A prospective randomized placebo-controlled study of the effect of acupuncture in infertile patients with severe oligoasthenozoospermia

In this first prospective, randomized, single-blind, placebo-controlled study, 28 infertile patients with severe oligoasthenozoospermia received acupuncture according to the principles of traditional Chinese medicine (TCM) and 29 infertile patients received placebo acupuncture. A significantly higher percentage of motile sperm (World Health Organization categories A–C), but no effect on sperm concentration, was found after acupuncture compared with placebo acupuncture. (Fertil Steril® 2009;92:1340–3. ©2009 by American Society for Reproductive Medicine.)

Acupuncture is part of traditional Chinese medicine (TCM). In infertility, prospective randomized clinical studies (1, 2) and a systematic review with meta-analysis (3) showed a significant effect of acupuncture at the time of embryo transfer on clinical pregnancy and live birth rates after in vitro fertilization. The physiologic mechanisms and effects of acupuncture on the circulatory, endocrine, and nervous systems have yet to be clarified.

A male factor is a common cause of infertility. Medical or surgical treatment options are limited. The role of acupuncture in the treatment of male infertility is unclear. Earlier studies suggested that acupuncture might have an effect on sperm concentration, motility, and morphology (4). However, the sample sizes were small and the evidence limited.

This study was designed as a prospective, randomized, single-blind, placebo-controlled trial. It was approved by the Institutional Review Board. All male partners from infertile couples with sperm concentrations <1 million sperm/mL who presented at the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Witten/Herdecke, were eligible. Sperm had to be found in at least one semen specimen of the patient. Azoospermia was not diagnosed until the semen specimen was centrifuged at 1800*g* for 10 minutes and the pellet examined. Patients with hypogonadotropic hypogonadism, obstructive azoospermia, or radio- or chemotherapy within 1 year before the study were excluded. Written informed consent was obtained from each patient.

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This acupuncture trial was in accordance with the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (5). Patients were randomized to receive either acupuncture or placebo acupuncture twice weekly for 6 weeks. For acupuncture 0.30 × 30 mm acupuncture needles (Asia-Med, Pullach, Germany) were inserted to a depth of 15–30 mm, depending on the region of the body. They were rotated manually to evoke the *Deqi* sensation. Ten minutes later, all needles were manipulated again for the *Deqi* sensation. Nonpenetrating 0.30 × 3.0 mm placebo acupuncture needles (Asia-Med) were used for placebo acupuncture. Acupuncture and placebo acupuncture were applied for 45 minutes. No explanations were given to the patients. Acupuncture and placebo acupuncture were carried out by two acupuncture specialists from Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China. Both acupuncturists had a university TCM education and acupuncture training, clinical experience, and expertise. No cointerventions were applied.

According to an earlier acupuncture study on sperm morphology in male infertility (6) the following acupoints were chosen for both groups: *Zusanli* (ST-36, bilateral), *Sanyinjiao* (SP-6, bilateral), *Taixi* (KI-3, bilateral), *Taichong* (LIV-3, bilateral), *Shenshu* (BL-23, bilateral), *Ciliao* (BL-32, bilateral), *Guilai* (ST-29, bilateral), *Xuehai* (SP-10, bilateral), and *Guanyuan* (Ren-4). *Bai Hui* (GV-20) was omitted because the fixation of a placebo needle is problematic at this acupoint.

Patients had an equal probability of assignment to the two groups. The random allocation sequence was generated using a computer-based random number generator to select random permuted blocks with six patients. Sealed numbered containers were used to implement the random allocation sequence. The sequence was concealed until interventions were assigned. The code was revealed for statistical evaluation once recruitment and data collection were complete. Generation of the allocation sequence, enrollment, and assignment of patients were carried out separately. All patients and study personnel were blinded

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to group assignment for the duration of the study. Only the acupuncture specialists knew the type of intervention but were blinded to laboratory data.

All semen samples were evaluated according to the World Health Organization (WHO) standard. Semen volumes and sperm concentrations and motility were assessed after liquefaction. Motility was categorized as percentage of rapid linear progressive (WHO category A), slow or nonlinear progressive (WHO category B), nonprogressive (WHO category C), and immotile (WHO category D) sperm. Four semen analyses were done for each patient. The first semen analysis was done $\leq$5 months before the intervention. The second semen analysis was carried out $<$3 months before the intervention. The third semen analysis was done $<$2 months after the intervention. The fourth semen analysis was carried out $\leq$3 months after the intervention.

Primary outcome measure was sperm motility (WHO categories A–C) before and after acupuncture. Secondary outcome measures were sperm concentration and semen volume before and after intervention. The difference of the percentage of motile sperm (WHO categories A–C) before and after acupuncture was used for sample size calculation. We estimated a sample size of 18 patients for the acupuncture group on the basis of the following assumptions: a minimum of 80% positive differences of motile sperm at a power of 80% and a type I error of 5%. The sample size calculation assumed a one-sided test situation and was performed using the Dixon and Mood sign test. The Mann-Whitney *U* test was applied to compare continuous parameters. The Wilcoxon matched pairs test was used for the comparison of dependent variables before versus after intervention (Bias 2008; Ackermann; Statistica 2005; Statsoft).

Patients were recruited between February 2006 and January 2008. The follow-up ended in April 2008. A total of 57 patients with sperm concentrations $<$1 million sperm/mL were randomized and allocated to intervention. Twenty-eight patients were treated with acupuncture (group I), 29 patients received placebo acupuncture (group II). Four patients with acupuncture and one patient with placebo acupuncture discontinued their treatment because of lack of time. The study protocol was completed by 24 patients with acupuncture and 28 patients with placebo acupuncture. No patient was lost to follow-up. Fifty-two patients were analyzed for the outcome. The clinical characteristics of the patients in both groups were not significantly different in terms of age, body mass index, duration of infertility, and abstinence.

The outcomes before and after acupuncture are shown in Table 1. The percentages of sperm motility, sperm

TABLE 1

Results.

Variable	Group I	Group II
Motility A before intervention (%)	11.5 ± 12.5	16.0 ± 13.4
Motility A after intervention (%)	12.1 ± 8.6	13.1 ± 13.3
P value	NS	NS
Motility B before intervention (%)	8.1 ± 10.2	8.0 ± 8.0
Motility B after intervention (%)	10.5 ± 11.8	8.8 ± 7.5
P value	NS	NS
Motility C before intervention (%)	4.6 ± 6.9	8.2 ± 8.4
Motility C after intervention (%)	11.2 ± 13.7	7.8 ± 7.8
P value	NS	NS
Motility A–C before intervention (%)	24.2 ± 17.0	32.2 ± 18.1
Motility A–C after intervention (%)	33.8 ± 18.2	29.7 ± 17.6
P value	.035	NS
Motility D before intervention (%)	75.8 ± 17.0	67.8 ± 18.1
Motility D after intervention (%)	66.2 ± 18.2	70.3 ± 17.6
P value	.035	NS
Concentration before intervention (million/mL)	0.039 ± 0.128	0.016 ± 0.085
Concentration after intervention (million/mL)	0.465 ± 1.206	0.468 ± 1.712
P value	NS	.0180
Volume before intervention (mL)	4.2 ± 1.8	4.0 ± 1.8
Volume after intervention (mL)	3.7 ± 1.4	3.8 ± 1.6
P value	.041	NS

Note: Data are presented as mean ± SD. A–D = World Health Organization motility categories: rapid linear progressive, slow or nonlinear progressive, nonprogressive, and immotile, respectively; NS = non significant.

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concentration, and semen volume were calculated as means of the two semen analyses before and and the two after the intervention. Sperm morphology was not statistically evaluated because of low sperm concentrations and the subjective assessment. There were no adverse events or side effects in both groups.

Uncontrolled case reports and nonrandomized case control studies suggested that acupuncture might have an effect on male infertility (7). Zhang et al. (8) reported that there was a significant increase in the percentages of rapid motile and of morphologically normal sperm after acupuncture in 22 patients with idiopathic male infertility and unsuccessful intracytoplasmic sperm injection.

In a prospective nonrandomized case-control study by Sitermann et al. (9), 16 subfertile patients were treated with acupuncture twice a week for 5 weeks. The control group consisted of 16 matched subfertile patients without treatment. The percentage of viability, the total motile sperm count per ejaculate, and the percentage of ultramorphologically normal sperm were significantly higher 1 month after acupuncture compared with the control group.

In a prospective controlled pilot study, Siterman et al. (10) examined patients with very low sperm concentrations. Twenty patients received acupuncture twice a week for 5 weeks. Twenty patients were not treated. The authors concluded that acupuncture may be useful for patients with very low sperm concentrations.

In a prospective, randomized, controlled, single-blind study by Gurfinkel et al. (11), 19 patients with semen abnormalities in concentration, morphology, and/or progressive motility received acupuncture and moxa treatment at therapeutic or indifferent points for 10 weeks. The percentage of morphologically normal sperm increased significantly after acupuncture and moxa treatment at therapeutic points compared with indifferent points.

In a prospective controlled study, Pei et al. (6) compared 28 infertile men with oligozoospermia, asthenozoospermia, and/or teratozoospermia who received acupuncture twice a week for 5 weeks with 12 untreated infertile men. Sperm morphology was quantitatively analyzed by transmission electron microscopy. Significantly more sperm without ultrastructural defects were found after acupuncture compared with no treatment.

In a recent systematic review of the role of acupuncture in male subfertility, Yu Ng et al. (4) did not find sufficient evidence of a significant effect.

The present study showed a significant effect of acupuncture on the percentage of total motile sperm (P=.035). There were no significant differences in each category (A, B, or C) before and after acupuncture. The decrease in semen volume after acupuncture (P=.041) has to be investigated. There was a significant increase in sperm concentration after placebo acupuncture (P=.018), but not after acupuncture. These results might be due to the number of patients included in this study. Forty-five patients would have been required in the acupuncture group for a statistically significant difference in sperm concentration.

Sham acupuncture (i.e., real acupuncture at places designed not to interfere) as control was criticized because physiologic effects might be possible. In the present study, placebo acupuncture was used as control. With this technique, it is possible to simulate acupuncture without penetrating the skin. Because patients are not able to differentiate between real and placebo acupuncture (12), a single-blind study design can be realized. However, an effect of placebo acupuncture can not be completely excluded. The German Acupuncture Trials showed effects of both acupuncture and sham acupuncture in chronic lower back pain (13). Further studies with more patients are necessary for further evidence.

To facilitate understanding and interpretation, the report of this randomized controlled trial follows the revised CONSORT (Consolidated Standards for Reporting Trials) statement (14). In addition, the STRICTA recommendations (5) were followed. The acupuncture rationale, needling details, treatment regimen, cointerventions, practitioner background, and control intervention are described.

When the effect of acupuncture is evaluated, it has to be taken into account that randomized controlled trials do not reflect the TCM perspective. In TCM, acupoints are chosen individually based on the diagnosis according to signs and symptoms. In clinical acupuncture trials, a fixed protocol is administered to all patients. This standardization might reduce the effect of acupuncture in individual patients.

The results of the present study support the significance of acupuncture in male patients with severe oligoasthenozoospermia. More evidence has to be accumulated before the efficacy and effectiveness of acupuncture in male infertility can be evaluated.

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