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Clinical Study

Tolerability and Efficacy of Spermon™ in Male Factor Infertility

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Summary

The tolerability and efficacy of Spermon™ soft gelatin capsule, a purely herbal spermatogenic formulation (phytomedicine) was investigated in 31 adult males with idiopathic oligo-asthenospermia to measure changes in seminal parameters. The study was an open, mono-centric clinical trial with good clinical practices (GCP) guidelines for 3 months of drug treatment.

A statistically significant increase in sperm density and sperm motility was observed in 84% of cases. Positive morphological changes were observed in some cases. In all the 31 completed cases, sperm density (count) increased by an average of 67.6% and sluggish linear progressive sperm motility (sperm motility - B) increased by an average of 33.4%, both these values are statistically significant.

Out of total 31 cases treated by Spermon™, 4 pregnancies occurred during the study period of 3 months. A thorough clinical examination, biochemical and hematological studies of each patient were carried out at the start and the end of the study. There were no reported clinical, biochemical or hematological adverse effects.

Therefore, the study proved that Spermon™ has therapeutic tolerability and efficacy in the medical management of idiopathic oligo-asthenospermia.

Spermon™ soft gelatin capsule is a safe, well tolerated and effective phytomedicine for medical management of male infertility mainly idiopathic oligo-asthenospermia.

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Introduction

Scientifically, infertility is defined as the failure to conceive after 18 months of cohabitation and unprotected sexual intercourse with the same partner[1].

The severity of male infertility can be measured by internationally accepted values of sperm count, motility and morphology.

According to the World Health Organization (WHO) guidelines[2]:

- Normal semen has a sperm count of 60-120 × 10^6 per ejaculate with 60-80%

progressive motility. A sperm density <20 × 10^6 /ml makes fertility less likely

- Oligospermia is defined as patient with sperm count, which is less than normal values, i.e. sperm count <20×10^6/ml
- Asthenospermia means patient with a progressive motility, which is less than normal values, i.e., sperm motility<50%
- Teratospermia is defined as patient with a sperm proportion of <30% with normal morphology in the ejaculate and is regarded as abnormal semen.

There is an evidence that human semen quality has decreased during the last few decades[3]. But the exact cause for decreased semen quality can be determined only in about 40% of cases. In most of the cases, infertility is regarded as idiopathic means without known specific causes[4,5]. Till date, no conclusively satisfactory treatment exists for idiopathic male infertility despite of a range of drugs having been tried all over world in last few decades.

Against this background, the utility of Spermon™ in idiopathic male infertility was studied in the current trial. Spermon™ is a purely herbal formulation (phytomedicine), which has been widely used for the empirical treatment of male infertility for more than 4 years. Due to time-tested natural ingredients present in Spermon™, such as Tribulus terrestris (Gokshura), Mucuna prurience (Kauncha), Withania somnifera (Indian Ginseng/ Ashwagandha) and Asphaltum (Shilajit), Spermon™ improves quality of semen in terms of sperm density (count), motility and morphology. The current study was conducted to establish tolerability and efficacy of Spermon™ in patients suffering from idiopathic oligo-asthenospermia.

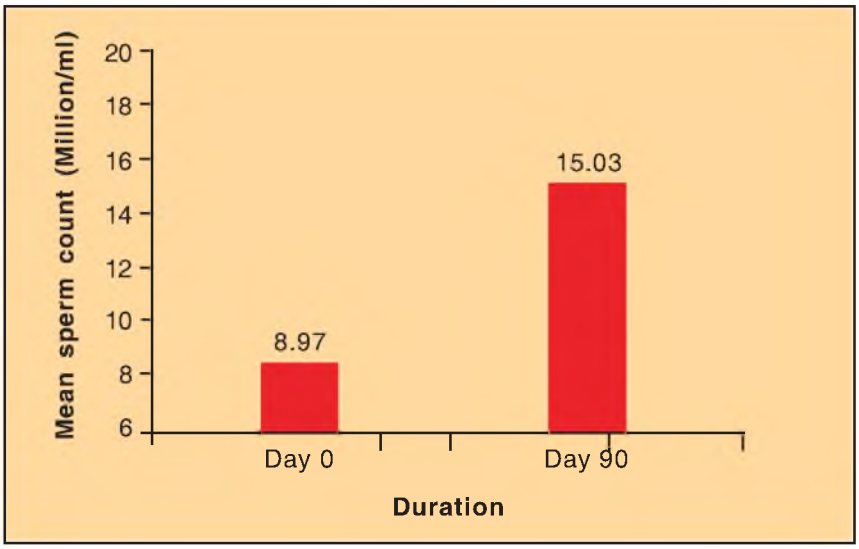

Figure 1. Comparison of sperm density at day 0 and day 90 (n = 31).

Materials and methods

A total of 35 patients with idiopathic male infertility were recruited on the basis of routine clinical examination and semen analysis. The inclusion and exclusion criterion were as follows:

Inclusion criteria

1. Patient not having child after having unprotected sex for 18 months of cohabitation.
2. Primary male infertility due to quantitative and qualitative defects in spermatogenesis (idiopathic oligo-asthenospermia).
3. Received no hormonal therapy for the same or other indication within 3 months of starting the study.
4. Infertility patients with sperm count <20 million/ml and sperm motility: Type I + II = 50% or less.
5. Infertility patients with seminal fructose present in sperm analysis.
6. Sex and age: Adult male, reproductive age group (with minimum age of 18 years).

Exclusion criteria

Patients suffering from any of the following conditions or disease:

1. History of chronic alcoholism
2. Diabetes mellitus
3. Hypertension
4. Peptic ulcer
5. Renal failure
6. Patients on steroids and hormonal therapy
7. Excessively obese patients (Grade II and III obesity)

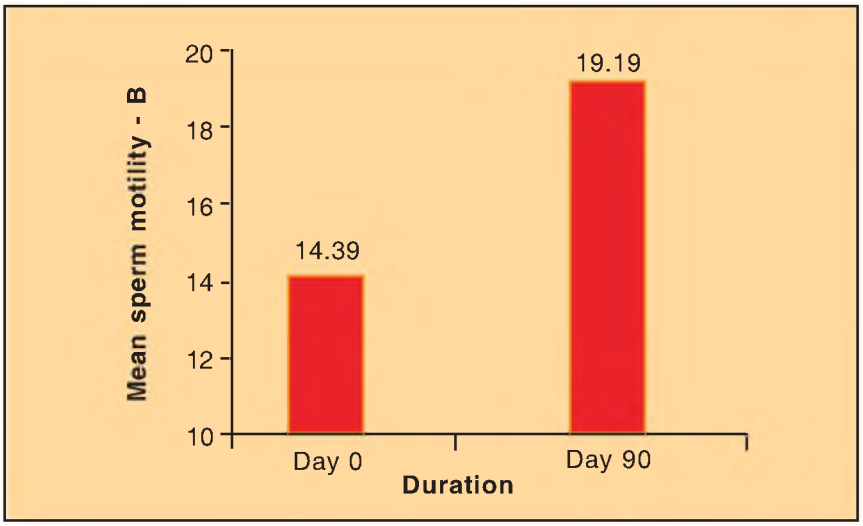

Figure 2. Comparison of sperm motility at day 0 and day 90 (n = 31).

8. Liver disorders
9. Undescended testis:Unilateral and bilateral
10. Varicocele
11. Other endocrine disorders-Hypothyroidism, Cushing's syndrome, etc.
12. Severe erectile dysfunction
13. Patients on psychotropic drugs
14. Immunological disorders-AIDS, HIV
15. Sexually transmitted diseases
16. Secondary male infertility due to surgical conditions or anatomical or physiological conditions.

As per inclusion and exclusion criteria, 35 patients were selected for the study. The following biochemical and hematological parameters were evaluated at the start (day 0) of study, after 45 days and at the end of the trial (day 90) at a single, nationally accredited laboratory maintaining international quality standards:

1. Semen analysis (after minimum 5 days abstinence)
2. Kruger's test (for abnormal morphology)
3. Complete blood count (CBC) and erythrocyte sedimentation rate (ESR)
4. Liver function test (LFT)
5. Renal profile
6. Hormonal analysis (S. testosterone, S. follicular stimulating hormone [FSH] and S. leutinizing hormone [LH]).

Each patient selected for the study was thoroughly explained the treatment schedule, follow up and probable effects of the study drug and written informed consent was obtained before initiation of the study. A detailed history of

Table 1

Parametric test (Student's paired 't' test) - Data are expressed as mean ± SD of 31 patients

Sr.	Variables	Basal (day 0)	2nd F.U.(day 90)	Comparison between day 0 and day 90 't' value, sign. and p value
1.	Sperm count (Million/ml)	8.97 ± 11.79	15.03 ± 14.26	t = 4.3, S, p < 0.001
2.	Sperm motility - A	2.42 ± 5.61	2.42 ± 4.98	t = 0.0, NS, p = 1.00
3.	Sperm motility - B	14.39 ± 12.04	19.19 ± 10.73	t = 3.6, S, p = 0.0015
4.	Kruger test-sperm morphology	73.42 ± 15.74	71.84 ± 13.88	t = 1.2, NS, p = 0.25
5.	S. testosterone	575.9 ± 228.0	548.7 ± 172.8	t = 0.7, NS, p = 0.25
6.	FSH	7.48 ± 3.74	3.62 ± 3.74	t = 0.4, NS, p = 0.7
7.	LH	6.54 ± 2.39	6.78 ± 2.54	t = 0.5, NS, p = 0.6

Table 2

Non-parametric test (Wilcoxon signed rank test) - Data are given as median (range) of 31 patients

Sr.	Variables	Basal (day 0)	2nd F.U. (day 90)	Comparison between day 0 and day 90 Z value, sign. and p value
1.	Sperm count (Million/ml)	8.(0, 62)	11 (0, 68)	Z = 3.7, S, p < 0.001
2.	Sperm motility - A	0.(0, 20)	0 (0,20)	Z = 0.3, NS, p = 0.8
3.	Sperm motility - B	10.0 (0, 30)	20.0 (0, 30)	Z = 3.2, S, p = 0.0015
4.	Kruger test- sperm morphology	76.0 (0, 20)	73.0 (0, 20)	Z = 3.2, S, p = 0.0013
5.	S. testosterone	524.0 (221, 1204)	498.0 (221, 1204)	Z = 0.7, NS, p = 0.5
6.	FSH	6.50 (1.93, 16.58)	6.14 (1.86, 16.20)	Z = 0.8, NS, p = 0.4
7.	LH	6.56 (2.09, 11.38)	6.79 (1.95, 14.55)	Z = 1.1, NS, p = 0.3

each patient was taken and they underwent a thorough clinical examination at basal visit (at starting of the study - day 0), after 1st follow up (day 45) and at final visit (at the end of the study - day 90 - after 3 months).

Each patient was administered 2 soft gelatin capsules of Spermon™, twice daily for 3 months. After completion of the study, the effects of Spermon™ on sperm count, motility, morphology and hormones were noted, as well as specific hematological and biochemical tests were carried out to observe any untoward side effects. Based on these findings at the end of treatment, the investigator has noted Clinical Global Impression (CGI) scores as follows:

- CGI score: 0 = Poor/no improvement in sperm density (count)
- CGI score: 1 = Moderate improvement in sperm density up to10 million/ml
- CGI score: 2 = Good improvement in sperm density up to15 million/ml
- CGI score: 3 = Excellent results - Excellent improvement in sperm density touching normal values (up to 20 million/ml and above) and/or occurrence of pregnancy in spouse of the patient.

Results

Out of the 35 originally selected patients, 4 cases were lost to follow up during the study period. Hence, a total completed cases for the study were 31.

There were no reported clinical, biochemical or hematological adverse effects during the study.

Results of statistical analysis

- The mean age of patients was 32.9 (the lowest being 18 years and highest being 46 years)..
- All the 5 clinical variables (pulse, respiratory rate, systolic and diastolic blood pressures, and weight) showed no significant differences between basal and final visits.
- All the 16 biochemical and hematological variables (CBC, ESR, liver function tests, renal profile, fasting blood sugar) showed no significant differences between basal and final visits.
- There was not a single adverse drug reaction (ADR) observed during the entire study.

Effect of Spermon™ on sperm density (Table 1, Fig. 1)

There was significant increase in the sperm density, specifically 67.6% over the basal, at the end of 90 days. That means in all 31 completed cases, sperm density (count) increased by an average of 67.6%, which is statistically

Table 3

CGI scores of patients

Response	CGI score	Number of patients	% of patients
No/very poor response	0	5	16
Average respons	1	10	32
Good response	2	7	23
Excellent response	3	9*	29

*Spouses of 4 out of these 9 patients reported pregnancy during 3 months of study period.

significant as mentioned in Table 1.

Effect of Spermon™ on sperm motility (Table 1, Fig. 2)

There was significant increase in the sluggish linear progressive motility (sperm motility - B/ MacLeod Grade - II), specifically 33.4 % over the basal at the end of 90 days. That means in all 31 completed cases, sluggish linear progressive sperm motility (Sperm Motility - B) increased by average 33.4%, which is statistically significant as mentioned in Table 1.

But there was no statistically significant difference observed between basal and final values of rapid linear progressive motility (sperm motility - A/MacLeod Grade - III and IV) and total forward progressive motility (sperm motility A + B/MacLeod Grade II, III and IV).That means in all 31 completed cases, rapid linear progressive sperm motility (sperm motility - A) and total forward progressive motility (sperm motility A + B) did not increased by statistically significant values as mentioned in Table 1.

Effect of Spermon™ on sperm morphology (Tables 1 and 2)

Kruger's test is an international parameter to assess the morphology of sperm[6]. We conducted all biochemical testes including Kruger's test for each patient with a single nationally accredited pathological laboratory with international quality control standards from Mumbai.

As per international standards, Kruger's test shows total number of abnormal spermatozoa. Hence, if this percentage is reduced, it is logical to conclude that the percentage of normal morphological sperms is increased.

During our study we observed that there was significant decrease in the percentage values of Kruger's test by Wilcoxon signed rank test (2.2% over the basal) at the end of 90 days, which is one of the non-parametric statistical test.

Effect of Spermon™ on hormones (Tables 1 and 2)

There was no significant

Table 4

Subgroup analysis of efficacy variables date are expressed as mean ± SD of 26 patients

Sr.	Variables	Basal (day 0)	2nd F.U. (day 90)	Comparison between (day 90) 't' value, sign. and p value
1.	Sperm count (Million/ml)	10.09 ± 12.3	17.43 ± 14.28	t = 4.7, S, p < 0.001
2.	Motility - A	2.50 ± 5.87	2.50 ± 5.15	t= 0.0, NS, p = 1.00
3.	Motility - B	16.31 ± 11.74	21.73 ± 9.27	t = 3.5, S, p = 0.002

difference observed between basal and final values of serum testosterone, FSH and LH.

All the above results were observed by conducting internationally accepted statistical tests-Student's 't' test (parametric test) and Wilcoxon Signed Rank test (non parametric test) as shown in Tables 1 and 2.

Effect of Spermon™ by CGI score

CGI score is the chief investigator's self-assessment towards tolerability and efficacy of the study drug as per individual results observed during the study and is shown in Table 3.

Results of sub-group (i.e., those patients who showed positive response) analysis

- A statistically significant increase in sperm density and sperm motility was observed in 84% of cases i.e., 26 patients out of 31 cases have shown positive response.
- The study drug was most effective for the age group 31-40 years than for other age groups.
- In this sub group of 26 patients, the study drug has shown statistically significant ncrease sperm density and sperm motility - B (MacLeod Grade-II) as shown in Table 4.

Discussion

The main objective of the present study was to evaluate tolerability and efficacy of Spermon™ in the management of idiopathic oligo-asthenospermia.

Spermon™ is a phytomedicine containing time-tested, clinically proven, spermatogenic, aphrodisiac and antioxidant herbs, commonly used by doctors practicing Ayurveda, an ancient Indian system of medicine in the management of male infertility. Different Ayurvedic and modern researchers in the past have studied each ingredient of Spermon™ individually for its specific mode of action and properties.

Tribulus terrestris (Gokshura) is one of the key ingredients of Spermon™, which improves spermatozoa motility and increases the efficiency of acrosome reaction in subjects diagnosed with oligoastheno-teratozoospermia[7]. Animal studies prove that the active ingredient of Tribulus terrestris stimulates spermatogenesis and Sertoli cell activity. The fertility potentiating and aphrodisiac activities of Tribulus terrestris have been well studied in various animal and human studies[8]. Spermon™ also contains seeds of Mucuna pruriens (Krauncha Beej), which is scientifically proven potent source of natural L-dopa, the natural hormone to enhance sexual functions in males[9-11].

Withania somnifera (Ashwagandha)[12], Asparagus racemosus (Shatavari)[13] and Asphaltum (Shuddha Shilajit)[14] present in Spermon™ are well known natural antioxidants that help restore the pro-oxidant: Antioxidant balance, thus maintaining genetic integrity of spermatozoa by preventing oxidative damage to the DNA of spermatozoa[15], this in turn results in enhanced fertility potential.

Therefore, as per this individual ingredient-wise research data, Spermon™ may have following activities:

- Spermon™ improves quality of semen in terms of sperm density, motility and morphology
- Spermon™ stimulates spermatogenesis
- Spermon™ is a natural antioxidant countering oxidative stress in reproductive system.

The present study appears to confirm that Spermon™ stimulates spermatogenesis thereby increases sperm density and motility. The sperm motility has probably improved as a consequence of the reduced oxidative stress in the male reproductive system. Spermon™ improved sperm morphology, though only marginally; but it can denote a significant combined effect of Spermon™ on spermatogenesis and its antioxidant action on reproductive organs.

Conclusion

The present open clinical study of Spermon™ in idiopathic oligo-asthenospermia at the end of 3 months of drug trial showed:

- Spermon™ increased sperm density by 67.6% over the basal values
- Spermon™ improved sperm motility (sluggish linear progressive motility) by 33.4% over the basal values

- Spermon™ appeared to have improved sperm morphology by 2.2% over the basal values.
- Four pregnancies occurred during the study period of 3 months
- No untoward clinical, biochemical or hematological effects were observed in the study.

Thus, we conclude that Spermon™ soft gelatin capsule is a safe, well tolerated and effective phytomedicine for medical management of male infertility mainly idiopathic oligo-asthenospermia.

We wish to continue the present study in larger population as well as for a longer duration and at multiple centers to reconfirm the therapeutic role of Spermon™ in idiopathic oligo-asthenoteratozoospermia.

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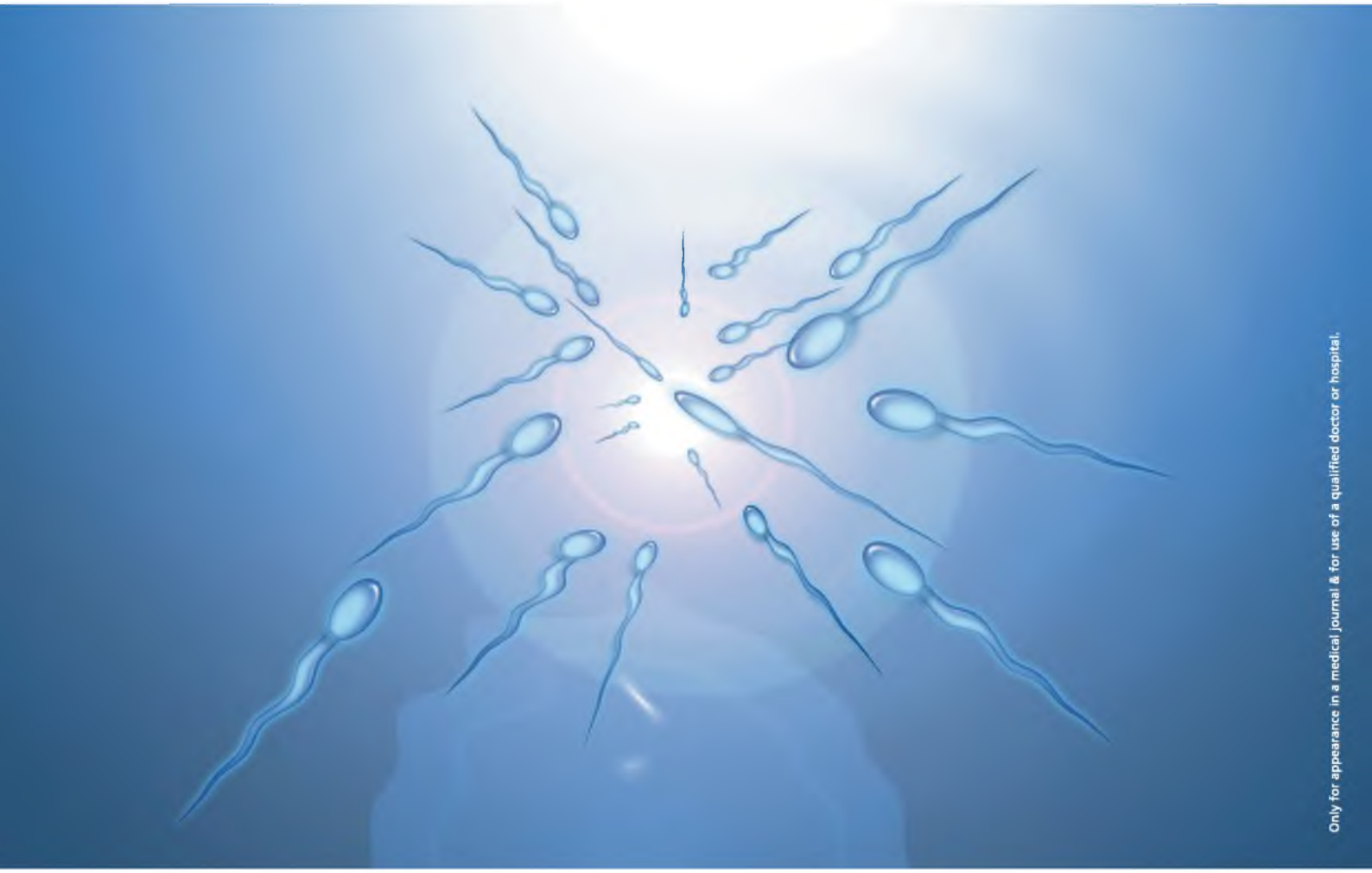

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