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The effect of oral administration of Pentoxifylline on sperm motility of asthenozoospermic ejaculates from men with or without testicular varicoceles

Mohammad Reza Moein,[1]M.D., Mohammad Ali Khalili,[2] Ph.D., Arash Davoudi,[3]M.D.

1 Assistant Professor, Research & Clinical Center for Infertility, Yazd University of Medical Sciences, Yazd, Iran.
2 Associate Professor, Fertility & Infertility Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
3 Research & Clinical Center for Infertility, Yazd University of Medical Sciences, Yazd, Iran.

Abstract

Background: Pentoxifylline (PX) is a methyxanthin derivative that influences the sperm motion characteristics. In general, PX has been reportedly effective in preserving sperm motility in vitro, also when administered orally to the asthenozoospermic patients.

Objective: The main objective of this prospective clinical trial study was to rule out the effect of oral administration of PX on sperm progressive motility of asthenozoospermic ejaculates obtained from men with or without mild testicular varicoceles. In addition, the role of patient's age on sperm motility following PX administration was investigated.

Materials and Methods: A total of 68 infertile men with asthenozoospermia were allocated to this study. Following physical examination, 20 cases were found with mild varicocele of testis. A dosage of 400 mg PX/ twice daily for duration of 3 months was administered to each patient. Two semen samples (one before and one after the PX therapy) were evaluated under blind condition. Semen parameters of sperm concentration, total and fast progressive motility (%) and morphology (%) were analyzed for each sample. Also, the sperm motion characteristics of asthenozoospermic patients with testicular varicocele were compared with cases lacking varicocele. The subjects were divided into two age groups of <30 and ≥30 years old.

Results: PX was significantly effective on the fast progressive motility of sperm ($p<0.01$). Also, total progressive motility was enhanced from 26.82±16.8 to 29.60±22.2 with PX therapy. However, PX did not have any negative effect on other semen parameters. Oral therapy of PX was also effective in improving the fast progressive motility of sperm of samples from cases with or without mild testicular varicocele ($p<0.01$). Fast progressive motility was also significantly enhanced in ejaculates of men from both age groups.

Conclusion: Our results demonstrate that low dose of oral therapy of PX is significantly useful in enhancing fast progressive motility of sperms from infertile men with asthenozoospermia. Also, testicular varicocele did not interfere with enhancing effect of PX on sperm motility.

Key words: Sperm Motility, Pentoxifylline, Varicocele, Asthenozoospermia.

Introduction

PX is a methyxanthin derivative in the same pharmacologic group as caffeine that inhibits the breakdown of cyclin adenosine monophosphate (cAMP). This generates cellular glycolysis and endogenous adenosine triphosphate (ATP) production that influences the sperm motion characteristics (1, 2). In general, PX has been reportedly effective in preserving sperm motility in vitro, also when administered orally to the asthenozoospermic patients (3-6).

One of the major causes of male factor infertility is related to asthenozoospermia, particularly severe cases, which may influence the pregnancy success rates following assisted reproductive techniques (ART) (7). Therefore, a potential pitfall exists for these infertile men where their only infertility problem resides in sperm

Corresponding Author:
Dr Mohammad Ali Khalili, Fertility & Infertility Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Email: khalili59@hotmail.com

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motility parameters. Thus, improvement of sperm motility with application of PX may not only be beneficial for intracytoplasmic sperm injection (ICSI) programs, but in some cases, it may also substitute treatment protocols for a more natural treatments, such as in vitro fertilization (IVF), or even intra-uterine insemination (IUI) cycles (3).

In our previous experimental as well as clinical studies, the role of in vitro application of PX on motility of spermatozoa retrieved from different sources of ejaculate, epididymis, and testis were investigated (3, 8). The results demonstrated that PX was successful in enhancing both non-progressive as well as progressive sperm motility. In addition, 60% of microsurgically retrieved samples with total sperm immotility showed motion ability following PX application. Therefore, the main objectives of this prospective study was to evaluate the role of oral administration of PX on sperm progressive motility from asthenozoospermic samples obtained from patients of different age groups. Also the effect of PX on sperm motility of asthenozoospermia from cases with or without mild varicocele of testis was investigated in a controlled setting. According to our knowledge, the later objective of this study has not been reported by other investigators yet.

Materials and Methods

Patients

A total of 68 infertile men with asthenozoospermia were allocated to this prospective clinical trial study. Following physical examination by urologist, 20 of them were found with mild varicocele of testis. The individuals were divided into 2 age groups of <30 and ≥30 years old. All the ejaculates were evaluated under blind conditions at our andrology laboratory. Every patient was assigned to collect two semen samples: one right before oral administration of PX (control) and one three months after PX oral therapy (PX). Asthenozoospermia was defined according to the WHO guideline as samples with <50% progressive sperm motility (9).

Ejaculate Samples

Fresh ejaculates were collected by masturbation in sterile containers. Following liquefaction, semen analysis was performed according to WHO guidelines (9). The semen parameters of concentration and 2 types of progressive motility (fast, fast + slow) were evaluated using Makler Chamber and light microscopy. Geimsa (Merck Co., Germany) staining and oil immersion were used for evaluating round cells and percentage of normal sperm morphology.

Oral Administration of Pentoxifylline

All patients were administered low dosage of 400mg PX (Apotex Inc., Canada) twice daily for 3 months. For each patient, semen parameters were measured right before and after the PX treatment period.

Statistical Analysis

The statistical analysis was performed using SPSS software for windows. Paired-t test and non-parametric test (two related sample Wilcoxon test) were applied for the comparison of sperm motility between control (before PX therapy) and PX (after PX therapy) samples. Results are expressed as mean ±SD. p value of <0.05 was considered as significant.

Results

The mean age of the patients was 39.3±7.7 years old (range: 20-58). Table I presents the results of semen parameters from asthenozoospermic men. The percentage of fast progressive motility of sperms was significantly enhanced by PX ($p<0.01$). Although, progressive motility of spermatozoa was improved following PX application, but this was insignificant (29.60% versus 26.82%). The rates of fast as well as progressive motility of spermatozoa from patients with or without varicocele of testis are presented in Table II. The results showed that significant fast progressive motility was observed in both groups of patients with or without varicocele. Table III represents the correlation between different age groups with rate of sperm progressive motility. In general, patients younger than 30 years were presented with higher rate of sperm motility than

Table I. Semen parameters of 68 asthenozoospermic samples from infertile men.

Variable	Control	PX
Sperm count ($x10^6$)	44.6±7.6	$40.1±10.3^n$
Round cell ($x10^6$)	2.5±0.8	$2.7±1.4^n$
Normal morphology (%)	32.92±14.4	$32.89±19.0^n$
Progressive motility (%)	26.82±16.1	$29.60±20.2^n$
Fast motility (%)	6.14±5.7	9.62±10.6*

n: non-significant,
**: p<0.01 compared with control samples*
Values represent the mean ± SD

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Table II. The rate of sperm motility of asthenozoospermic samples from men with or without varicocele.

	Varicocele (n=20)		No varicocele (n=48)	
Type of motility	**Control**	**PX**	**Control**	**PX**
Progressive (%)	27.75±15.8	31.40±22.4n	25.02±17.3	28.43±22.3n
Fast (%)	5.62±6.4	11.06±12.4*	6.40±5.5	8.90±9.8*

n: non-significant,
**p<0.05 compared with control samples*

Table III. The correlation between patient's age and the rate of sperm motility in asthenozoospermic samples.

	Age<30 (n=38)		Age≥30 (n=30)	
Type of motility	**Control**	**PX**	**Control**	**PX**
Progressive (%)	30.55±15.8	34.75±22.0n	20.50±16.9	23.81±21.3n
Fast (%)	7.03±6.4	10.32±10.6*	4.52±5.8	8.35±10.9*

n: non-significant,
**p<0.05 compared with control samples*

older men before application of PX. Following PX therapy, fast motility of spermatozoa from both age groups enhance significantly ($p<0.05$).

Discussion

In our previous study on the effect of in vitro application of PX on motility of spermatozoa from asthenozoospermic samples, progressive motility was significantly increased from 26.5% to 44.8% ($p<0.001$) (3). This is not in agreement with our current study, where progressive motility was slightly increased following oral administration of PX. However, the results showed that significant improvement of fast progressive motility was achieved after PX oral therapy. Therefore, it seems that PX is more effective in stimulating sperm motility when applied in vitro to the culture media. In a study done by Shen *et al*. (1991), in vitro and in vivo effect of PX on sperm motility was measured for the treatment of male infertility (10). In vitro application of PX increased the motility of ejaculated sperm of asthenozoospermic patients. Also, oral application of PX for three months significantly enhanced the progressive motility, with no effect on concentration of spermatozoa. They concluded that PX may be used either in vitro or in vivo for improving asthenozoospermia. In another study, 15 young men with asthenozoospermia were admitted for oral therapy of 1200 mg/day PX (high dosage) for over four months (11). The results showed a significant improvement of progressive motility. It is important to note that five patients achieved a normalization of their semen quality. Therefore, it seems that PX is a beneficial alternative for treatment of men with asthenozoospermia. In addition, 65 infertile men with either asthenozoospermia or oligozoospermia were treated with oral PX for three months. In asthenozoospermia group, a significant increase of progressive motility of sperm was noted which concurrently improved the conception rate. However, the semen parameters in oligozoospermic men were not affected. It was proposed that PX treatment improves the microcirculation within the epididymis as well as male accessory sex glands. This may lead to an improved sperm maturation / motility (12). In the present study, we noticed that PX was a safe drug with no deteriorating effect on semen parameters of concentration or sperm morphology. This is important in clinical settings, because while the quality of motility is improved with a useful drug-PX, other parameters such as sperm concentration, should not be negatively affected.

In one study, 1200mg/day of PX was administered orally to twenty-five patients with asthenozoospermia, sperm motility was enhanced from 25.5% to 35.5% and 42% after three and six months of treatment, respectively. Control semen samples showed some, but insignificant, change in sperm motility with PX. Also, no statistical changes were found in other semen parameters. The results suggested that PX is useful treatment in cases of male infertility with asthenozoospermia (4). Furthermore, role of oral administered PX on motility and density of sperms, as well as fertilization rate were investigated by Faka *et al*. in 1994 (13). In contrast to our results, their study showed that PX did not improve the motility, density, or fertilization rate. However, they only investigated their work on 14 patients with poor

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semen parameters. It is, therefore, possible that if they would study on a larger series of cases with only asthenozoospermia, a different outcome would be achieved.

Another finding generated from this investigation was the effect of oral PX on sperm fast motility obtained from men with or without mild testicular varicoceles. In humans, varicoceles have a variable influence on testicular function, leaving it unaltered in some cases, but causing spermatogenic arrest in others (14). Also, it may result in impairment of sperm production and abnormal semen quality ranging from oligospermia to azoospermia (15). Our findings showed that a comparable motility characteristic was observed in cases with or without varicoceles. However, the oral therapy of PX improved the fast sperm motility in both groups of men ($p<0.05$). This may indicate that presence or absence of varicoceles is not involved with the enhancing effect of PX on motility. Pasqualotto *et al*. (2005) also found that sperm motility was lower in patients with varicocele (37.2%) than cases without varicocele (58.9%) (16). The difference was, of course, significant. In contrast, our results showed that the rate of sperm progressive motility in patients with varicoceles, and those lacking varicoceles were similar.

The other goal of the present study was to rule out the association of male age and sperm motility. The results confirmed that men under the age of 30 had higher rate of progressive motility of sperms, when compared with older men. However, the stimulating effects of PX on sperm motility of both age groups were similar. This shows that, although in natural condition the age is directly associated with quality of sperm motility, but PX is not. A recent study by Eskenazi *et al*. (2003), on 97 non-smoking men aged from 22 to 80 years showed that sperm progressive motility decreased by 3.1% per year. It was shown that sperm motility decreased continuously between 22-80 years of age, with no evidence of a threshold (17). However, Kumtepe and associates (2003) did not observe any differences in sperm parameters in 2 groups of patients <40 (n=692) or >40 (188) years old (18). There is still controversy whether advanced male age is associated with poor sperm quality or not. In our study, we divided the infertile men into two age groups of <30 and ≥30 years old. There were two reasons to define 30 years for dividing the study population into the aforementioned age groups. First, the number of cases were comparable in two groups of <30 and ≥30 years (38 vs. 30). Secondly, the number of men beyond 40 was very limited in our patients under study. Therefore, to draw a conclusion on the sperm motility in relation to male age, we noticed that advancing age is directly related with poor sperm progressive motility. However, PX was significantly effective in improving sperm fast motility in different age groups.

Conclusion

In conclusion, our results showed that PX is a useful drug for treating the sperm motion characteristics of patients with asthenozoospermic ejaculates. Also, asthenozoospermic patients with mild varicocele of testis may benefit from the oral therapy of PX. Finally, regardless of the male age, the results showed that significant improvement was observed on sperm fast motility. Whether PX should be applied in vitro or in vivo to enhance sperm motility needs further investigation.

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