THE EFFECT OF TRENTAL ON SPERMIOGRAFIC PARAMETERS, A CLINICAL STUDY IN PATIENTS WITH REDUCED FERTILITY

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Many married men attending an infertility clinic for advice show normal clinical findings and regular hormone patterns for basic values of testoterone, LH and FSH. Hormone function tests such as HCG-test. (Leyding cell function test) or GnRH — test also turn out normal. A biopsy from the testicle, even of young men, usually shows a more or less pronounced fibrosis of the walls of the tubuli seminiferi. Besides the thickening of the tubulus wall the spermiogenetic epithelial cells are disorganized. Frequently there is a stop of spermiogenesis, often at the stage of presperms. Some tubuli have atrophied considerably with only a few layers of markedly reduced spermiogenetic epithelial cells without differentiation. Some tubuli have perished completely. The pathogenesis of the disturbance of spermiogenesis which is developping chronically and slowly is not yet known. Thus according to Hofmann Loose (1978), who calls this condition "a chronic orchitis", an inflammatory process might be considered as *primum movens*. It was noticed in our clientele that many of the patients were heavy smokers. It has been known for many years that in patients with nicotine abuse, reduced sperm count and motility are often found in the spermiogram which improves after restraining from smoking. Therefore it can be assumed that disturbed blood flow resulting in impaired nutrition of the spermiogenetic epithelium might be a factor in the pathogenesis of this chronic degenerative disease of the testicles. This conception is supported by findings of Loose (1970) who found in 500 serial aortographies in almost one fourth of the patients disturbed circulation and occlusion of the arteria iliaca interna and of it's branches. Clinical experiences disclose that disturbance of blood flow in the testicle region reduces the sexual potency. Positive reports by Loose on therapeutic success with pharmacological agents or vascular surgery in patients with disturbed sexual potency support the recommendation to improve nutritive circulation in the testicles.

It therefore appeared indicated to submit patients with reduced values of the spermiogram to a therapy which improves circulation and nutrition and monitoring the effect by objective spermiographic parameters. As test substance we chose Trental (pentoxifylline). This drug improves circulation and metabolism by influencing the flow properties of blood and effects in particular the inhibition of phosphodiesterase, increasing the cAMP, a so-called "second messenger", which mediates the effects of numerous hormones.

Pilot investigation

The starting point of our systematic research were two case studies on the change of spermiogram parameters before and after a treatment with Trental over a few months.

Case 1: 30 year old patient, married for 2 years, children are desired. Considerable abuse of nicotine (30 — 40 cigarettes per day) for many years. Normal genitals, right side of testicle equals left side, volume about 25 ml, consistency normal. Epididymis inconspicious, no varicocele, prostate gland normal. Figure 1 presents the values of sperm count, motility rate and malformation rate before, during and after a 9-month treatment with Trental, 400 mg t. i. d. There is a rise in sperm count after 5 months. The sperm count remains markedly elevated also after 7 and 9 months compared to the initial findings (Fig. 1).

Case 2: 30 year old patient, married for 4 years, no children. The patient himself had normal male genitals, testical size right equal to left, about 20 ml, no varicocele. His 23 year old spouse had no findings inhibiting conception. Repeated spermiograms showed a typical OAT-syndrome, i.e. oligozoo-astheno-teratospermia. 6 months treatment with gonadotropic agents (daily injection of HMG-preparation, every 5th day in addition 1000 units of a HCG-preparation) disclosed no signs of amelioration: sperm count and motility continued dropping. Assuming that treatment with gonadotropic agents requires sufficient nutritive blood flow in the testicles, Trental was given for 12 months. Already after 6 months there was an evident amelioration. Sperm count and motility rate were increased. The improvement was still present after 12 months of therapy (Figure 2).

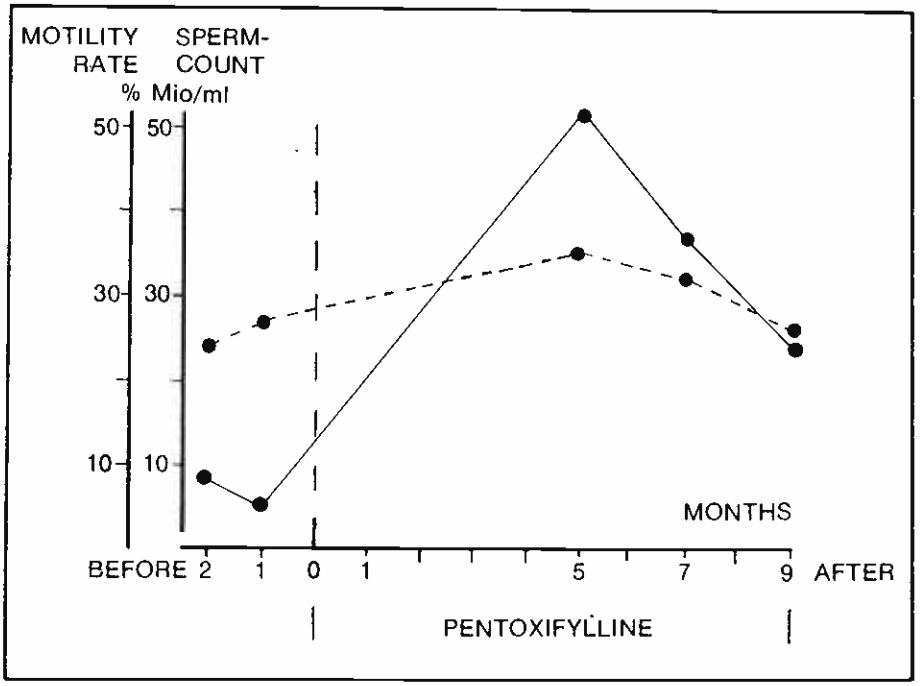

Fig. 1: Sperm count motility rate and malformation rate before and during a 9-month treatment with Trental in a 30-year old patient with OAT-syndrome.

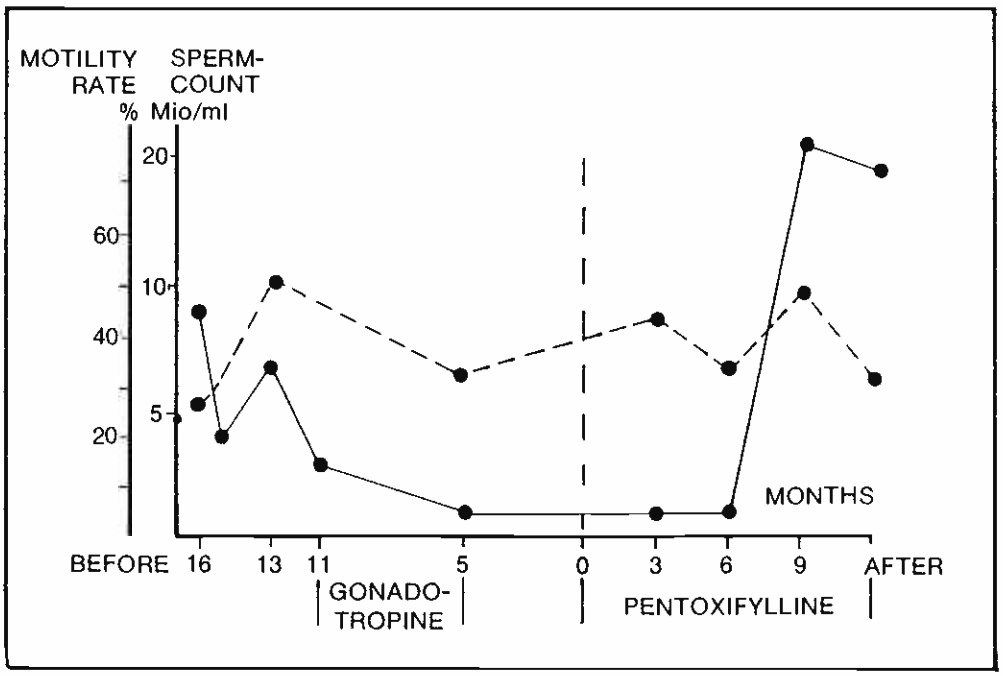

Fig. 2: Changes in sperm count, motility rate and malformation rate during and after therapy with gonadotropic agents and 12 month of Trental administration in a 30-year old patient with OAT-syndrome.

Design of clinical study

Based on the results of the pilot study we submitted all patients with OAT-syndrome to Trental therapy, 3 times 400 mg per day for at least 4 months, usually for 6 to 9 months. In total 172 patients with impaired fertility started the therapy. To prove efficacy the following parameters of the spermiogram were determined before and after onset and termination of treatment:

sperm volume (ml)

sperm count (ml)

motility rate (%)

eosin positive spermatozoa (%)

malformation rate (%)

carnitine levels in seminal fluid (mg %).

For statistical evaluation we included only patients with compliance for regular check ups and drug intake. Spermiograms of less than 2 and more than 5 days of sexual abstinence were rejected. There had to be at least one spermiogram before Trental treatment according to the rules for abstinence. Neither gonadotropic agents nor vasoactive preparations should have been taken during a period of at least 6 months prior to Trental therapy. Patients with severe oligozoospermia were excluded. This also applies to those patients whose oligozoospermia, or OAT-Syndrome respectively, was explainable by other pathological conditions. Based on this selection there were 44 patients with 145 spermograms for evaluation of therapeutic efficacy. For each patient the difference from mean values before and after treatment was calculated. Because of large variations in sperm count oligospermia grade III (1 — 10 mio/ml), grade II (more than 10 — 25 mio/ml) and grade I (25 — 35 mio/ml) have been assessed separately. In asthenospermia (motility rate) the severe type (3 — 28%) was separated from minor deviation (30 — 49%). The same goes for malformation rate, i.e. minor teratospermia (25 — 30%) and severe teratospermia (more than 30%).

RESULTS

Impressive improvements could be achieved in the spermiogram-parameters sperm count, motility rate and malformation rate. In the following these changes are described in detail.

Sperm count: the number of spermatozoa in seminal fluid was determined as usual in a counter-chamber and defined in millions per ml. Table 1 shows the analysis of changes in sperm count under Trental administration. The separate evaluation of oligospermia grade III, II and I verified an average rise of sperm count by approximately 8.4, 7.6 or 8.7 mio/ml, respecitvely. The differences proved highly significant.

AVERAGE RISE IN SPERM-COUNT AFTER 4-10 MONTHS TREATMENT WITH PENTOXIFYLLINE

OLIGOZOO-SPERMIA	N	X	s	t	p
I	5	+ 8,7	12,1	4,5	$<0,05$
II	15	+ 7,6	11,0	4,2	$<0,001$
III	20	+ 8,4	11,9	3,1	$<0,01$
TOTAL	40	+ 9,7	12,9	5,03	$<0,001$

Table 1: Average change in sperm count (difference in numbers of spermatozoa compared to basic values) in 20 patients with oligozoospermia grade III, 15 patients with grade II and 5 patients with oligozoospermia grade I. The mean augmentation of sperm count was highly significant (T-test).

Motility rate: this rate was established by counting 200 spermatozoa two hours after ejaculation distinguishing the mobile cells from those withot motion. The results are given in percent of mobile spermatozoa. Subdivision was made between severe asthenospermia (3 — 28%) and minor asthenospermia (motility rate 30 — 49%). In severe asthenospermia the average rise was about 6.8%, in minor asthenospermia about 2.8%. Significance on the 5%-level was established in severe asthenospermia and when evaluating both types together (Table 2).

AVERAGE INCREASE OF MOTILITY-RATE AFTER 4-10 MONTHS TREATMENT WITH PENTOXIFYLLINE

ASTHENO-SPERMIA	N	X	s	t	p
3-28%	14	+ 6,8%	11,2	2,26	$\leq$ 0,05
30-49%	20	+ 2,8%	13,9	0,89	N.S.
TOTAL	34	+ 4,4%	12,9	2,01	$\leq$ 0,05

Table 2: Average changes in motility rate (difference in percentage compared to baseline value) in 14 patients with severe asthenospermia (motility rate less than 30%) and 20 patients with moderate asthenospermia (motility rate 30 — 50%) In the 14 cases with severe asthenospermia the changes were significant at the 5% — level.

Malformation rate: from the dyed smear of the sperm specimen 200 sperms were counted at a magnification of 10 x 100. The single spermatozoon was judged for regular or malformed shape. Figure 5 gives the statistical evaluation of malformation rates. Two stages of teratospermia were differentiated: slight disorder (malformation rate 25 — 30%) and severe deficiency (malformation rate over 30%). In both groups the number of malformed spermatozoa notably decreased, being on average 6.5% for the light type and 13.2% for the severe type. There was statistical significance at the 5%-level in the severe type and also in the total material (Table 3).

There was no evident influence on the parameters sperm volume and carnitine levels in seminal fluid.

The following adverse reactions have been observed during the treatment periods: gastrointestinal disturbances in 4 patients, therapy was interrupted in 2 cases, fatigue in 2 patients, insomnia in 2 patients and cramps and paraesthesia in the legs in 2 patients.

AVERAGE DECREASE OF MALFORMATION-RATE (%) AFTER 4-10 MONTHS TREATMENT WITH PENTOXIFYLLINE

TERATO-SPERMIA	N	X	s	t	p
33-55%	10	- 13,2%	14,6	2,86	$<$0,05
25-30%	8	- 6,5%	10,2	1,8	N.S.
TOTAL	18	- 10,2%	12,9	3,35	$<$0,05

Table 3: Malformation rates during or after administration of Trental, respectively (differences in percentage as compared to baseline values) in 8 patients with moderate teratospermia (malformation rate over 30%) The decrease of malformation rate was significant at the 5% — level for the group with severe teratospermia.

DISCUSSION

After long term treatment with Trental for at least 4 months, but usually longer, significant changes in some parameters of the spermiogram, namely sperm count, motility rate and malformtion rate could be proven. The motility rate showed significant increases in cases of asthenospermia with considerable reduction of motility below 30%. The count of malformed spermatozoa from the severe type of teratospermia also showed major alterations. The most impressive results have been found in the sperm count. In all grades of oligozoospermia highly significant alterations could be established the most obvious improvements in grades III and that is in those cases with the most severe initial impairment.

Therefore one can conclude that the administration of Trental for several months exerts a special influence on sperm count.The positive effect on motility rate and decrease of malformation rate became visible when comparing the mean values, however was not apparent in all patients.

It is known that in patients with varicocele, surgical treatment of the impaired circulation in the venous sytem (via high ligation of the vena spermatica) will increase the motility rate. Compared with this Trental in addition effects a rise in sperm count and a decrease in malformation rate. Both therapeutical measures provide an improvement of disturbed circulation of the testicles and epididymis by different sites of action.Whereas the surgical treatment removes the venous stasis, Trental effects an amelioration of blood flow in the nutritive microcirculation.

Our own investigations have shown that lesions of the parenchyma of the testicle (i.e. in the course of orchitis) effects a change preferrably in sperm count, while pathological changes int he epididymis (i.e. epididymitis, varicocele and others) can be judged by their influence on sperm motility. Any manipulation which brings about a rise in sperm count will, as a rule, influence the testicles rather than the epididymis. For these reasons we would expect Trental to affect the testicles more than the epididymis due to the quantitatively larger vascular bed. Considering the fact, that with long term Trental treatment a highly significant rise in sperm count can already be proven with a small number of patients there are no doubts about an improved nutritive situation. It may still be discussed, though, whether the mechanism inducing this improved condition is part of ameliorated microcirculation or part of metabolic effects of Trental.

CONCLUSIONS

From the clinical and practical point of view and on account of the results presented, a therapy with Trental can be recommended in case of an idiopathic OAT-syndrome so far as functional hypogonadism can be excluded on account of history, clinical findings and hormone tests. If after three spermiogenetic cycles no effect becomes visible it may be concluded that Trental is without benefit in the special case.

Trental therapy is definitely indicated in cse of spermiogram deterioration occurring during combined HMG-HCG-therapy, because this signals an impaired nutritional situation of the testicles which cannot bring about the additional performance as demanded by the stimulation with gonadotropic agents.

SUMMARY

On account of observations in 44 male patients with reduced fertility, it is recommended to approach every single OAT-syndrome by Trental prior to the initiation of hormone-therapy in every case of idiopathic oligozoospermia. The treatment should be continued for at least three spermiogenetic cycles (3 months each). From our experience the following therapeutic results may be achieved with Trental: augmentation of sperm count, increase of motility rate and decrease of malformation rate.

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