Randomised clinical trial of comparing effects of acupuncture and varicocelectomy on sperm parameters in infertile varicocele patients

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Summary
The aim of the study was to evaluate the effect of the acupuncture treatment on sperm parameters and pregnancy rates in patients with primary infertility. Between January 2008 and May 2010, 30 men with the primary infertility (one year of unprotected intercourse, healthy wife) and varicocele with normal hormone levels and abnormal semen analysis were randomised into two groups. Group 1 underwent subinguinal microscopic varicocelectomy, and Group 2 underwent acupuncture treatment twice a week for 2 months. Both groups were evaluated with semen analysis at 6 months after the treatment. Patients in both groups evaluated with telephone calls and e-mail in terms of pregnancy. The mean age of the patients was 27.2, and groups were comparable regarding the age ($P = 0.542$). The pre-treatment sperm concentration, motility and morphological characteristics were similar in both groups. Sperm concentration and motility improved significantly in both groups after the treatment. Increase in sperm concentration was higher in the acupuncture group compared to the varicocelectomy group ($P = 0.039$). The average follow-up was 42 months, and pregnancy rates were emphasised 33% in both groups. Acupuncture treatment in primary infertile varicocele patients with semen abnormalities seems to be effective and has comparable results with the varicocelectomy treatment.

Introduction
Infertility affects 2–10% of couples (Boivin et al., 2007; Mascarenhas et al., 2012). In 2010, about 48.5 million couples worldwide were infertile (Mascarenhas et al., 2012). About 50% of the infertility was attributable to the male factor and most of the cases were found together with the abnormal semen parameters. In 30% of the infertile male patients, no male-associated infertility factor is found (Jungwirth et al., 2012). Varicocele is the main known factor of infertility and found 25% of men with semen abnormalities (World Health Organization, 1992). Varicocelectomy is the most performed surgery for the primary and secondary infertile patients with varicocele. However, outcomes of varicocelectomy treatment in infertile patients with varicocele remained the subject of controversy so far. This controversy encourages urologists to search for the alternative treatment modalities for these patients.

Acupuncture treatment has been used in several studies in andrology for the treatment of the male infertility and to increase the success of in vitro fertilisation. A meta-analysis made by Manheimer et al. (2008) concluded that acupuncture given with embryo transfer significantly improved pregnancy and the live birth rates among women undergoing in vitro fertilisation. Several studies revealed that acupuncture might have a positive effect on the sperm parameters of subfertile patients and patients with oligoasthenozoospermia (Siterman et al., 1997; Zhang et al., 2002; Gurfinkel et al., 2003; Pei et al., 2005; Dieterle et al., 2009). However, most of these studies focused on the treatment of idiopathic male infertility. So far, as our knowledge, there is not any study on the effect of the acupuncture treatment in the patients with clinical varicocele.

In this prospective randomised novel study, we aimed to evaluate the effect of the acupuncture treatment on sperm parameters and pregnancy rates in the patients...
with clinical varicocele and to compare the results with varicocelectomy.

**Material and methods**

We estimated that a total of 28 patients would be needed to detect the difference between two groups with an \( \alpha \) of 0.05 and a \( (1-\beta) \) of 80%. Between January 2008 and May 2010, 30 male patients, aged 24–35 (mean age 27.2) who had unprotected, regular intercourse at least 12 months with a healthy partner and had a unilateral clinical varicocele (Grade I–III), included in this study. Bilateral varicocelectomy cases were excluded and patients were selected consecutively. The local ethics committee of our hospital approved the study, and we gave informed consent to all patients. All the patients had a normal follicle-stimulating hormone (FSH), testosterone levels. All the patients had two consecutive abnormal semen samples in concentration, motility and morphology according to the 1999 World Health Organization (WHO) manual. Exclusion criteria were as follows: sperm concentrations under 5 million ml\(^{-1}\), leucocytospermia, known genetic abnormalities any treatment for fertilisation within 1 year, previous reproductive system surgery, bleeding disorders, chronic inflammatory diseases, localised skin infection and severe chronic diseases including cancer. Gynaecologists evaluated the partners of the participants. Any female with documented ovulatory dysfunction, uterine or cervical pathology were also excluded from this study (Fig. 1).

Patients were randomised into two groups prospectively, the varicocelectomy group (Group 1, \( n = 15 \)) and the acupuncture group (Group 2, \( n = 15 \)). Group 1 underwent subinguinal microscopic varicocelectomy operation. All the operations were performed under the general anaesthesia with the same surgeon (E.V.K.). Operation performed after a 3-cm incision was made above the external inguinal ring. Camper fascia and scarpa fascia opened either blunt or sharp dissection. Without opening external oblique fascia, the spermatic cord was isolated, any seen external spermatic vein was ligated, and the internal spermatic fascia was opened. Any seen internal spermatic veins were ligated. Testis was not delivered, and gubernacular veins were not ligated.

In the acupuncture group, CV3 (Zhongji), CV4 (Guan-yan), CV6 (Qihai), BL23 (Shenshu), BL32 (Ciliao) and ST29 (Guilai) acupuncture points were used for stimulation using a disposable acupuncture needles (Hua Long, 25 × 40 mm Sterile Acupuncture Needles, China) and the electrical pulse generator (AGISTIM Duo, 4 × 4 mA rms max/99 Hz max, France), twice a week for 8 weeks (Table 1). Acupuncture needles were inserted on the acupuncture points to a depth of approximately 20 mm.

![Flow diagram](Fig. 1)
The needles were rotated manually to evoke *Daqi*, and then, electrical stimulator was connected to the acupuncture points. The needles were left for 25–35 min and then removed. Acupuncture points were selected according to earlier clinical trials on sperm parameters in infertile males (Jeng *et al.*, 2014).

Both groups were evaluated with a semen analysis at 6 months after the treatment. Also patients were evaluated with telephone calls and electronic mail after 36 months in terms of pregnancy. The change from the baseline sperm concentration, motility and progression were the primary outcomes, and the pregnancy rates were the secondary outcome for this study.

We used NCSS (Number Cruncher Statistical System) 2007 and PASS 2008 Statistical Software (Utah, USA) for the data analyses, definitive statistical methods (mean, standard deviation), Student’s *t*-test for quantity variations between two groups, Mann–Whitney *U*-test for alternative hypothesis between two groups and Wilcoxon signed-rank test for comparison quantities inside the group (*P* < 0.05 was regarded as significant).

### Results

A total of 48 patients were involved, 18 of them excluded, and 30 of them met the inclusion criteria and were randomised. The study was made with 30 patients, aged between 23 and 34 years. The mean age of varicocelectomy group was 26.3, and the mean age of acupuncture group was 28.1 years. There was no significant difference between the ages of the two groups (*P* > 0.05). The ethnicity of the patients was Turkish. All the participants were primary infertile. The majority of the participants’ varicocele grade was 2. Only four patients in each group had grade-3 varicocele (Table 2). In varicocelectomy group, mean number of veins (internal and external spermatic) ligated was 6.2 ± 4.5. In group 1, 3 (20%) patients and in the group 2, 4 (27%) patients were smoker. All the patients followed up at least for 36 months, and no adverse effects or complications were reported in both groups.

Baseline and post-treatment semen parameters were given in Table 3. Baseline mean sperm concentration (group 1, 11.3 vs. group 2, 10.9 million ml⁻¹) (*P* = 0.768), total progressive (A + B) motility (group 1, 25.1% vs. group 2, 19.4%) (*P* = 0.27) and normal morphology (group 1, 50.9% vs. group 2, 55.1%) (*P* = 0.33) were similar between the groups.

Mean increase in the sperm concentration after the treatment in the group 1 and group 2 was 3.5 and 9.4 million ml⁻¹ respectively. Mean increase in the sperm concentration was statistically significant in both groups (*P* < 0.05). Furthermore, change in sperm concentration in the acupuncture group compared to varicocelectomy group was higher and statistically significant (*P* = 0.015). Mean progressive motility statistical significantly increased in both groups (group 1, 25.1–25.6% vs. group 2, 19.4–26.3%) (*P* < 0.05). Mean sperm morphology increased in the group 1 but decreased in group 2, and it was not statistically significant (*P* > 0.05).

There was no significant inconsistency in terms of pregnancy rates in this study. At the end of follow-up (42 months), pregnancy rates were 33% in both groups.
Discussion

Varicocele is an abnormal dilatation and tortuosity of the internal spermatic veins within the Pampiniform plexus. The well-known and correctable factor of infertility in men is varicocele. Varicocele can be detected in 10–20% of adult men and 25–35% of men with the abnormal semen parameters (Gorelick & Goldstein, 1993). The mechanism of varicocele-induced male infertility is still not known enough. Reduced Sertoli cell function due to the elevated intrascrotal temperature, gonadotoxicity of the renal and adrenal metabolites, oxidative stress and hypoxia as a result of impaired venous drainage are proposed mechanisms for varicocele-induced infertility (Ito et al., 1982; Allamaneni et al., 2004 Khera & Lipshultz, 2008).

Various surgical approaches including open, laparoscopic, microsurgical varicocelectomy and sclerotherapy have been used for the treatment of the varicocele. So far, there is not gold standard approach for the treatment of the varicocele. However, subinguinal microscopic varicocelectomy appears to be safer and associated with better outcomes. Subinguinal microscopic varicocelectomy significantly improves sperm concentration in men with clinical varicocele compared to other surgical procedures (Ding et al., 2012). Nevertheless, meta-analysis is not able to find sufficient evidence to demonstrate a statistically significant effect of varicocelectomy on spontaneous pregnancy rates (Bazaeem et al., 2011; Kim et al., 2013; Wang et al., 2015). As a result of these findings, alternative treatment methods have been tried so far.

Acupuncture, invented in ancient China, is a traditional Chinese treatment, in which the theory is based on the premise that there are patterns of energy flow (Qi) through the body that are essential for health. Acupuncture aims to correct imbalances of the ‘Qi’ and restore health through stimulation. The needles are inserted through the skin at points along the meridians, representing various organs and ailments of the body. In an acupuncture session, patients lie on a bed either supine or prone. A length of 25–70 mm and a diameter of 0.2–0.3 mm, disposable needles are used to stimulate acupuncture points. For needle stimulation, heat, electrical current, and moxibustion can be used.

Mechanisms of action of acupuncture on male infertility are not well known. Acupuncture stimulates somatic afferent (mostly type A and C sensory) nerves and possibly modulates the autonomic nervous system and controls the hypothalamus–pituitary–gonadal and the adrenal axis. This may lead to change in ACTH, FSH, LH, neuropeptides, neurotransmitters and growth factors (Franconi et al., 2011; Hu et al., 2013).

Varicocele can have a role to create oxidative stress and to reduce arterial blood flow of the testis. The pressure gradient between venous and arterial blood flow and the impaired microcirculation may lead to hypoxia in the testis (Tarhan et al., 2003; Gat et al., 2006). Thus, hypoxia may lead to the ageing of the testis and the impaired spermatogenesis. Cakmak et al. reported that the electroacupuncture treatment at 10 Hz in an anatomical region ST-29 (Guilai) improved testicular blood flow in a prospective randomised study (Cakmak et al., 2008). It has been reported that the varicocele is associated with a reduction of locally and systemic antioxidant defences (Barbieri et al., 1999) and the seminal antioxidant agent levels are lower in infertile men compared to normal population (Lewis et al., 1997; Bhardwaj et al., 2000). Also, inflammation of the genital tract may have a role in scrotal hyperthermia and Siterman et al. (2009) indicated that these patients could benefit from the acupuncture treatment. In our previous study of the effectiveness of acupuncture treatment on chronic prostatitis, we also found that the patients with chronic inflammation could benefit from the acupuncture treatment (Kucuk et al., 2015). Raise in scrotal temperature may influence the sperm concentration and motility; thus, the positive effect of acupuncture to reduce temperature in scrotum might reveal the benefit of the acupuncture arm in our study.

Several trials showed that the acupuncture has a positive effect on the sperm concentration, motility and morphology. In a prospective controlled study by Pei et al. (2005), 28 patients received acupuncture treatment twice a week for 5 weeks and semen samples analysed using transmission electron microscopy. They found statistically significant improvement in the morphology of the spermatozoa in treatment arm. Also in a prospective, randomised, controlled study, 19 primary infertile patients with the semen abnormalities were randomised into study and control group. The study group underwent acupuncture and moxibustion treatments at the therapeutic points and the control group underwent acupuncture and moxibustion treatments at nontherapeutic indifferent points for 10 weeks, and it was reported that in the study group, the percentage of normal-form spermatozoa significantly increased (Gurflinkel et al., 2003).

A recent systemic review and meta-analysis, including four randomised clinical trial that compared acupuncture treatment against placebo, sham or no treatment, concluded that the acupuncture treatment might significantly improve the sperm motility and sperm concentration in infertile men with poor semen quality. However, they did not find a significant impact on the pregnancy rate of couples (Jerng et al., 2014). Despite the exact effect of the acupuncture treatment or the varicocelectomy had not proven yet, our trial showed that both study groups gain benefit in terms of pregnancy rates.
Acupuncture vs. varicocelectomy

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In our study, there was a statistically significant increase in the sperm concentration and motility in both groups. The change in the sperm concentration in the acupuncture group was statistically significantly higher compared to the varicocelectomy group. Numerous patients’ sperm concentrations decreased after the treatment in the varicocelectomy group compared to the acupuncture group. However, we did not find significantly improvement in the sperm morphology in both groups. The mean motility change after the treatment in the varicocelectomy group was statistically significant but not clinically. This effect might be due to the limited number of patients included in this study. Current evidence suggests that microscopic varicocelectomy is the most effective method comparing the other surgical techniques. Acupuncture treatment on infertile patients with varicocele is an experimental treatment method. Despite the absence of ‘gold treatment’ method, both groups seem to be benefit from the acupuncture and the varicocelectomy treatments. The exact mechanism of the acupuncture and the varicocelectomy treatments on the effect of sperm parameters were not known well. Thus, the molecular pathology and the effects of treatment modalities on varicocelectomy have to be discovered.

The main limitation of the study was the absence of the control group. Measuring the serum testosterone levels before and after the treatment might strengthen the study. Despite not having a control group and limited number of patients, the present study indicated that the acupuncture treatment is effective as varicocelectomy in terms of sperm concentration, motility and pregnancy rates in the follow-up.

Acupuncture treatment in the primary infertile varicocele patients with semen abnormalities seems to be effective and has comparable results with the varicocelectomy treatment. However, further large-scale randomised clinical studies are needed to investigate the efficacy of the acupuncture treatment in the patients with varicocele.

References


