Effect of Saffron on Semen Parameters of Infertile Men

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Introduction: We conducted this study to determine the effects of saffron (Crocus sativus) on the results of semen analysis in men with idiopathic infertility.

Materials and Methods: In this clinical trial, 52 nonsmoker infertile men whose problem could not be solved surgically were enrolled. They were treated by saffron for 3 months. Saffron, 50 mg, was solved in drinking milk and administered 3 times a week during the study course. Semen analysis was done before and after the treatment and the results were compared.

Results: The mean percentage of sperm with normal morphology was 26.50 ± 6.44% before the treatment which increased to 33.90 ± 10.45%, thereafter ($P < .001$). The mean percentage of sperm with Class A motility was 5.32 ± 4.57% before and 11.77 ± 6.07% after the treatment ($P < .001$). Class B and C motilities were initially 10.09 ± 4.20% and 19.79 ± 9.11% which increased to 17.92 ± 6.50% ($P < .001$) and 25.35 ± 10.22% ($P < .001$), respectively. No significant increase was detected in sperm count; the mean sperm count was 43.45 ± 31.29 × 10^6/mL at baseline and 44.92 ± 28.36× 10^6/mL after the treatment period ($P = .30$).

Conclusion: Saffron, as an antioxidant, is positively effective on sperm morphology and motility in infertile men, while it does not increase sperm count. We believe further studies on larger sample sizes are needed to elucidate the potential role and mechanism of action of saffron and its ingredient in the treatment of male infertility.

Keywords: male infertility, Crocus sativus, antioxidants, sperm motility, sperm count

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INTRODUCTION

Approximately, 8% of the Iranian couples suffer from infertility after 2 years of attempting conception.(1) Where the issue lies with the male partner, 2 groups of patients are seeking treatment, namely those suffering from idiopathic infertility and those in whom the etiology of infertility is known. Various therapeutic agents including clomiphene citrate, tamoxifen, kallikreins, and antioxidant agents such as vitamin E and glutathione are used to help these patients; nevertheless, none is a definite treatment.(2-4) This necessitates utilization of other alternative agents.

Recent studies have investigated the role of reactive oxygen species (ROS) on sperm. Even though, small amounts of ROS are necessary for sperm activation, these agents can cause damage to the sperm in higher concentrations.(5-7) Increased levels of ROS are related to decreased motility of the spermatozoa and DNA damage, and may even lead to germ cell apoptosis.(8-12) In fact, studies have shown that more than

40% of infertile men have augmented levels of ROS in their seminal plasma.[13] Therefore, many studies have focused on antioxidant agents in order to prevent this damage on sperm metabolism, motility, morphology, and as a consequence, fertilizing capacity.

Crocus sativus (saffron) is a perennial herb of the Iridaceae family with antioxidative prosperities.[14-16] It is widely cultivated in Iran, India, Greece, Spain, and France. Its dried red stigma is commercially used as a food spice. Saffron has also been widely used in folk medicine as an antispasmodic, eupeptic, pain killer, anticatarrhal, carminative, diaphoretic, expectorant, stimulant, stomachic, aphrodisiac, and emmenagogue.[17,18] In some countries such as India, Spain, and China, saffron has been used to treat infertility and impotence from long ago.[19,20] We undertook this study to investigate the effect of saffron on semen parameters and infertility.

MATERIALS AND METHODS

Between 2006 and 2007, we evaluated infertile men referring to the urology clinic of Shohada-e-Ashayer Hospital in Khorramabad, Iran. All patients were initially interviewed and questioned about their sexual behavior, history of prior surgical interventions or childhood diseases such as cryptorchidism that affect fertility, and family history of infertility. Complete drug history was obtained; the patients were specifically asked about administration of sulfasalazine, cimetidine, marijuana, cocaine, and tobacco. Moreover, history of contact with chemicals and ionizing radiation was acquired. All patients were then assessed for systemic diseases such as fever, viremia, and acute infections (eg, mumps). Finally, the participants underwent full urologic examination. Smokers and patients whose problems could be solved surgically were excluded. Eligible patients provided informed consent and entered the study. The study protocol was approved by the ethics committee of the Urology and Nephrology Research Center, Shahid Beheshti University (MC).

Before initiating the treatment with saffron, semen analysis was performed. Samples were obtained 48 to 72 hours after the patient's last sexual contact. Analyses were performed by the aid of the Computer-Assisted Sperm Analysis in less than 1 hour after sample collection. Using this method, sperm motility was determined in 4 classes defined by the World Health Organization.[21] These 4 classes are characterized as follows: class A, fast progressively motile sperm (4th degree); class B, progressively motile sperm (3rd degree); class C, nonprogressively motile sperm (2nd degree); and class D, immotile sperm (1st degree).

By the end of initial evaluation and semen analysis, the patients were asked to administer 50 mg of saffron solved in milk, 3 times a week for 3 months. A specific brand of the available saffron in Khorramabad was obtained for all the patients. The amount to be used was weighed and divided in separate doses by the trained research assistants. No other treatment options were considered during the study period. After finishing the treatment course, semen analysis was again carried out by Computer-Assisted Sperm Analysis method. Results were compared and analyzed by paired *t* test.

RESULTS

A total of 52 eligible patients were enrolled in the study, all of whom finished the study course and underwent a secondary semen analysis. The mean age of the patients was 31.0 ± 4.6 years (range, 21 to 48 years). The mean percentage of sperm with normal morphology was 26.50 ± 6.44% before the treatment which increased to 33.90 ± 10.45%, thereafter ($P < .001$), which corresponded to a 7.4% improvement in this index. Significant increases were also seen in the percentages of class A to class C morphology of the sperm. The mean percentage of sperm with Class A motility was 5.32 ± 4.57% before and 11.77% ± 6.07% after the treatment ($P < .001$). Class B and C motilities were initially 10.09 ± 4.20% and 19.79 ± 9.11% which increased to 17.92 ± 6.50% ($P < .001$) and 25.35 ± 10.22% ($P < .001$), respectively. Overall, 6.4%, 7.8%, and 5.6% increases were detected in the percentage of sperm with class A, B, and C motility, respectively. We could not detect a significant increase in terms of sperm count with saffron therapy; the mean sperm count was initially 43.45 ± 31.29 × 10^6/mL which changed to 44.92 ± 28.36× 10^6/mL, afterwards (*P* = .30).

DISCUSSION

About 8% of the Iranian couples are infertile, and male factor accounts for nearly 40% of infertility cases.[1,22] Recent advances in fertility medicine are indicative of ROS, which impairs sperm function, as one of the reasons behind this dilemma.[1,8-13,23] As mentioned earlier, in contrast to the semen of a healthy man, seminal plasma of up to 40% of infertile men shows increased amounts of ROS.[13] Thus, reducing the ROS may help in the treatment of male-factor infertility. Pursuing this hypothesis, we examined saffron stigma as an antioxidant and found that semen parameters improved after a period of saffron administration.

Reactive oxygen species consist of a wide range of molecules including radicals, nonradicals, and oxygen derivatives.[22] A small amount of ROS is necessary for the function of cells including germ cells. However, in increased levels, these molecules are capable of damaging cell membranes and genetic content. Polyunsaturated fatty acids found in the sperm cell membrane are one of the primary targets of ROS due to their lipid nature. Reactive oxygen species cause lipid peroxidation in the sperm cell membrane, and as a result, impair sperm motility and its ability to fuse with the oocyte.[24,25] Moreover, ROS may induce DNA damage, which in turn will result in poor fertilization. This DNA damage happens through modification of all bases, production of base-free sites, deletions, frame shifts, DNA cross links, and chromosomal re-arrangements. Also, they may induce high frequencies of single-strand and double-strand DNA breaks.[11,12,24] Finally, high levels of ROS disrupt the inner and outer membranes of the mitochondria; as a consequence, cytochrome c is released and caspases are activated which lead to apoptosis.[24]

Antioxidants preserve fatty acids from oxidation, and therefore, may play an important role in male fertility.[25] Many studies have investigated the role of different antioxidants on infertility. In an investigation by Lenzi and colleagues, it was shown that utilizing glutathione (600 mg/d for 2 months) had a significant effect on increasing sperm motility and morphology.[26] They carried out another study in 1993 on 20 infertile men and re-established the role of glutathione in improving sperm motility and morphology.[27] In 1996, Suleiman and coworkers determined the role of vitamin E in the treatment of infertile men. They treated 82 infertile men with vitamin E and demonstrated that sperm motility increased from 31.1% to 48.9%, compared to a slighter increase from 30.6% to 35.9% in the control group of infertile men.[28] In the group receiving vitamin E, 11 pregnancies took place, 9 of which led to birth; however, no pregnancies happened in the control group. In another research project, Martin-Du Pan and Sakkas treated 14 infertile men with vitamin E and gave another 20 infertile men glutathione.[29] They concluded that vitamin E improved sperm count, while glutathione increased sperm motility. Five years later, Ibrahim and colleagues investigated the effect of vitamin E on 65 infertile men.[30] Sperm motility and sperm count increased from 32.46% and 11.9 × 10^6/mL to 37.2% and 12.15 × 10^6/mL in their patients, respectively. Eskenazi and associates performed another study on 96 healthy male participants in California University in 2005.[31] They established the fact that using antioxidants (vitamin E, vitamin C, L-carnitine, and beta carotene) had beneficial effects on concentration and motility of the sperm; especially, class A motility. Increased absorption of antioxidants led to increased effect on concentration and motility of the sperm. Therefore, those with higher absorption, had 80 × 10^6/mL more sperm than those with lower absorption; furthermore, the number of sperm with class A motility was 36 × 10^6/mL more in those with a high absorption rate.[32]

Crocetin and *dimethylcrocetin* are derived from *crocin* which is a water-soluble carotenoid found in the stigmas of saffron.[16] Their antioxidant effect has been documented in several studies.[14-16] We tested this effect on the sperm of infertile men and found no significant change in sperm count after a period of treatment with saffron; however, significant alterations were observed in sperm morphology and motility. The normal morphology of the sperm increased from a mean of 26.5% to 33.9%; class A motility was initially

5.3% that later increased to 11.8%. As for class B and C motility, the preliminary amounts of 10.1% and 19.8% changed to 17.9% and 25.4% after the treatment course, respectively. Overall, the introductory amount of motile sperm (35.2%) increased to the final amount of 55.1%. Although the study did not have the strength of a randomized controlled trial, results were promising and the effect of saffron on semen parameters was documented. This can be a basis of further investigation on saffron ingredients in infertility research.

CONCLUSION

Saffron has a positive effect on semen parameters in terms of sperm motility in men suffering from idiopathic infertility. It comprises several ingredients and even though its antioxidative effect may be the reason behind its positive value on spermatic parameters, further studies are required to define its exact mechanism of action. Moreover, we acknowledge the need for further studies on larger groups of patients. We also believe that a longer period of follow-up, possibly up to 1 year, will be more beneficial in determining the role of saffron on seminal fluid.

CONFLICT OF INTEREST

None declared.

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