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ORIGINAL ARTICLE

An Open-Label, Multi-Center, Prospective, Interventional, Clinical Study to Evaluate the Efficacy and Safety of Ayuvigo Forte Capsules in Patients Suffering from Oligospermia

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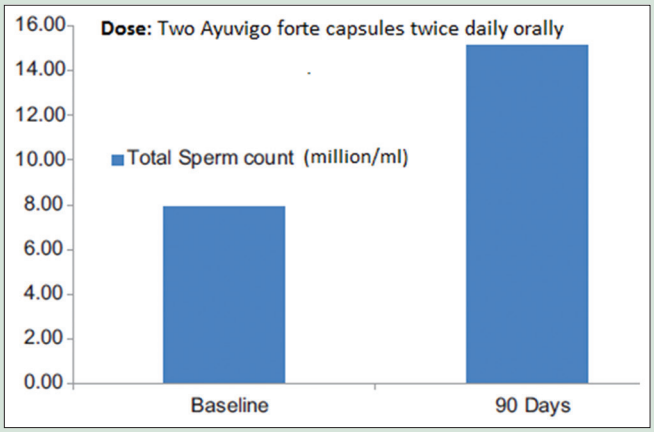
ABSTRACT

Background: Oligospermia refers to semen with a low concentration of sperms. Oligospermia is one of the common causative factors of male infertility. **Objectives:** The objective of this study was to assess the efficacy and safety of Ayuvigo forte capsule in patients suffering from oligospermia. **Materials and Methods:** This was an open-label, prospective, interventional, multi-center clinical study. A total of 30 patients were completed the study. All patients were advised to consume two Ayuvigo forte capsules twice daily orally after meals with a cup of milk for 90 days. Data describing quantitative measures are expressed as a mean ± standard deviation. **Results:** The mean total sperm count, mean progressive sperm motility, and total number of spermatozoa increased significantly ($P < 0.05$) by 90.54%, 33.65%, and 98.88% at the end of the study, respectively. Most patients had shown significant ($P < 0.05$) improvement in subjective parameters of low sperm count assessed as per *Ayurveda*. Furthermore, significant ($P < 0.05$) improvement was observed in mean serum free testosterone level. No statistically significant ($P > 0.05$) changes were observed in mean serum luteinizing hormone, follicle-stimulating hormone, prolactin, safety laboratory parameters, and vitals. Excellent overall efficacy and tolerability were observed in majority of patients. **Conclusion:** Ayuvigo forte capsule is safe and effective for the management of oligospermia.

Key words: Ayuvigo forte capsule, oligospermia, sperm count, sperm motility, testosterone level

SUMMARY

- Oligospermia is common condition of male infertility. The present study was conducted to assess the efficacy and safety of Ayuvigo forte capsule in patients suffering from oligospermia. All 30 patients were advised to consume two Ayuvigo forte capsules twice daily orally after meals for 90 days. Significant improvement was observed in subjective and objective parameters of oligospermia at the end of the study. Significant improvement was observed in mean total sperm count, mean progressive sperm motility, total number of spermatozoa, and mean serum free testosterone at the end of the study. No significant changes were observed in hormonal profile, safety laboratory parameters, and vitals. The study concluded that Ayuvigo forte capsule is safe and effective to use in patients suffering from oligospermia.



Abbreviations Used: ADRs: Adverse drug reactions, AEs: Adverse events, CBC: Complete blood count, CNS: Central nervous system, ECG: Electrocardiogram, ESR: Erythrocyte sedimentation rate, FSH: Follicle-stimulating hormone, Hb%: Hemoglobin %, HDPE: High-density polyethylene, HIV: Human immunodeficiency virus, LFTs: Liver function tests, LH: Luteinizing hormone, NO: Nitric oxide, PA view: Posteroanterior view, RFTs: Renal function tests, USG: Ultrasonography; WHO: World Health Organization.

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DOI: 10.4103/pr.pr_158_18

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INTRODUCTION

Oligospermia refers to semen with a low concentration of sperm. It is a common causative factor for male infertility.[1] According to the World Health Organization (WHO), sperm count <15 million/mL semen is considered as oligospermia.[1] There are three types of oligospermia, namely mild, moderate, and severe. Sperm count between 10–15 million/mL, 5–10 million/mL, and 0–5 million/mL is considered as mild oligospermia, moderate oligospermia, and severe oligospermia, respectively.[2]

The diagnosis of oligozoospermia is done by semen analysis. There are many factors which are responsible for oligospermia.[3,4] Causes of oligospermia are divided into the following three categories: pretesticular causes, including hypogonadism, use of excess alcohol, smoking, and medications; testicular causes, including Klinefelter syndrome, neoplasm (seminoma), varicocele, trauma, hydrocele, and mumps; and post testicular causes, including vas deference and ejaculatory duct obstruction may cause oligospermia in many cases.[5-8]

Cite this article as: Tamoli SM, Mundhe NB, Deshmukh DA, Pande SP, Kamde RR, Kumbhar VS, *et al*. An open-label, multi-center, prospective, interventional, clinical study to evaluate the efficacy and safety of Ayuvigo forte capsules in patients suffering from oligospermia. Phcog Res 2019;11:290-4.

Treatment of oligospermia varies according to the underlying causes and degree of impairment.[9,10] Pretesticular conditions can often be treated by medications like hormonal pills.[10,11] Obstructive causes of posttesticular infertility can be overcome with either surgery or *in vitro* fertilization (IVF).[12] Ejaculatory factors may be treatable by medication or by intrauterine insemination (IUI) therapy or IVF, with which very few pregnancies can be achieved.[12,13] Although these treatment options are useful, most of these options possess side effects and these treatment options are very expensive.[14,15] Thus, physicians and patient tend to move toward alternative treatment approaches such as *Ayurveda*.[14,15]

Keeping in mind the basic concepts of Ayurveda, Welex Laboratories Pvt. Ltd., has developed Ayuvigo forte capsule for the effective management of oligospermia and male infertility. Ayuvigo forte capsule is unique combination of 14 ingredients. Most of the ingredients possess aphrodisiac, rejuvenator, spermatogenic, and libido enhancer activities.[12-15] Few ingredients of Ayuvigo forte capsule help to improve stamina, a sense of well-being, semen, and sperm count.[15]

Looking at the various activities of the ingredients present in Ayuvigo forte capsule, a hypothesis was postulated that Ayuvigo forte capsule may be helpful in the management of oligospermia. Hence, to test this hypothesis, a clinical study titled "An open-label, multi-center, prospective, interventional, clinical study to evaluate the efficacy and safety of Ayuvigo forte capsules in patients suffering from oligospermia" was conducted.

MATERIALS AND METHODS

Study design

This was an open-label, prospective, multi-center, interventional clinical study. The study protocol and related documents were reviewed and approved by the Institutional Ethics Committee (IEC), Ayurved Sanshodhan Vibhag, Ayurved Seva Sangh Hospital, Ganeshwadi, Panchvati, Nashik-3; Independent Ethics Committee, Dhanashree Hospital, Navi Sangvi, Pune-61 and IEC, KVTR Ayurvedic College, Boradi, Taluka Shirpur, District-Dhule-425 428, India. The CTRI registration number is CTRI/2017/06/008799 dated 09/06/2017. The study was conducted in accordance with Good Clinical Practices Guidelines, issued by the Department of AYUSH in March 2013.

Primary and secondary outcomes

The primary outcome of the study was to evaluate the efficacy of Ayuvigo forte capsule in patients suffering from oligospermia by assessing changes in total sperm count. The secondary outcomes of study were to evaluate the efficacy of Ayuvigo forte capsule in patients suffering from oligospermia by assessing changes in sperm motility with progressive sperm motility; total number of spermatozoa per ejaculate; semen volume; sperm morphology; viability of spermatozoa; serum levels of total and free testosterone; serum luteinizing hormone (LH); serum follicle-stimulating hormone (FSH); subjective parameters of low sperm count (if any) were assessed as per *Ayurveda*; and evaluation of spontaneous achieved pregnancies and global assessment for overall change by the patient and investigator at the end of the study treatment. Furthermore, the secondary outcomes were to assess the safety and tolerability of study drug by assessing adverse events (AEs) and adverse drug reactions and laboratory parameters such as liver function tests, renal function tests (RFTs), lipid profile, complete blood count (CBC), erythrocyte sedimentation rate (ESR), hemoglobin % (Hb%), and urine examinations at the end of the study.

Sample size

Anticipating 25% dropouts, we enrolled 38 patients to get 30 evaluable cases at the end of the study. The sample size calculation was based on the assumption that a sample size of 30 evaluable cases would provide an 80% power to estimate the improvement in sperm count at 5% level of significance at the end of the study.

Subject selection

Married male patients between 21 and 45 years of age having a history of oligospermia without any organic cause or having a history of infertility were included in the study. Patients with sperm concentration <15 million/ml (the WHO laboratory manual for the examination and processing of human semen, fifth edition, 2010) with normal sperm morphology, with or without sperm total motility <40% or sperm forward progressive motility <32% were included in the study. Patients with active stable sexual relationship with spouse, willing to give informed consent, ready to comply with the protocol, and ready to provide regular follow-ups till the completion of the study were included in the study. Patients suffering from major illnesses, hypotension or uncontrolled hypertension, uncontrolled diabetes, hepatic impairment, major psychiatric disorders, central nervous system disorders, endocrine disorders, renal impairment or hematological disorders and patients with anatomical, surgical, and/or pharmacological causes were excluded from the study. Patients with continuing history of alcohol and/or drug abuse were excluded from the study. Patients who were using dependency or failure to keep abstinence for antioxidant agents, vitamins, anti-inflammatory drugs, hormones, *Ayurvedic*, herbal, homeopathic, naturopathy medications for oligospermia and having known hypersensitivity to any ingredient of the study drug were excluded from the study.

Study drug

Ayuvigo forte capsule is manufactured and supplied by Welex Laboratories Pvt. Ltd., Ayuvigo forte capsule contains 14 ingredients as mentioned in Table 1.

Study procedure

Male patients having a history of oligospermia and/or infertility attending the outpatient clinics of study centers were screened for eligibility criteria. Patients were asked for history of the last sexual intercourse. If, it was before 3 days, then patients were advised to undergo semen analysis. If patient had sexual intercourse within the last 3 days, he was advised to keep sexual abstinence for the next 3 days and then his semen analysis was done. Patient's semen analysis was repeated after 7 days (at baseline visit) to reconfirm the diagnosis. If the sperm concentration was <15 million/ml of semen, then that patient were screened for other inclusion and exclusion criteria.

Next day morning, patient's blood sample was collected on empty stomach at the respective study centers for laboratory tests, i.e.,

Table 1: Composition of investigational drug, i.e., ayuvigo forte capsule (each capsule contains)

Ingredient	Scientific name	Quantity (mg)
Kapikacchu	*Mucuna pruriens*	40
Ashwagandha	*Withania somnifera*	30
Gokshur	*Tribulus terrestris*	30
Shatavari	*Asparagus racemosus*	30
Bala	*Sida cordifolia*	30
Kokilaksha	*Asteracantha longifolia*	30
ShwetMusli	*Asparagus racemosus*	30
Vidari	*Pueraria tuberosa*	30
Shankhpushpi	*Convolvulus pluricaulis*	30
Amalaki	*Emblica officinalis*	30
Akarkara	*Anacyclus pyrethrum*	30
Shilajeet	*Shilajeet*	30
Pippali	*Piper longum*	25
Jatiphala	*Myristica fragrans*	25

serum prolactin, serum LH, serum FSH, serum total and free testosterone, CBC, ESR, Hb%, LFTs, lipid profile, RFTs, and Human Immunodeficiency Virus I and II. Furthermore, patient's fasting blood sugar level and urine routine and microscopic were done. Patient's chest X-ray posteroanterior view, electro cardiogram (ECG), and ultrasonography of testes along with color Doppler (if required) were done. Patient's physical and systemic examinations and *Prakruti* evaluation were done. A washout period of 7 days was advised during which and till the end of the trial, patients had to refrain from antioxidant agents, vitamins, hormones, *Ayurvedic*, herbal, and homeopathic medications indicated for sexual disorders.

On baseline visit, patients were recruited in the study, if he met all the eligibility criteria. At baseline visit and at every follow-up visit, patients were asked for the occurrence of any AEs. Patients underwent general and systemic examinations. Patients were asked about the incidence of spontaneous achieved pregnancies. Assessment of subjective parameters of low sperm count (as per *Ayurveda*) was done on baseline visit.

At baseline visit and at every follow-up visit (except last follow-up visit), patients were provided with two high-density polyethylene containers of Ayuvigo forte capsules. Patients were advised to consume given medication in a dose of two capsules twice daily orally after meals with a cup of milk for the next 90 days.

Patients were advised to continue his concomitant medications other than antioxidant agents, vitamins, anti-inflammatory drugs, hormones, herbal/homeopathic medications. On each study visit, drug compliance was assessed by the investigator. Patients were advised to continue diet and exercise regimen (which they were already following) during the entire study. Patients were called at the respective study site for follow-up visits at every month, up to 3 months, i.e., on day 30, day 60, and day 90, after the baseline visit.

On final follow-up visit (i.e., day 90), patient's semen analysis (after at least 3 days of sexual abstinence) was done. Subject's laboratory investigations, i.e., serum LH, serum FSH, serum total and free testosterone levels, CBC, ESR, Hb%, LFTs, RFTs, lipid profile, urine routine, and microscopic and ECG were done. Global evaluation for overall improvement was made by investigator and subject. Furthermore, tolerability of the trial drug was assessed by the investigator and patient. All patients were asked to stop trial medication and take the advice of the investigator for further treatment.

Statistical analysis

Consultant statistician performed the analysis of data using statistical software SPSS 10.0 (SPSS Inc., Chicago, Illinois, USA). Data describing quantitative measures were expressed as a median or mean ± standard deviation or standard error or the mean with range. Qualitative variables were presented as counts and percentage. Comparison of variables representing categorical data was performed using the Chi-square test. All *P* values were reported based on two-sided significance test and all the statistical tests were interpreted at least up to 5% level of significance.

RESULTS

Out of 31 recruited patients, 30 patients completed the study, whereas 1 patient dropped out prematurely due to loss to follow-ups. All patients who took even a single dose of study drug were considered for safety evaluation.

Prakruti-wise distribution of patients in the study showed that there were 8 (26.66%) patients of *Vata-Pitta Prakruti*, 3 (10%) patients of *Vata-Kapha Prakruti*, 10 (33.33%) patients of *Pitta-Vata Prakruti*, 7 (23.33%) patients of *Pitta-Kapha Prakruti* and 1 (3.33%) patient each of *Kapha-Pitta Prakruti* and *Tridoshaj Prakruti*.

At baseline visit, the mean total sperm count (million/ml) was 7.93 ± 4.06 which increased significantly ($P < 0.05$) to 15.11 ± 16.68 at the end of the study (day 90). There was 90.54% increase in total sperm count in 90 days. The details are given in Figure 1.

The mean progressive sperm motility (percentage) at baseline visit was 21.75 ± 12.26 which increased significantly ($P < 0.05$) to 29.07 ± 15.07 at the end of the study (day 90). There was 33.65% increase in progressive sperm motility in 90 days. The details are given in Figure 2.

The mean total number of spermatozoa (million per ejaculate) at baseline visit was 14.31 ± 9.44 which increased significantly ($P < 0.05$) to 28.46 ± 33.55 at the end of the study (day 90). There was 98.88% increase in total sperm count per ejaculate in 90 days. The details are given in Figure 3.

No statistically significant ($P > 0.05$) change in mean semen volume (ml per ejaculate) was observed over 90 days of the study period. The mean baseline semen volume was 1.81 ± 0.62 which increased slightly to 1.95 ± 0.33 at the end of the study.

There was no major abnormality observed in the mean sperm morphology at the baseline visit and at the end of the study. Majority of the patients were reported to have normal sperm morphology at baseline and on day 90.

The mean sperm viability was measured immediately after ejaculate, after 1 h, and after 2 h of ejaculation. The immediate mean sperm viability at baseline visit was 47.35 ± 9.37 which increased significantly ($P < 0.05$) to 55.56 ± 8.56 at the end of the study (day 90). The mean sperm viability after 1 h was 30.29 ± 7.17 at baseline visit which ($P > 0.05$) increased to 31.67 ± 7.86 (non-significant) at the end of the study (day 90). Furthermore, the mean sperm viability after 2 h was 20.88 ± 6.18 at baseline visit which ($P > 0.05$) increased to 21.11 ± 4.71 (non-significant) at the end of the study (day 90). The details are given in Figure 4.

The mean serum free testosterone level at the baseline visit was 10.10 ± 7.21 mg/dl which increased significantly ($P < 0.05$) to 12.77 ± 8.27 mg/dl (26.43%) at the end of the study. The mean total testosterone level at baseline visit was 379.00 ± 214.87 mg/dl, which increased to 435.45 ± 191.74 ($P > 0.05$), i.e., by 14.89% (nonsignificant) at the end of the study.

The mean serum LH level at baseline visit was 6.28 ± 4.57 IU/L which increased nonsignificantly ($P > 0.05$) to 6.63 ± 5.31 IU/L at the end of the study (day 90). The mean serum FSH level at baseline visit was 10.11 ± 9.08 IU/L which increased nonsignificantly ($P > 0.05$) to 11.45 ± 12.41 IU/L at the end of the study. The mean serum prolactin level at baseline visit was 6.48 ± 2.67 ng/dl which increased nonsignificantly ($P > 0.05$) to 6.84 ± 3.19 ng/dl at the end of the study (day 90). The mean serum LH, FSH, and prolactin levels were

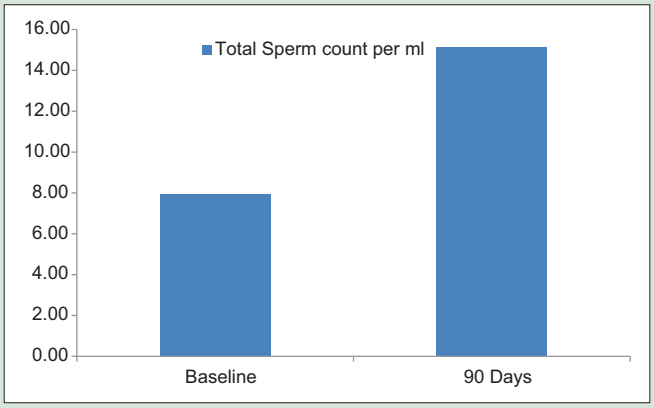

Figure 1: Assessment of total sperm count (mil/ml)

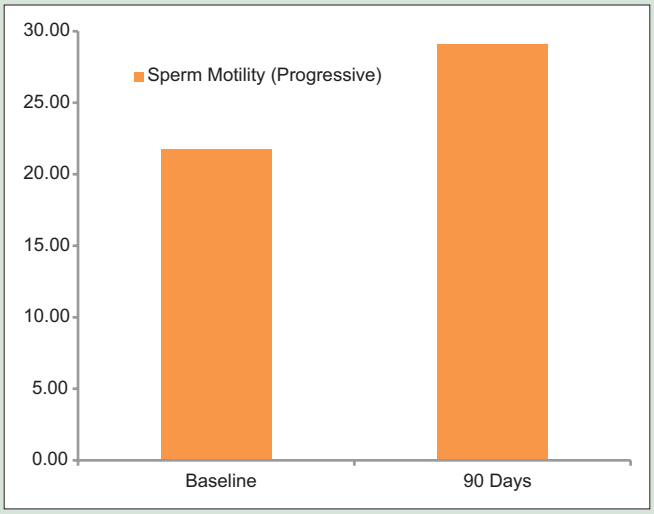

Figure 2: Assessment of sperm motility with progressive sperm motility

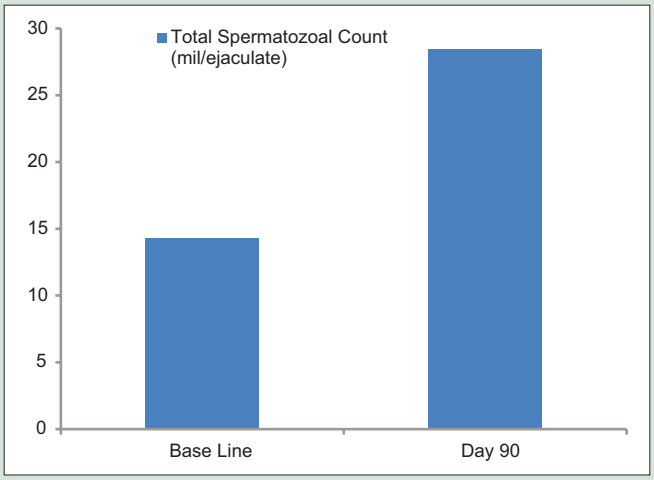

Figure 3: Assessment of total number of spermatozoa per ejaculate

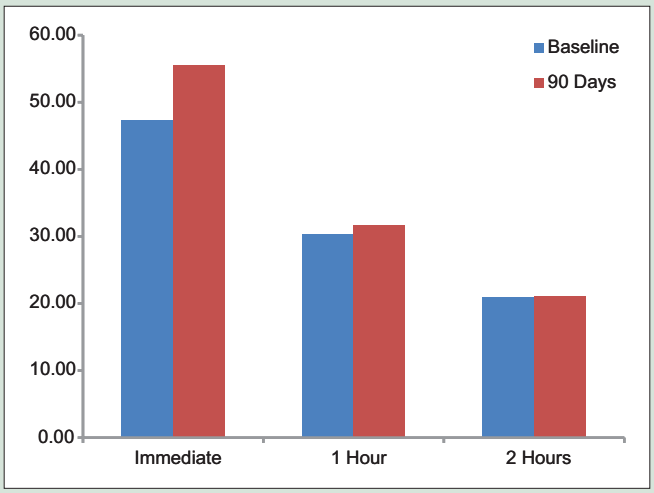

Figure 4: Assessment of viability of spermatozoa

within the normal range both at the baseline visit and at the end of the study.

Assessment of subjective parameters (11 symptoms) of low sperm count and sexual weakness as mentioned in *Ayurveda* was done on baseline visit and on follow-up visits. Significant improvement in most of the symptoms was observed at the end of the study. The details are given in Table 2.

As per the global assessment for overall change/improvement done by the physician at the end of the study, 12 (40.00%) patients had very much improvement, 7 (23.33%) patients had much improvement, 5 (16.66%) patients had minimal improvement, and 3 (10.00%) patients had no change or improvement. One (3.33%) patient showed minimal and much worsening in condition at the end of the study. As per the global assessment for overall change/improvement done by the subject at the end of the study, 13 (43.33%) patients had very much improvement, 5 (16.66%) patients had much improvement, 7 (23.33%) patients had minimal improvement and 2 (6.66%) patients had no change or improvement. One (3.33%) patient showed minimal and much worsening in condition at the end of the study.

In safety evaluation, no significant changes were observed in laboratory parameters such as CBC, ESR, Hb%, LFTs, RFTs, lipid profile, blood sugar level, and urine examination when compared between baseline visit and day 90 visit. All laboratory values were within normal range.

No clinically significant change in vitals parameters such as pulse rate, temperature, respiration rate, and blood pressure (systolic and diastolic pressure) was observed from baseline visit to every follow-up visits and at the end of the study.

Of 31 completers, 12 patients were reported to have AEs. Total 12 AEs including abdominal discomfort, fever, cough, pain in abdomen, backache, body ache, and itching were noted during the trial. Among 12 AEs, 9 AEs were unrelated, 1 AE was possibly related, whereas 2 AEs were unlikely related to the study drug. No treatment or procedure or interruption of study drug was required to resolve these episodes. All patients showed excellent to good tolerability to the study medication.

DISCUSSION

The aim of the present clinical trial was to evaluate the efficacy and safety of Ayuvigo forte capsule in patients suffering from Oligospermia. It was observed that 90 days of treatment with Ayuvigo forte capsule significantly increased the mean total sperm count at the end of the study. The increase in sperm count was found to the extent of patients having moderate oligospermia achieved almost normal levels as prescribed in the WHO guidelines (sperm count of >15 mill/ml). Furthermore, significant increase was observed in the mean progressive sperm motility and the mean total number of spermatozoa at the end of the study. Although the mean semen volume had shown insignificant changes, the mean sperm viability (measured at immediately after ejaculation) showed significant improvement at the end of the study. Majority of patients were reported to have normal sperm morphology during the whole study period.

Treatment with Ayuvigo forte capsule showed significant improvement in the mean serum free testosterone level at the end of the study. However, the mean total testosterone level, mean serum LH level, mean serum FSH level, and mean serum prolactin level were not increased significantly at the end of the study. There was a significant improvement in the clinical symptoms of low sperm count and sexual dysfunction as mentioned in *Ayurveda*. Majority of patients were reported very much improvement to much improvement as per the assessment done by physician and by the patient himself. Only a few patients were reported worsening of any sign or symptom of oligospermia during and at the end of the study. These findings suggest that Ayuvigo forte capsule is effective in the management of oligospermia.

Most of the ingredients of Ayuvigo forte capsule possess aphrodisiac, rejuvenator, spermatogenic, and libido enhancer activities. Few

Table 2: Assessment of changes in subjective parameters

Symptoms	Mean±SD			
	Baseline visit	Day 30	Day 60	Day 90
Daurbalya (weakness or general debility)	1.16±069	0.9±0.6	0.86±0.73	0.44±0.57
		P<0.05	*P*<0.05	*P*<0.05
Panduta (paleness or pall or)	0.83±0.79	0.53±0.57	0.6±0.62	0.25±0.44
		P<0.05	*P*<0.05	*P*<0.05
Shrama (fatigue or tiredness)	1.23±0.62	0.9±0.66	1.2±1.74	0.66±0.55
		P<0.05	*P*>0.05	*P*<0.05
Timira Darshana (black outs)	0.36±0.49	0.23±0.43	0.2±0.4	0.11±0.32
		P<0.05	*P*<0.05	*P*<0.05
Medhra Vrishna Vedana (pain in scrotum and penis)	0.36±0.49	0.26±0.44	0.23±0.43	0.03±0.19
		P<0.05	*P*<0.05	*P*<0.05
Medhra Dhumayana (burning sensation in penis or urethra)	0.56±0.67	0.3±0.46	0.16±0.37	0.03±0.19
		P<0.05	*P*<0.05	*P*<0.05
Chirat praseka or *Alpa-Rakta-Yukta Shukra Pravritti* or *Shukra Avisarga* (delayed or blood mixed or no ejaculation)	0.56±0.67	0.5±0.57	0.33±0.47	0.14±0.45
		P<0.05	*P*<0.05	*P*<0.05
Rati Anabhimukhata (lack of sexual desire)	0.62±0.67	0.46±0.57	0.33±0.54	0.07±0.26
		P<0.05	*P*<0.05	*P*<0.05
Maithune asakti (problematic or not satisfactory coitus)	1.33±0.95	0.96±0.85	1.1±0.99	0.51±0.75
		P<0.05	*P*<0.05	*P*<0.05
Agnisada (decreased capacity of digesting the food properly)	0.63±0.61	0.63±0.55	0.73±0.73	0.66±0.63
		P>0.05	*P*>0.05	*P*>0.05
Mukha shosha (dryness of mouth)	1.03±0.71	1.06±0.63	1.26±0.52	1.12±0.85
		P>0.05	*P*>0.05	*P*>0.05

SD: Standard deviation

ingredients help to facilitate penile erection through nitric oxide pathway.[12-15] Few ingredients of Ayuvigo forte capsule help to improve stamina, a sense of well-being vigor, semen, and sperm count.[12-15] It was observed from the results of this study that the synergistic effect of ingredients present in the formulation has contributed to overall spermatogenic, aphrodisiac, and libido enhancer effects.

In the present clinical study, 12 patients reported AEs. Most of the AEs were unrelated to the study drug. Furthermore, no treatment or interruption of the study drug or procedure was required to resolve AEs.

The mean values of almost all laboratory parameters were within normal limits at the end of the study. No significant change in any of the vital parameter (viz., heart rate, respiratory rate, body temperature and blood pressure) was observed during and at the end of the trial. Taken together these observations demonstrated that Ayuvigo forte capsule is safe and effective in patients with oligospermia.

CONCLUSION

Three months of treatment with Ayuvigo forte capsule showed statistically significant improvement in sperm count. Thus, Ayuvigo forte capsule is a safe and effective treatment option for the management of oligospermia.

Acknowledgements

The authors sincerely thank clinical trial team of Ayurveda Research Centre, Ayurved Seva Sangh Nasik, Ganeshwadi Nashik; KVTR Ayurvedic College, Boradi, Tal-Shirpur, Dist-Dhule and Sunad Ayurved Center, Chinchwad, Pune for their contribution in conduct of the present clinical study. The authors also sincerely thank to all the staff of Target Institute of Medical Education and Research, Malad (west), Mumbai for providing all the research guidance, courage, and moral support.

Financial support and sponsorship

The authors are grateful to Welex Laboratories Pvt. Ltd., for the financial assistance.

Conflicts of interest

There are no conflicts of interest.

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