxifylline has been used effectively invitor with IVF and ICSI. To asses its efficacy in treatment of idiopathic infertility, oral pentoxifylline HCl (tronteral) has bees prescribed orally to 60 patients with idiopathic infertility. It has been given twice daily for three months, after that a new SFA show no response in the majority of patients. In the nine percent who got some response, no pregnancy occurred.We concluded from this study that oral pentoxifylline is ineffective in treatment of idiopathic infertility.

Introduction

Infertility is defined as failure to conceive after one year of unprotected sexual intercourse.[1]Roughly 40% of cases involve male contribution or factor.[2] The causes underling male infertility can be conventionally grouped into: pretesticular ,testicular and posttesticular.[2,3]In twenty five percent of cases a comprehensive array of investigations fail to determine the underling cause of male infertility and idiopathic infertility is said to occur.[4] Unexplained or idiopathic infertility is defined as the infertility in which the pathophysiology of the underling cause is ill-defined. [5] This form of infertility is usually treated by empiric therapy that seeks to overcome the ill-defined or untreated pathological conditions. [2, 4, 5]A number of agents have been proposed as specific treatments for men with idiopathic infertility such as anti-estrogens, aromatase inhibitors, gonadotropins, kallikrein, indomethacin, low dose corticosteroids, androgens, zinc, antioxidants and phosphodiesterase inhibitors such as pentoxifylline .Pentoxifylline and other methylxanthines have been used to increase sperm motility in vitro with possible improvements in fertilization rates. [6]In this study we decided to assess the efficacy of pentoxifylline after its oral use for idiopathic infertility.Pentoxifylline (Trental) is a xanthine derivative, its chemical name is 1-(5-oxohexyl)-3, 7-dimethylxanthine. Pentoxifylline is a PDE4 inhibitor increasing intracellular cAMP and stimulating PKA activity.It is used to treat intermittent claudication resulting from obstructed arteries in the limbs.It also helps prevent strokes by improvement of blood flow to the brain. [7] Pentoxifylline, or Trental, has been used in humans(in divided doses of 800-1600 mg per day) in a variety of inflammatory and fibrotic conditions, including radiation fibrosis, radiation proctitis, cystic fibrosis, radiation pneumonitis and steatohepatitis and recently in Pyeronies disease.[7,8]Several adverse effects may occur after its systemic use the most important of these are gastric upset and cardiac arrhythmias. [6, 7, 8]

Aim of the study

This study aimed to evaluate the efficacy of systemic pentoxifylline in treatment of idiopathic male infertility.

Patients and methods

From 2003 to 2006, infertility work up has been done for 240 patients attend the clinic with primary infertility. The workup included

1. **Careful history inquiring about** :

a. Medical history: asking about fevers, systemic illness, and genetic diseases.
b. Surgical history; asking about history of orcheopexy or herniorrhaphy, trauma and torsion.
c. Fertility history: including the onset of puberty, duration of infertility, previous pregnancies, and infertility treatment.
d. Sexual history.
e. Family history.
f. Drug history: asking about used drug as anabolic steroid.
g. Social history; asking about smoking and alcohol drinking.
h. Occupational history; as exposure to ionizing radiation and chronic heat exposure.

2. **Physical examination directed toward :**

a. Secondary sexual characters.
b. Scrotal content; the scrotum should be examined in standing position to assess the size and texture of the testicles and the state of pampiniform plexus and the vas.
c. The penis for the presence of hypospadias or other abnormalities.

3. Seminal fluid analysis (SFA): After 3 days of sexual abstinence, semen collected in the lab by masturbation and examined immediately.
4. Hormonal analysis including serum testosterone, FSH, LH, and prolactin done in some patients.

After this work up the patients fall in either of the following categories:

1. Normal SFA despite history and examination and no treatment was required.
2. Azospermea (zero count) and testicular biopsy suggested.
3. Abnormal SFA (other than azospermea) with obvious cause in the history or physical examination or in seminal analysis and treatment directed toward the underlying cause.
4. Abnormal SFA (other than azospermea) with out obvious cause in the history, physical examination or seminal analysis, in those patients hormonal analysis done and any abnormality has been corrected carefully.
5. Abnormal SFA with out obvious cause in the history, physical examination, or seminal analysis and with normal hormonal analysis. Those patients cited as idiopathic infertility and included in the study.Pentoxifylline HCl (trenteral) has been prescribed orally for those patients in a dose of 400 mg twice a day. They have been advised to keep on medication for three months if pregnancy not occurred before that. Those patients have been followed -up by another SFA three months after trenteral therapy.

Results

The numbers of patients in different categories are explained in the following table.

Table no. 1: the number of patients in different category.

Category	*Description*	*Number*
1	**Normal SFA**	**76 (31%)**
2	**Azospermea**	**25 (11%)**
3	**Abnormal SFA + obvious cause**	**44 (18%)**
4	**Abnormal SFA + abnormal hormones**	**35 (15%)**
5	**Idiopathic infertility.**	**60 (25%)**
Total number		**240**

Twenty-five percent of the included patients fall under the category of unexplained infertility, where their semen abnormalities failed to be explained by history, examination,

semen analysis and their hormonal levels was normal.The seminal abnormalities in the selected group were variable, oligospermea; asthenospermea and abnormal morphology were encountered. The following table showing the number of patients in different seminal abnormality.

Table no. 2: the numbers of patients with different seminal abnormalities.

Seminal abnormality	*Number of patients*
Oligospermea	**16 (27%)**
Asthenospermea	**18 (30%)**
Abnormal morphology	**6 (10%)**
Combination of the above	**20 (33%)**

After three months of tronteral therapy, no improvement in seminal abnormality(s) encountered in the majority of patients (55 (91%). Five patients (9%) got some response but no pregnancy has occurred.

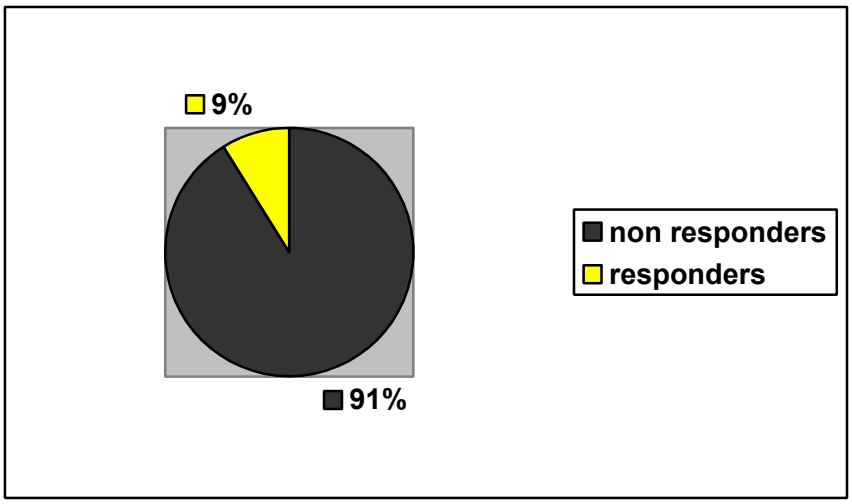

Figure 1: chart showing the response to tronteral therapy.

Discussion

Ten to fifteen percent of couples are infertile. Approximately 50% of infertile cases involve male factors. [9] In 25% of infertile men, no identifiable cause can be attributed to the problem.

Because the pathophysiology is ill-defined, this is termed idiopathic infertility [1, 10] .Infertility work up is usually started if one year of unprotected sexual intercourse fails to give rise to pregnancy.

The work up involves careful history taken and physical examination and seminal fluid analysis after three days of sexual abstinence. If aided by hormonal assay, this work up may diagnose the cause of the underling seminal abnormalities. Despite that 25% of infertile patients got no diagnoses for their seminal abnormalities and those patients cited under the category of idiopathic infertility. Sixty patients from the 240 patients included in the study have a seminal abnormality(s) of unexplained etiology , as the history gives no relevant evidences and testicular examination reveal normal sized testis and normal pampiniform plexus in addition to that ,the seminal fluid analysis has no evidences of infection or antisperm antibody formation, their serum hormonal levels were normal.The seminal abnormalities of the patients were variable; the most common abnormality (30%) was asthenospermea (weak sperm motility) where the actively motile sperm percent was less than 5o%. The second most common abnormality (27%) was oligospermea (sperm concentration less than $20x10^6$).Six percent of the patients have large percent of abnormal sperm morphology. Twenty percent of the patients have a combination of the mentioned semen abnormalities.Patients with idiopathic infertility are candidate for empiric medical therapy. [11] Many drugs and agents have been used, in this study we tried the use of systemic pentoxifylline for treatment of idiopathic infertility due to increase its use with invirto fertilization (IVF).Treating fresh sperm with pentoxifylline has been shown to increase success with in vitro fertilization (IVF) and intrauterine insemination (IUI). However, sperm samples vary considerably in their reaction to pentoxifylline, with about 10% failing to respond at all. Pentoxifylline has been added to cryopreserved semen. Cryopreservation impaired sperm motility and motion characteristics. Treatment with pentoxifylline did not improve the percentage of sperm that were motile after thawing; in fact,

motility was slightly poorer in the treated group.Pentoxifylline treatment, however, did confer two important advantages. It reduced the frequency of acrosome loss caused by the freeze-thaw process, and it increased the rate at which post-thaw spermatozoa underwent further acrosome reactions, including spontaneous reactions and those induced by calcium ionophore challenge. These findings may suggest that pentoxifylline has a third mechanism of action, the protection of sperm membranes from damage caused by freezing. The acrosome reaction rate is highly predictive of success rates with IVF; and pentoxifylline may, therefore, have the potential to improve the fertilizing capacity of cryopreserved sperm in procedures such as intrauterine insemination and in vitro fertilization. [12, 13, 14] Besides the effects of pentoxifylline on sperm motility and acrosome reaction discussed above, this PDE inhibitor has also effects on reactive oxygen species (ROS). It has repeatedly been shown that pentoxifylline significantly reduces the superoxide release of human spermatozoa following phorbol myristate acetate stimulation. This effect is possibly due to the reduction of the formation of endoperoxides as a consequence of the elevated cAMP levels that inhibit the cyclo-oxygenase within the arachidonic pathway. [15, 16]Owing to these advantages we decided to try its oral use to improve sperm number and quality in idiopathic infertility.Pentoxifylline was introduced as a hematological agent for the treatment of intermittent claudication, putatively by decreasing blood viscosity through enhanced deformability of erythrocytes It has been also used for many other conditions ,all later claims are controversial.[15,16,17,18,19, 20,21,22,23,24,25)

Tronteral prescribed for the selected patients in a form of 400 mg tablets twice a day. We advise the patients to take it after meal and to keep on for three months. Adverse gastro-intestinal effects occurred in some patients especially those taken it before meal.

After three months of therapy no patient comes back with the good new of pregnancy. We repeat SFA which in the majority (91%) show no improvement. Some improvement in semen abnormality occurred in (9%) of the patients, but they not reach

normality.The Department of Dermatology and Andrology, Justus Liebig University, in Germany have use pentoxifylline in vitro for sperm preparation for assisted reproductive technology (ART).

They found that the beneficial effect of pentoxifylline on sperm motility and motion characteristics like sperm velocity or hyperactivity has repeatedly been described for both fresh and cryopreserved spermatozoa. This stimulatory effect can clearly be attributed to the increased intracellular levels of cAMP. Cyclic AMP, in turn, is believed to stimulate a cAMP-dependent kinase which itself induces sperm tail protein phosphorylation with subsequent increase in sperm motility. Apart from the effects on sperm motility, they also reported that pentoxifylline augments acrosome reaction. [26, 27, 28, 29]The Cornell Institute for Reproductive Medicine in Cornell University state that the systemic use of pentoxifylline has not shown a reliable response in sperm production or function [6, 30]

In a comparative study, Okada et al. confirmed the ROS scavenging and motility stimulating effect of pentoxifylline in vitro in 15 patients and 18 controls, respectively. However, in vivo pentoxifylline at low dosages (300 mg per day) failed to decrease ROS generation and to increase motility. On the other hand, at high dosages (1,200 mg per day), motility and beat cross frequency were increased but the drug still did not have a beneficial effect on sperm fertilizing ability. [31]

Conclusion

We concluded from this study that the systemic use of pentoxifylline is ineffective in treatment of idiopathic infertility.

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