Received: 1 March 2023 | Revised: 27 June 2023 | Accepted: 6 July 2023

DOI: 10.1002/hsr2.1431

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Semen's parameters after varicocelectomy surgery with mast cell stabilizers treatment in infertile varicocele patients: Randomized clinical trial study

Alireza Akhavan Rezayat[1] | Amirmohammad Soleimanian[2] | Neda Kamandi[2] | Mohammad Aslzare[1] | Mohammad Mustafa Shaikh Zada[2]

[1]Department of Urology, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Department of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence
Mohammad Mustafa Shaikh Zada, Department of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: mostafa_shikhzade@yahoo.com

Funding information
Mashhad University of Medical Sciences

Abstract

Background and Aims: Varicocele is one of the most common causes of male infertility in which testicular function is progressively damaged. This study aims to investigate the effect of varicocelectomy and mast cell stabilizers on reducing sperm DNA fragmentation in infertile patients with varicocele.

Methods: In this randomized clinical trial, after obtaining ethical approval and informed consent, infertile patients with varicocele were randomly assigned to three groups: varicocelectomy, 1 mg ketotifen, and varicocelectomy plus with 1 mg ketotifen for 3-month follow-up. Semen analysis and estimation of DNA fragmentation index (DFI) were obtained from all people in the studied time periods.

Results: In this study, 420 infertile patients with varicocele were included with an average age of 31.6 years. The results showed that sperm morphology, sperm motility, sperm count, and sperm DFI had significant differences after the intervention ($p < 0.05$). Also, the results of semen analysis for each group showed that there was a significant improvement in sperm morphology, motility, count, and DFI index of infertile people with varicocele after the intervention ($p < 0.05$). But the difference was statistically higher in the varicocelectomy plus with 1 mg ketotifen group than in the other groups ($p < 0.01$).

Conclusion: The evidence and results of this study showed that the use of varicocelectomy plus ketotifen in infertile people with varicocele was more effective in improving Semen parameters than the use of mast cell stabilizers or varicocelectomy alone.

KEYWORDS

infertility, mast cell stabilizers, sperm DNA fragmentation, varicocelectomy

1 | INTRODUCTION

Infertility is the inability to create a clinical pregnancy after 12 months of unprotected and regular sexual activity.[1] Over 60–80 million people worldwide suffer from infertility at some point in their lives, impacting an estimated 8%–12% of all couples. Males are mainly responsible for 20%–30% of infertility cases but contribute to 50% of all cases.[2] A varicocele is characterized by dilated tortuous veins of the pampiniform plexus in the spermatic cord.[3] Most men are unaware of varicocele. It is the most commonly diagnosed and the major curable cause of infertility in men who go to an infertility clinic for evaluation. It is generally reported to be present in 15% of the general male population, in 35% of men with primary infertility, and in 80% of men with secondary infertility. The link between varicocele and infertility is unclear because varicocele is often found in fertile men as well. However, varicocele is associated with significant changes in semen patterns in men.[4]

Several mechanisms account for varicocele-related infertility, including scrotal hyperthermia, hormonal disturbances, and hypoxia in the testes.[5] Varicocele is also considered to be a cause of increased sperm DNA fragmentation index (DFI) among infertile men, which has been significantly associated with poor pregnancy outcomes.[6,7] Varicocelectomy is considered the most common choice for the treatment of varicocele. It has been shown that varicocelectomy improves semen quality, and chromatin integrity and reduces DNA fragmentation. A review study by Birowo et al., published in 2020, showed that varicocelectomy reduced DNA fragmentation and improved sperm concentration, motility, and morphology. In addition, the analysis showed that abnormal levels of DFI should be considered an indication of varicocelectomy.[8]

Ketotifen is a mast cell stabilizer, as well as an antagonist of the H1 receptor. It is commonly used in the treatment and prevention of respiratory allergies. As well it can be used as a mast cell stabilizer in the treatment of varicocele.[9] A previous study by Saharkhiz et al. showed that ketotifen may be a novel therapeutic approach for improving sperm count and motility in infertile men.[10] Therefore, we aimed to investigate whether mast cell stabilizers with/without varicocelectomy can improve DFI and spermogram parameters in infertile men.

2 | MATERIALS AND METHODS

2.1 | Participants

This randomized clinical trial was designed according to the Consolidated Standards of Reporting Trials[11] and reporting of evidence from Clinical research[12] in the Urology department of Ghaem Educational and Medical Center and Milad Infertility Center in 2020–2021 after IEC approval (approved with the code IR.MUMS.MEDICAL.REC.1399.689; Trial registration number: IRCT20181106041575N1 in 17/05/2019).

According to the Zaazaa et al.[13] study, the improvement of the sperm count in the varicocelectomy group was about 45% and in the varicocelectomy+ ketotifen group was about 64%, and the minimum sample size was calculated at 140 participants in each group. Accordingly, we assigned 86 patients to each treatment group.

This study was performed on a total of 420 patients with varicocele with a mean age of 31.6 ± 6 years and an age range of 20–47 years. The participants in this study were recruited from men of childbearing age who complained of infertility and varicocele (grades II and III) with normal female factors.

Varicocele was diagnosed in patients by clinical examination and was validated using a scrotal ultrasound, which visualized a vein at least 3 mm in diameter and longer than 1 s in duration during the Valsalva maneuver. Gray-scale and duplex color Doppler ultrasonography was performed on the patients using a 7.5-MHz probe (Diagnostic ultrasound equipment, Toshiba Corporation). The minimum duration of infertility was considered as a failure to establish a pregnancy for at least 12 months. All patients gave informed consent before trial commencement. Exclusion criteria were leucocytospermia, azoospermia, smoking, diabetes, allergic reaction or drug complication, and reluctance to continue the study. Eligible individuals entered the study after being informed of the study process by completing informed consent.

2.2 | Randomization and allocation

The patients were randomized into three equal groups; patients that underwent microsurgical subinguinal varicocelectomy (control group), patients on 1 mg oral ketotifen twice daily for 3 months, and patients that underwent varicocelectomy and postoperative oral ketotifen for 3 months (Figure 1). Individuals were divided based on random sequences generated by Excel software. Afterward, the specified

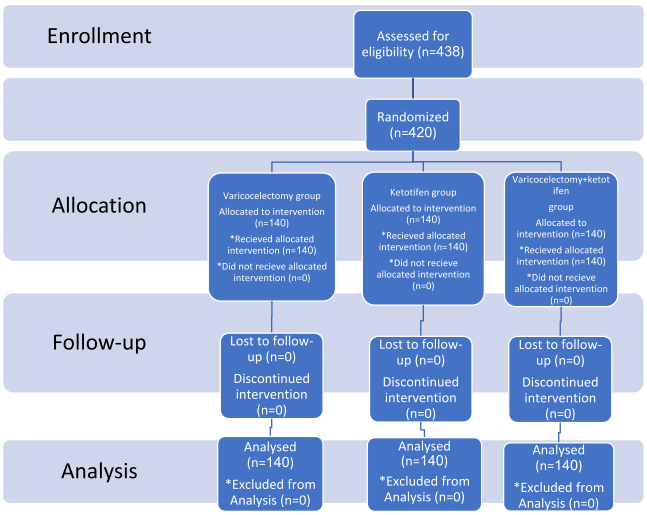

FIGURE 1 Enrollment and randomly assignment patients to each intervention group.

codes were written on separate sheets and each sheet was placed in a sealed envelope. Each eligible patient took an envelope in sequence and placed it into one of the three study groups according to the code written on the envelope.

2.3 | Intervention

The sperm sample was obtained in two steps by masturbation—at the beginning and end of the 3-month treatment period—4 days after the last sexual activity according to World Health Organization (2010) guidelines. Each sample was collected in a clean container. For later assessment of sperm DNA damage, aliquots of raw semen (containing 1 × 106 spermatozoa) were routinely frozen and stored at −80°C. Then we analyzed the samples for sperm DFI and the spermogram parameters. The sperm chromatin structure assay method was used to measure Sperm DNA damage as first described by Evenson et al.[14] The sperm chromatin dispersion test was performed with the Idehvarzan-Farda kit.

It should be noted that due to the mentioned treatments in this study (with/without surgery), it was not possible to blind patients and physicians and only the analyst was unaware of the grouping of patients.

2.4 | Statistical methods

Descriptive statistics, including mean and standard deviation, was used to describe the data. Due to the abnormal distribution of data (with the Kolmogorov–Smirnov test), the Kruskal–Wallis test was used to compare the quantitative variables of the three groups. Wilcoxon test was used to compare the quantitative variables before and after the intervention in each group. Statistical analyses were performed in Stata version 12 (Stata Corp), and $p < 0.05$ was considered statistically significant and all reported p values were two-sided.

3 | RESULTS

This study was performed on a total of 420 patients with varicocele with a mean age of 31.6 ± 6 years and an age range of 20–47 years. As described above, patients were randomly divided into three groups. The mean age of patients, sperm morphology, sperm motility, sperm count, and sperm DFI were not significantly different in the three groups before treatment (Table 1).

In the varicocelectomy group, the postoperative sperm DFI amount (19.20 ± 4.75) decreased compared to the preoperative amount (30.58 ± 5.65), which was statistically significant ($p < 0.01$). After the operation, the sperm counts (36.57 ± 12.90), sperm motility (31.16 ± 10.13), and sperm morphology (6.56 ± 1.11) were significantly improved compared to preoperative amounts (31.03 ± 8.89, 23.08 ± 4.40, and 5.12 ± 1.32, respectively; $p < 0.01$). Statistical analysis was performed using the Wilcoxon test (Table 2).

In the ketotifen + varicocelectomy group, the sperm DFI amount after treatment (18.79 ± 5.26) significantly decreased compared to before treatment (30.31 ± 7.02; $p < 0.01$). Also, after treatment, the sperm counts (41.07 ± 9.04), sperm motility (36.95 ± 8.01), and sperm

TABLE 1 Comparison of age and spermogram results before and after treatment in different groups.

Characteristic	Varicocelectomy + ketotifen, N = 120	Ketotifen, N = 120	Varicocelectomy, N = 120	p Value[a]
Age (years)	31.0 (26.5–36.0)	31.0 (26.0–37.5)	31.0 (28.0–35.0)	0.798
Sperm count (million/mL)				
Before treatment	9.01 ± 33.20	32.45 ± 10.63	31.03 ± 8.89	0.154
After treatment	41.07 ± 9.04	35.86 ± 11.79	36.57 ± 12.90	<0.01[b]
Sperm motility (%)				
Before treatment	23.63 ± 6.62	23.73 ± 5.22	23.08 ± 4.40	0.829
After treatment	36.95 ± 8.01	26.63 ± 5.40	31.16 ± 10.13	<0.01[b]
Sperm DFI (%)				
Before treatment	30.31 ± 7.02	31.08 ± 10.87	30.58 ± 5.65	0.928
After treatment	18.79 ± 5.26	23.32 ± 6.69	19.20 ± 4.75	<0.01[b]
Sperm morphology (%)				
Before treatment	5.19 ± 2.36	5.39 ± 2.29	5.12 ± 1.32	0.711
After treatment	6.96 ± 1.52	5.84 ± 1.08	6.56 ± 1.11	<0.01[b]

Abbreviation: DFI, DNA fragmentation index.

[a]Kruskal–Wallis test.

[b]Significant difference before and after treatment in study groups.

TABLE 2 Comparison of spermogram parameters before and after treatment in each of the three groups.

Groups	Sperm DFI	Sperm count	Sperm motility	Sperm morphology
Varicocelectomy group				
Before treatment	30.58 ± 5.65	31.03 ± 8.89	23.08 ± 4.40	5.12 ± 1.32
After treatment	19.20 ± 4.75	36.57 ± 12.90	31.16 ± 10.13	6.56 ± 1.11
p Value[a]	<0.01[b]	<0.01[b]	<0.01[b]	<0.01[b]
Varicocelectomy + ketotifen group				
Before treatment	30.31 ± 7.02	33.20 ± 9.01	23.63 ± 6.62	5.19 ± 2.36
After treatment	18.79 ± 5.26	41.07 ± 9.04	36.95 ± 8.01	6.96 ± 1.52
p Value[a]	<0.01[b]	<0.01[b]	<0.01[b]	<0.01[b]
Ketotifen group				
Before treatment	31.08 ± 10.87	32.45 ± 10.63	23.73 ± 5.22	5.39 ± 2.29
After treatment	23.32 ± 6.69	35.86 ± 11.79	26.63 ± 5.40	5.84 ± 1.08
p Value[a]	<0.01[b]	<0.05[b]	<0.01[b]	<0.05[b]

Abbreviation: DFI, DNA fragmentation index.

[a]Wilcoxon test.

[b]Significant difference before and after treatment in each study group.

morphology (6.96 ± 1.52) were significantly improved compared to pretreatment amounts (33.20 ± 9.01, 23.63 ± 6.62, and 5.19 ± 2.36, respectively; $p < 0.01$; Table 2).

In the ketotifen group, the sperm DFI amount after treatment (23.32 ± 6.69) significantly decreased compared to before treatment (31.08 ± 10.87; $p < 0.01$). After treatment, the sperm counts (35.86 ± 11.79), sperm motility (26.63 ± 5.40), and sperm morphology (5.84 ± 1.08) were significantly improved compared to pretreatment amounts (32.45 ± 10.63, 23.73 ± 5.22, and 5.39 ± 2.29, respectively; $p < 0.05$, $p < 0.01$, and $p < 0.05$, respectively; Table 2).

After treatment, the rate of DFI reduction was greater in the group undergoing varicocelectomy + ketotifen than in the other groups. In the follow-up of patients after treatment based on the post hoc test, the absolute level of DFI in the varicocelectomy +ketotifen and varicocelectomy group was significantly lower than in the ketotifen group ($p < 0.01$; Table 3).

The sperm count after treatment in the varicocelectomy + ketotifen group was higher than in the varicocelectomy group and this difference was significant ($p < 0.01$). Sperm count in the varicocelectomy + ketotifen group was significantly higher than in the ketotifen group ($p < 0.01$). But there was no significant difference between the varicocelectomy group and the ketotifen group in sperm count ($p > 0.05$; Table 3).

After treatment, sperm motility in the varicocelectomy + ketotifen group was higher than in the varicocelectomy group and the difference was significant ($p < 0.01$). Sperm motility in the varicocelectomy + ketotifen group was significantly higher than in the ketotifen group ($p < 0.01$). Also, sperm motility in the varicocelectomy group was significantly higher compared to the ketotifen group ($p < 0.01$; Table 3).

There was a significant difference in sperm morphology between the varicocelectomy + ketotifen group and the varicocelectomy group after treatment ($p < 0.01$). In the varicocelectomy + ketotifen group, sperm morphology was significantly higher than in the ketotifen group ($p < 0.01$). Also, sperm morphology in the varicocelectomy group was significantly higher compared to the ketotifen group ($p < 0.01$; Table 3).

4 | DISCUSSION

The combination of factors, including oxidative stress and scrotal hyperthermia, can damage the testes and cause seminal changes and infertility in varicocele patients.[15] Besides, varicocele has been associated with an increase in mast cells in the testis, which can result in the abnormal spermatogenic function of the testis and testicular fibrosis.[16] Identification of the underlying mechanisms may provide new opportunities for the treatment of male infertility with varicocele.

In the current study, we found that all three groups of patients showed significant improvement in DFI, sperm count, motility, and morphology after treatment compared to before. DFI reduction was greater in the varicocelectomy + ketotifen group than in the other groups. In the follow-up of patients after treatment, the level of DFI in the varicocelectomy group was significantly lower than in the other two groups, which could be due to the lower amount of DFI in this group before treatment. The sperm count after treatment in the varicocelectomy + ketotifen group was higher than in the varicocelectomy group, but this difference was not significant. In addition, the sperm count in the varicocelectomy + ketotifen group was significantly higher compared to the ketotifen group. Also, the sperm

TABLE 3 Comparison of postoperative parameters among the study groups based on Tukey post hoc test.

Groups	Mean difference	95% Confidence interval		*p* Value
		Upper bound	Lower bound	
DFI after treatment				
Ketotifen group versus varicocelectomy group	4.110	2.530	5.700	<0.01[a]
Varicocelectomy group versus varicocelectomy + ketotifen group	0.414	−1.170	2.000	0.812
Ketotifen group versus varicocelectomy + ketotifen group	4.520	2.950	6.110	<0.01[a]
Sperm count after treatment				
Ketotifen group versus varicocelectomy group	−0.714	−3.910	2.480	0.859
Varicocelectomy group versus varicocelectomy + ketotifen group	−4.500	−7.690	−1.310	<0.03[a]
Ketotifen group versus varicocelectomy + ketotifen group	−5.210	−8.410	−2.020	<0.01[a]
Sperm motility after treatment				
Ketotifen group versus varicocelectomy group	−4.520	−6.800	−2.260	<0.01[a]
Varicocelectomy group versus varicocelectomy + ketotifen group	−5.780	−8.060	−3.510	<0.01[a]
Ketotifen group versus varicocelectomy + ketotifen group	−10.310	−12.590	−8.040	<0.01[a]
Sperm morphology after treatment				
Ketotifen group versus varicocelectomy group	−0.721	−1.07	−0.37	<0.01[a]
Varicocelectomy group versus varicocelectomy + ketotifen group	−0.400	−0.75	−0.05	<0.01[a]
Ketotifen group versus varicocelectomy + ketotifen group	−1.121	−1.47	−0.77	<0.01[a]

Abbreviation: DFI, DNA fragmentation index.

[a]Significant difference between the results after treatment.

count in the varicocelectomy group was significantly higher compared to the ketotifen group. The other spermogram parameters were considerably more improved in the varicocelectomy + ketotifen group than in the other two groups. Besides, these parameters in the varicocelectomy group were significantly higher than in the ketotifen group. Mast cells are multifunctional heterogeneous cells that play an important role in inflammation, hypersensitivity, and fibrosis.[17] A higher number of mast cells in the interstitium and lamina propria has been associated with different causes of infertility, including varicocele.[18] In a 2017 study by Mostafa et al., a significant reduction in the number of seminal mast cells was found after varicocelectomy.[19] As mast cells and their products play a role in the pathogenesis of asthenozoospermia, it suggests a possible target for the medical treatment of infertile men. Therefore, drugs that could block mast cell mediator release may have a beneficial effect on sperm development.[20]

In a study conducted in 2021 by Fathi et al.,[21] 85 infertile men with a minimum history of 1-year infertility were followed up for 12 months. All of them had palpable varicocele, normal semen factors, and increased DFI to enter the study. Forty-five patients underwent varicocelectomy (study group), and for 40 patients, no intervention was given (control group). Six months after varicocelectomy, the mean DFI for both groups had been reduced; however, this reduction was statistically greater in the varicocelectomy group. Sixty-two percent of the varicocelectomy group achieved spontaneous pregnancy after 1 year compared with 30% of the control group.[13]

In a study by Zaazaa et al.,[13] 120 infertile patients with varicocele were studied. A random sampling of patients was done and three equal groups were formed. The first group underwent varicocelectomy, the second group of patients was on 1 mg oral ketotifen twice daily for 3 months, and the third group of patients underwent varicocelectomy and postoperative oral mast cell stabilizer for 3 months. After 3 months, mean sperm count, sperm concentration, sperm motility, and sperm DFI all improved significantly in all groups. Also, the sperm DFI in patients with grade III varicocele compared with grade II in all groups showed a significantly higher improvement.[21]

A 2011 study by Azadi et al.,[18] evaluated 103 infertile men who had varicocelectomy at the Isfahan Fertility and Infertility Center. Patients with varicocele were randomly divided into a control group (52) and a treatment group (51). The results of this study showed that mast cell inhibitors such as ketotifen improve semen parameters, chromatin integrity, and pregnancy rate when prescribed as adjunctive therapy after varicocelectomy.

In our study, mean sperm count, total sperm motility, sperm morphology, and sperm DFI improved significantly after treatment in all groups. Also, in our study, the amount of DFI reduction was higher in the group that underwent varicocelectomy + ketotifen than in the other groups.

Another point that was shown in our study was a significant improvement in spermogram parameters and DFI levels after treatment compared to before in the ketotifen group. A study by Multinger et al., published in 2006, showed that a course of oral ketotifen significantly improved sperm motility after 4 weeks of treatment and normal sperm morphology, 8 weeks after treatment, and that these changes persist for at least 4 weeks after the end of treatment.[22]

Improvement of semen parameters and sperm DFI after varicocele repair and administration of mast cell stabilizers can be explained by the fact that both varicocele and mast cells are associated with increased oxidative stress. Several studies have suggested that the accumulation of mast cells is associated with the production of oxygen-free radicals.[6,20,23]

Evidence obtained from previous studies clearly showed that improvement of sperm parameters and repair of varicocele was associated with a significant reduction of seminal oxidative stress. In other words, some studies stated that the increase in the varicocele grade led to increased oxidative stress and reactive oxygen species (ROS) and decreased sperm accumulation. On the contrary, the repair and reduction of the varicocele grade were associated with a significant reduction of oxidative stress.[24,25] In this study, the improvement of seminal parameters after varicocelectomy and treatment with Mast cells could be attributed to the reduction of oxidative stress. This finding requires further investigation.

According to the results of this study, varicocelectomy reduces the DFI and improves sperm concentration, progressive motility, and morphology. This study had the limitations of a relatively short follow-up period and lacked information on pregnancy rates for each group after varicocele repair. Another limitation of this study was the significant difference in DFI between the study groups before starting treatment. In the varicocelectomy group, the DFI before treatment was significantly lower.

One of the strengths of this study is that it is a clinical trial with a sufficient number of samples. Similar limited studies on the effect of mast cell stabilizers on varicocele have been performed. It is proposed that, in the future, studies can be carried out on different grades of varicocele and the effect of treatment can be studied separately for each grade.

In this study, oxidative stress, such as total antioxidant capacity, 8-hydroxyguanosine, and ROS, was not addressed due to the limited resource, and it is suggested that future studies investigate these factors.

5 | CONCLUSION

Our study also showed that the DFI reduction would increase if ketotifen was administered. In addition, ketotifen can improve spermogram parameters in patients with varicocele. As a result, the administration of ketotifen in addition to varicocelectomy can prove beneficial for patients.

AUTHOR CONTRIBUTIONS

Alireza Akhavan Rezayat: Methodology; supervision; validation; writing—review and editing. **Amirmohammad Soleimanian**: Data curation; formal analysis; writing—original draft. **Neda Kamandi**: Data curation; formal analysis; writing—original draft. **Mohammad Aslzare**: Investigation; methodology; project administration; software; supervision; writing—review and editing. **Mohammad Mustafa Shaikh Zada**: Conceptualization; formal analysis; investigation; project administration; writing—original draft.

ACKNOWLEDGMENTS

This study was supported by the Mashhad University of Medical Sciences.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

TRANSPARENCY STATEMENT

The lead author Mohammad Mustafa Shaikh Zada affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Mohammad Mustafa Shaikh Zada https://orcid.org/0000-0002-3745-7560

REFERENCES

1. Ramalingam M, Kini S, Mahmood T. Male fertility and infertility. *Obstet Gynaecol Reprod Med*. 2014;24(11):326-332.
2. Vander Borght M, Wyns C. Fertility and infertility: definition and epidemiology. *Clin Biochem*. 2018;62:2-10.
3. Baigorri BF, Dixon RG, eds. *Varicocele: A Review. Seminars in Interventional Radiology*. Thieme Medical Publishers; 2016.
4. De Kretser DM, Baker HW. Infertility in men: recent advances and continuing controversies. *J Clin Endocrinol Metab*. 1999;84(10):3443-3450.
5. Zhang Y, Zhang W, Wu X, et al. Effect of varicocele on sperm DNA damage: a systematic review and meta-analysis. *Andrologia*. 2022;54(1):e14275.
6. Taha EA, Ezz-Aldin AM, Sayed SK, Ghandour NM, Mostafa T. Smoking influence on sperm vitality, DNA fragmentation, reactive oxygen species and zinc in oligoasthenoteratozoospermic men with varicocele. *Andrologia*. 2014;46(6):687-691.
7. Check JH, Graziano V, Cohen R, Krotec J, Check ML. Effect of an abnormal sperm chromatin structural assay (SCSA) on pregnancy outcome following (IVF) with ICSI in previous IVF failures. *Arch Androl*. 2005;51(2):121-124.
8. Birowo P, Rahendra Wijaya J, Atmoko W, Rasyid N. The effects of varicocelectomy on the DNA fragmentation index and other sperm parameters: a meta-analysis. *Basic Clin Androl*. 2020;30(1):15.

9. Virkud YV, Wang J, Shreffler WG. Enhancing the safety and efficacy of food allergy immunotherapy: a review of adjunctive therapies. *Clin Rev Allergy Immunol*. 2018;55(2):172-189.
10. Hemadi M, Nikbakht R, Saharkhiz N. Ketotifen, a mast cell blocker improves sperm motility in asthenospermic infertile men. *J Hum Reprod Sci*. 2013;6(1):19.
11. Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for reporting outcomes in trial reports: the CONSORT-Outcomes 2022 extension. *JAMA*. 2022;328(22):2252-2264.
12. Assel M, Sjoberg D, Elders A, et al. Guidelines for reporting of statistics for clinical research in urology. *BJU Int*. 2019;123(3):401-410.
13. Zaazaa A, Adel A, Fahmy I, Elkhiat Y, Awaad AA, Mostafa T. Effect of varicocelectomy and/or mast cells stabilizer on sperm DNA fragmentation in infertile patients with varicocele. *Andrology*. 2018;6(1):146-150.
14. Evenson DP, Larson KL, Jost LK. Sperm chromatin structure assay: its clinical use for detecting sperm DNA fragmentation in male infertility and comparisons with other techniques. *J Androl*. 2002;23(1):25-43.
15. Lara-Cerrillo S, Gual-Frau J, Benet J, et al. Microsurgical varicocelectomy effect on sperm telomere length, DNA fragmentation and seminal parameters. *Hum Fertil*. 2022;25(1):135-141.
16. Nasr-Esfahani MH, Abasi H, Razavi S, Ashrafi S, Tavalaee M. Varicocelectomy: semen parameters and protamine deficiency. *Int J Androl*. 2009;32(2):115-122.
17. Meineke V, Frungieri MB, Jessberger B, Vogt H-J, Mayerhofer A. Human testicular mast cells contain tryptase: increased mast cell number and altered distribution in the testes of infertile men. *Fertil Steril*. 2000;74(2):239-244.
18. Azadi L, Abbasi H, Deemeh MR, et al. Zaditen (Ketotifen), as mast cell blocker, improves sperm quality, chromatin integrity and pregnancy rate after varicocelectomy: mast cell blocker and varicocele. *Int J Androl*. 2011;34(5pt1):446-452.
19. Mostafa RM, Abol-Magd R, Younis SE, Dessouki OF, Azab M, Mostafa T. Assessment of seminal mast cells in infertile men with varicocele after surgical repair. *Andrologia*. 2017;49(3):e12625.
20. El-Karaksy A, Mostafa T, Shaeer OK, Bahgat DR, Samir N. Seminal mast cells in infertile asthenozoospermic males. *Andrologia*. 2007;39(6):244-247.
21. Fathi A, Mohamed O, Mahmoud O, et al. The impact of varicocelectomy on sperm DNA fragmentation and pregnancy rate in subfertile men with normal semen parameters: a pilot study. *Arab J Urol*. 2021;19(2):186-190.
22. Oliva A, Multigner L. Ketotifen improves sperm motility and sperm morphology in male patients with leukocytospermia and unexplained infertility. *Fertil Steril*. 2006;85(1):240-243.
23. Chelombitko MA, Fedorov AV, Ilyinskaya OP, Zinovkin RA, Chernyak BV. Role of reactive oxygen species in mast cell degranulation. *Biochemistry*. 2016;81(12):1564-1577.
24. Cocuzza M, Athayde KS, Alvarenga C, Srougi M, Hallak J. Grade 3 varicocele in fertile men: a different entity. *J Urol*. 2012;187(4):1363-1368.
25. Mostafa T, Anis TH, El-Nashar A, Imam H, Othman IA Varicocelectomy reduces reactive oxygen species levels and increases antioxidant activity of seminal plasma from infertile men with varicocele. *Int J Androl* 2001;24(5):261-265.

How to cite this article: Akhavan Rezayat A, Soleimanian A, Kamandi N, Aslzare M, Shaikh Zada MM. Semen's parameters after varicocelectomy surgery with mast cell stabilizers treatment in infertile varicocele patients: randomized clinical trial study. *Health Sci Rep*. 2023;6:e1431. doi:10.1002/hsr2.1431