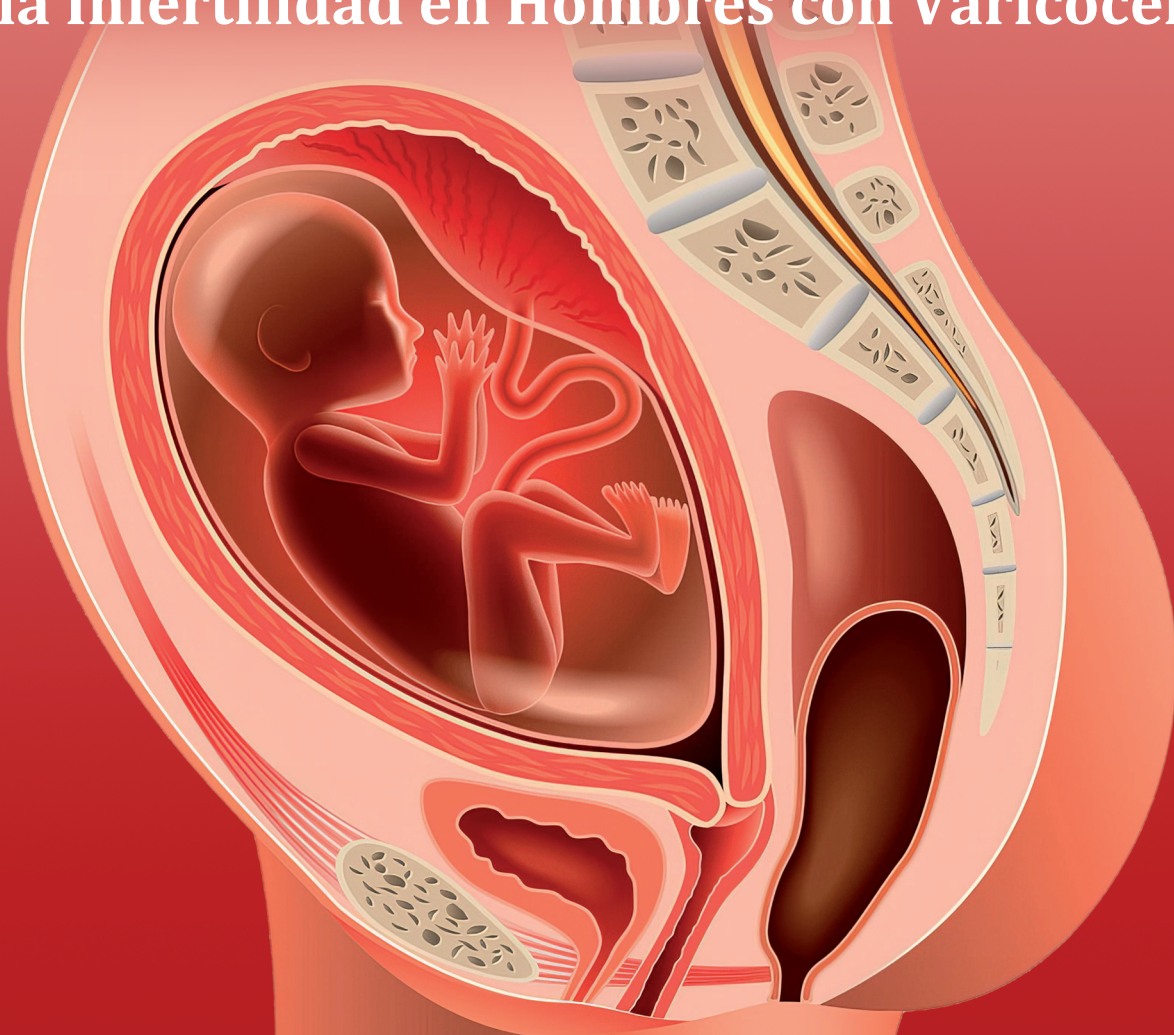


Advances in Reproductive Sciences

**Spermatrend Mejora la Calidad del Semen
y la Infertilidad en Hombres con Varicocele**



Spermotrend Mejora la Calidad del Semen y la Infertilidad en Hombres con Varicocele

— Spermotrend y la infertilidad masculina

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RESUMEN:

Antecedentes: La infertilidad afecta entre el 8% y el 12% de las parejas en todo el mundo, y aproximadamente la mitad de los casos se reportan en hombres. El estrés oxidativo es un factor común aumentado en la condición de varicocele y afecta particularmente a los espermatozoides, debido a su sensibilidad a las señales oxidativas y a la hipotrofia testicular. El objetivo de este ensayo clínico es estudiar la eficacia de Spermotrend en la mejora de los parámetros espermáticos en la infertilidad masculina. **Métodos:** Un total de 170 hombres mayores de 18 años con un diagnóstico de infertilidad y varicocele se inscribieron consecutivamente en un ensayo clínico abierto de Fase II. A Spermotrend se le administró 1 cápsula (450 mg) por vía oral cada 8 horas durante 6 meses y se evaluó mediante análisis de semen a los 4 y 6 meses de seguimiento. **Resultados:** Los resultados del ensayo muestran una mejora significativa después de la administración de Spermotrend durante 6 meses en la concentración de espermatozoides (44,1% al inicio frente a 64,1% a los 6 meses), supervivencia de los espermatozoides (28,2% con supervivencia de espermatozoides $\geq$ 2 horas frente a 56,5%), normalización de la morfología de los espermatozoides (31,2% frente a 72,9%). La condición de varicocele disminuyó en todos los pacientes y, al final del estudio, el 55,3% de los pacientes tenían flujo venoso y dilatación normales. Sólo el 5,9% de los pacientes mostró varicocele de grado 2 al final del estudio, mientras que el 38,8% mostró varicocele de grado 1, y ningún paciente mostró varicocele de grado 3. En cuanto a la hipotrofia testicular, el 90,6% de los pacientes finalizaron el estudio con volumen testicular normalizado recuperando el flujo venoso normal. **Conclusión:** Un tratamiento a corto plazo con Spermotrend puede mejorar significativamente los parámetros espermáticos asociados con la infertilidad masculina. **Registro de ensayos clínicos:** El protocolo del ensayo clínico fue registrado en el registro internacional de ensayos clínicos, ClinicalTrials.gov, con el código: NCT05222841 el 15/06/2021.

Spermotrend Improves Semen Quality and Infertility in Men with Varicocele

—Spermotrend and Male Infertility

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Abstract

Background: Infertility affects 8% - 12% of couples globally, with approximately half of the cases reported in males. Oxidative stress is a common factor increased in the varicocele condition and particularly affects spermatozoa, due to their sensitivity to oxidative signals and testicular hypotrophy. The objective of this clinical trial is to study the effectiveness of Spermotrend in the improvement of sperm parameters in male infertility. **Methods:** A total of 170 males aged > 18 years with a diagnosis of infertility and varicocele were consecutively enrolled in a Phase II, open-label clinical trial. Spermotrend was administered 1 capsule (450 mg) orally every 8 hours for 6 months and was evaluated through semen analysis at 4 and 6 months of follow-up. **Results:** The trial results show a significant improvement following the administration of Spermotrend over 6 months in sperm concentration (44.1% at baseline vs. 64.1% at 6 months), sperm survival (28.2% with sperm survival ≥ 2 hours vs. 56.5%), normalization of sperm morphology (31.2% vs. 72.9%). Varicocele condition decreased in all patients and, by the end of the study, 55.3% of patients had normal venous flow and dilation. Only 5.9% of the patients showed grade 2 varicocele at the end of the study, while 38.8% showed grade 1 varicocele, with no patients showing grade 3 varicocele. Regarding testicular hypotrophy, 90.6% of the patients completed the study with normalized testicular volume by recovering normal venous flow. **Conclusion:** A short-term course of Spermotrend may significantly improve sperm parameters associated with male infertility. **Clinical Trial Registration:** The clinical trial protocol was registered in the international clinical trial registry, ClinicalTrials.gov, with the code: *NCT05222841* on 15/06/2021.

Keywords

Antioxidants, Dietary Supplementation, Male Infertility, Spermatogenesis,

1. Introduction

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse [1].

An increasing number of couples of reproductive ages seek specialized centers in the hope of resolving their infertility problems [2] [3]. Historically, the social burden of infertility has been attributed to women. With the progress in diagnostic studies and infertility treatments, it is now known that male infertility impacts in the same proportions as female infertility. Male infertility individually affects 20% - 30% of cases and contributes to approximately 50% of cases [4] [5] [6]. Therefore, the male factor is the main cause of infertility in numerous couples who seek medical assistance daily, a percentage that exceeds female infertility in many places [6].

The main risk factors in the development of male infertility can be classified based on their origin as congenital, acquired, and idiopathic [7] [8] [9]. Among the acquired factors, the most common in daily clinical practice is varicocele, with a prevalence of 20% in healthy men and up to 40% in men with infertility [10] [11] [12], and infections caused by bacteria, viruses, or protozoa in the genitourinary tract account for approximately 10% - 15% of infertility cases in men [13].

In men with infertility, the most common sperm abnormalities are low sperm concentration (oligospermia, $<15 \times 10/\text{mL}$; the total number of ejaculated sperm $<39 \times 10/\text{mL}$), low sperm motility (asthenospermia), and anomalies in sperm morphology (teratospermia) [14].

So far, many studies have been conducted in the hope of improving sperm quality in men [8] [15] [16] [17]. However, not all therapies are completely effective, and not everyone has access to high-tech assisted reproductive techniques that may offset possible defects in spermatogenesis.

Among the various risk factors mentioned above, inflammation and oxidative stress appear as common factors affecting sperm quality in patients with infertility [18] [19] [20] [21]. Under normal conditions, low levels of reactive oxygen species (ROS) are essential for carrying out various biochemical reactions and physiological functions [22]. However, oxidative stress (OS) has been identified as the core common mechanism by which various endogenous and exogenous factors may induce idiopathic male infertility [23].

Recent studies have shown that increased oxidative damage plays a significant role in changes in sperm quality in male patients with infertility, especially those who also have varicocele [24]. In normal situations, cellular machinery and endogenous antioxidants restore the balance of reduction and oxidation (REDOX).

In the specific case of varicocele, the abnormal dilation, elongation, and tortuosity of the veins in the pampiniform plexus of the spermatic cord can increase testicular hyperthermia, testicular hypoxia/ischemia, reflux of adrenal metabolites, and oxidative stress [25] [26]. Antioxidants could therefore play an important role in the proper development of spermiogenesis, especially in patients with associated varicocele [27].

Different trials have studied daily supplementation with antioxidant agents and micronutrients that help control the REDOX balance, such as vitamin C, vitamin E, zinc, selenium, folic acid, or L-carnitine, with positive results in sperm parameters and ultimately on pregnancy rates [27] [28] [29] [30].

Spermotrend[®], a natural product manufactured by Catalysis S.L., is formulated with different antioxidants and micronutrients with adequate concentrations to have the necessary antioxidant ability to help maintain the integrity of the tissues that are part of the male genitourinary tract, thereby improving sperm parameters. Among its chemical ingredients, Spermotrend[®] includes zinc, selenium, and L-arginine which have shown important benefits in men suffering from infertility. Zinc deficiency has been linked to infertility cases in men. Zinc supplementation has been studied in male patients with infertility, improving sperm quality parameters [31] [32]. The selenium supplementation has shown an increase in motility, sperm survival, and reduction of spermatozoa with DNA fragmentation [33] [34]. L-arginine supplementation has been found to have a crucial role in sperm production in men with varicocele and may improve fertility outcomes [35] [36] [37], as well as erection aid [37] [38].

The objective of this clinical trial is to study the efficacy of daily supplementation with Spermotrend[®] in improving sperm quality and quantity in men suffering from male infertility with additional oxidative conditions such as varicocele.

2. Materials and Methods

2.1. Study Population

A total of 170 male patients >18 years of age diagnosed with infertility were recruited and evaluated between June 2021 and June 2022 by *Clinica Seniors*, Managua (Nicaragua) for the clinical trial. This research was designed to assess the influence of supplementation with Spermotrend (Catalysis S.L.) on the fertility of men with low sperm quality and varicocele.

Inclusion and Exclusion Criteria

Men older than 18 years old were included if they had altered sperm parameters including sperm concentration, morphology, and motility evaluated by spermogram, without testicular pathology, with negative HIV and serology.

Other exclusion criteria were patients with associated pathologies (epididymal-orchitis, radiation, or chemotherapy), patients with resolved testicular pathology, patients with non-communicable chronic pathologies, patients undergoing treatment with antioxidants, vitamins, hormones, and/or anti-inflammatory drugs, or who have completed such treatment in the last six months, and

patients with positive HIV or serology.

2.2. Duration of the Trial

In this trial, Spermotrend® (Catalysis S.L., Spain) was the study product used, at a dosage of one capsule of 536.62 mg three times a day, taken with meals for 6 months (Table 1). A healthy lifestyle routine was recommended to patients. After study enrollment, patients were assessed at 4 and 6 months of follow-up.

2.3. Study Design

The study process was designed as a single-arm, open-label, clinical trial (ClinicalTrials.gov Identifier: NCT01857310).

The pre-treatment evaluation included patient history, clinical examination, semen analysis, hormonal determination (total testosterone), and ultrasound to assess signs of obstruction, varicocele, and/or testicular hypotrophy with a differential volume (DV) of less than 20%.

To assess the effectiveness of daily treatment with Spermotrend®, clinical examination, semen analysis, and ultrasound were repeated for the trial participants at 4 and 6 months.

2.3.1. Hormone Analysis

Testosterone levels were determined in the trial participants at the time of recruitment using analytical methods for plasma determination of total testosterone (TT) by Elisa kit.

2.3.2. Semen Analysis

After 3 - 4 days of sexual abstinence, semen samples were obtained from the

Table 1. Qualitative-quantitative composition of the product Spermotrend capsules.

Composition	mg/capsule
Fructose	104 mg
African plum extract (<i>Pygeum africanum</i> Hook. f.)	100 mg
Maltodextrin	89 mg
L-carnitine fumarate	70.5 mg
L-arginine	50 mg
Microcrystalline cellulose	50 mg
Vitamin C (L-ascorbicacid)	30 mg
Vitamin E (DL-Alpha-tocopherylacetate)	22 mg
Zinc sulfate	20 mg
Vitamin B6 (Pyridoxine hydrochloride)	1 mg
Folic acid (Pteroylmonoglutamic acid)	0.1 mg
Sodium selenite	0.02 mg
Vitamin B12 (cyanocobalamin)	0.0005 mg

patients via masturbation. Sperm parameters (semen volume in ejaculation, sperm concentration, sperm morphology, sperm motility, presence of blood cells in seminal fluid, and seminal pH) were determined using a spermogram test according to the criteria of the World Health Organization (WHO). Microscopic evaluation of sperm morphology and concentration was performed manually using the *Makler* counting chamber. The sperm count in the samples obtained from the patients was calculated as millions/mL. Sperm morphology was determined according to a spermogram. Additionally, the patients were classified based on the determination of sperm concentration as patients with hyperspermia, oligospermia, azospermia, aspermia, or normospermia following the criteria of the WHO. The sperm evaluation was performed at baseline, at 4 months, and at 6 months of treatment with Spermotrend®.

2.3.3. Imaging Study

The varicocele condition in the recruited patients was diagnosed through Color Doppler Ultrasound (CDU) and physical examination. The grade of varicocele was classified according to the *Dubin and Amelar* criteria into three categories [39]. The patients were re-assessed at 4 and 6 months of treatment.

All patients underwent a scrotal ultrasound in B-mode, including measurements of the width, length, and height of both testicles. Testicular volume was calculated using the formula $\pi/6 \times \text{length} \times \text{height} \times \text{width}$. A testicular volume of less than 12 mL was suggested as testicular hypotrophy, with a testicular differential volume (DV) of less than 20% [40].

2.3.4. Statistical Analysis

Baseline characteristics were summarized in numbers and percentages for categorical variables. The data obtained from the study were analyzed with *IBM SPSS-26* software for *Windows* (SPSS Inc. USA). Differences in the study end-points between the various time points in patient follow-up [baseline, after 4 months of treatment, and after 6 months of treatment) were calculated using the parametric *Student's* t-test and the non-parametric Mann-Whitney test. A *p*-value of less than 0.05 was considered significant.

2.4. Ethics Committee

The study was approved by the Ethics Committee “Clinica Seniors”, in Managua (Nicaragua), with reference number: 5626, and certified that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The purpose and the methodology of the study were explained to every recruited patient. All study subjects were provided with information about the trial product Spermotrend. Before being recruited, all patients signed the informed consent form and were explained that they could withdraw from the trial at any time if they decided to do so.

3. Results

A total of 170 patients were enrolled in the clinical trial at Clinica Seniors (Ma-

nagua, Nicaragua). There was no dropout or withdrawal among the recruited patients, and all 170 patients completed the trial protocol.

Table 2 shows that 65.3% of patients had primary infertility, while 34.7% of the recruited patients had previously achieved pregnancy and were diagnosed with secondary infertility at the time of recruitment. The age range of most of the patients recruited for the trial was 30 to 40 years old both for those with primary (84.7%) or secondary (79.7%) infertility. In the evaluation of the medical history of the patients recruited for the trial, 47.1% of the total number of patients had dyslipidemia at the time of recruitment, 24.1% had diabetes mellitus, and 3.5% had thyroid-related disease. 25.3% of the recruited patients did not have a medical history of any previous metabolic-related condition. In the determination of testosterone levels, 44.1% of the recruited patients with infertility had levels below 300 ng/dL, while 55.9% of the patients had testosterone levels between 300 ng/dL and 1000 ng/dL.

Sperm quality parameters were determined at baseline, at 4 months, and at 6 months of treatment through a spermogram (**Table 3**). At the time of recruitment, 38.2% of the patients had an ejaculate volume of less than 2 CC. 68.8% of the study population had abnormalities in sperm morphology, with the most common structural alteration being head abnormality, observed in 43.5% of them. The baseline sperm survival rate was equal to or less than 30 minutes in 43.5% of the patients. 40% of the recruited patients had oligospermia at the beginning of the study. Additionally, 76.5% of the patients showed alterations in the pH of the seminal fluid. Besides, the baseline testosterone levels were less than 300 ng/L in 44.1% of the recruited patients.

After 4 and 6 months of daily use of Spermotrend, 1 capsule of 536.62 mg/8 hours with meals, sperm parameters were re-assessed. At 4 months, sperm volume and motility improved significantly. However, it was not until 6 months of

Table 2. Demographic data of the study population.

Variable		N = 170
Type of infertility	Primary infertility	111 (65.29%)
	Secondary infertility	59 (34.71%)
Predominant age in patients with primary infertility	30 - 40 years old	94 (84.68%)
	40 - 50 years old	17 (15.32%)
Predominant age in patients with secondary infertility	30 - 40 years old	47 (79.66%)
	40 - 50 years old	12 (20.34%)
Previous metabolic diseases	Diabetes mellitus	41 (24.12%)
	Hyperthyroidism or hypothyroidism	6 (3.53%)
	Dyslipidemia	80 (47.06%)
	None	43 (25.29%)
Baseline Testosterone Levels	300 - 1000 ng/dL	95 (55.88%)
	<300 ng/dL	75 (44.12%)

Table 3. Evolution of sperm quality parameters at recruitment time, at 4 and at 6 months after treatment with Spermotrend®.

Variable		Baseline	4 months	<i>p</i>	6 months	<i>p</i>
Volume				0.001		<0.001
	Less than 2 CC	65 (38.23%)	50 (29.41%)		24 (14.12%)	
	Between 2 CC and 5 CC	75 (44.12%)	88 (51.76%)		84 (49.41%)	
	More than 5 CC	30 (17.65%)	32 (18.83%)		62 (36.47%)	
Morphology				0.643		0.034
	Head abnormality	74 (43.53%)	20 (11.77%)		11 (6.47%)	
	Neck abnormality	40 (23.53%)	22 (12.94%)		12 (7.06%)	
	Tail abnormality	3 (1.76%)	73 (42.94%)		23 (13.53%)	
	No abnormalities	53 (31.18%)	55 (32.35%)		124 (72.94%)	
Motility				0.012		0.010
	1/2-hour survival	74 (43.52%)	30 (17.65%)		22 (12.94%)	
	1-hour survival	48 (28.24%)	69 (40.59%)		52 (30.59%)	
	2-hour survival	48 (28.24%)	71 (41.76%)		96 (56.47%)	
Concentration				0.666		0.004
	Hyperspermia	5 (2.94%)	9 (5.29%)		28 (16.47%)	
	Oligospermia	68 (40.00%)	76 (44.71%)		31 (18.23%)	
	Azoospermia	18 (10.59%)	6 (3.53%)		2 (1.18%)	
	Aspermia	4 (2.35%)	2 (1.18%)		0 (0.00%)	
	Normospermia	75 (44.12%)	77 (45.29%)		109 (64.12%)	
pH				0.495		<0.001
	Acid	34 (20.00%)	47 (27.35%)		54 (31.76%)	
	Base	96 (56.47%)	60 (35.29%)		15 (8.82%)	
	Normal	40 (21.18%)	63 (37.06%)		101 (59.41%)	
Hematospermia				0.387		<0.001
	Yes	70 (41.18%)	74 (43.53%)		14 (8.24%)	
	No	100 (58.82%)	96 (56.47%)		156 (91.76%)	

daily Spermotrend® administration that significant differences in sperm morphology, concentration, and pH were observed.

After 6 months of Spermotrend®, the patients recruited for the trial showed the following results: a sperm ejaculate volume greater than 2 CC in 85.9% of the cases, normal sperm morphology in 72.9%, normal seminal pH in 59.4%, and no presence of blood in semen in 91.8% of cases.

On the other hand, ultrasound imaging studies were performed (**Table 4**). The 170 patients recruited in this study additionally showed varicocele associated with infertility at grades 1, 2, and 3 (52.9%, 31.8%, and 21.2%, respectively) according to *Dubin and Amelars'* criteria [39] at the time of recruitment.

Table 4. Evolution of varicocele grade and testicular volume at baseline, at 4 months, and at 6 months of treatment with Spermotrend®.

Variable		Baseline	4 months	<i>p</i>	6 months	<i>p</i>
Grade of varicocele	Varicocele grade 0	0 (0.00%)	23 (13.53%)	0.001	94 (55.30%)	0.001
	Varicocele grade 1	90 (52.94%)	106 (62.35%)		66 (38.82%)	
	Varicocele grade 2	54 (31.76%)	33 (19.41%)		10 (5.88%)	
	Varicocele grade 3	36 (21.18%)	8 (4.71%)		0 (0.00%)	
Alterations in testicular volume	Testicular hypotrophy	60 (35.29%)	40 (23.53%)	<0.001	16 (9.41%)	<0.001
	Testicle without hypotrophy	110 (64.71%)	130 (76.47%)		154 (90.59%)	

Furthermore, out of the total number of patients, 35.3% had testicular hypotrophy with DV < 20% at the time of recruitment.

The evolution of the participants treated with Spermotrend® showed a significant and progressive improvement in the grade of varicocele. After 6 months of treatment with Spermotrend®, no varicocele was observed in 55.3%, and 90.6% of the patients presented improved testicular volume (testicles without hypotrophy).

4. Discussion

According to the latest WHO statistics, approximately 50 - 80 million people worldwide suffer from infertility, and male factors are responsible for approximately 20% - 30% of all infertility cases [41]. Male infertility may be influenced by various factors that negatively impact spermatogenesis [20] [41]. Increased oxidative stress is a common factor that negatively affects sperm quality, especially in fertile-age men who have varicocele, metabolic disorders such as dyslipidemia, or inflammatory processes such as viral infections [11] [13] [14] [21] [24]. Therefore, in recent decades, the potential therapeutic benefit of administering mono and poly-formulations of antioxidants in male infertility has been assessed. The most studied antioxidants in infertility and those most administered so far include vitamins A, C, and E, L-carnitine, coenzyme Q10, folic acid, selenium, and zinc. However, the results of the studies conducted to date are inconclusive, and the efficacy of using antioxidants in the clinical improvement of male infertility has not been clarified. The main reasons for the significant difference in efficacy results lie in the reduced number of recruited patients, the considerable variability in the antioxidant doses, and the treatment periods.

Our study examines the efficacy of daily supplementation with Spermotrend® in improving sperm quality and quantity in men suffering from male infertility with additional oxidative conditions such as varicocele. This clinical study shows that the administration of Spermotrend®, a product containing antioxidants and balanced micronutrients, improved sperm parameters after 6 months of daily

use. The components of Spermotrend are balanced to provide the required daily dose of antioxidants, which are associated with male infertility under oxidative stress conditions.

The initial study sample presented male infertility in fertile age associated with varicocele at stages I, II, and III (52.9%, 31.8%, and 21.2%, respectively), and 74.7% showed metabolic diseases (diabetes mellitus 24.1%; thyroid disorders 3.5%; and dyslipidemia 47.1%), both conditions being considered as baseline oxidative stress in the recruited patients. 44.1% had testosterone levels below the set normal range of 300 ng/dL. The development of varicocele may lead to testicular deficiency, resulting in a decrease in testosterone production by Leydig cells, oligospermia, and testicular hypotrophy with DV < 20%. Moreover, it has also been associated with DNA fragmentation in sperm, leading to a decrease in sperm motility, viability, count, and morphology [42].

Based on all these findings, and taking into account the baseline conditions of the patients recruited, the study population was considered to have associated oxidative conditions that affected sperm quality. Of the total number of infertile patients who participated in the study, 38.2% had a seminal fluid volume of less than 2 ml (normal ejaculate volume is between 2 and 6 ml); 78.8% showed alterations in seminal pH; 68.8% had morphological abnormalities; 71.8% had low sperm survival; and 55.9% had alterations in sperm concentration.

After 4 months of daily administration of Spermotrend®, no significant changes were observed in the morphological parameters or the sperm concentration. However, there were notable improvements in ejaculate volume and sperm motility. This is in alignment with a previous study showing that after 90 days of Spermotrend® administration, sperm motility improved significantly, without significant changes in sperm morphology or concentration [43]. Regarding the varicocele condition, the percentage of patients with varicocele grade 2 decreased from 31.8% to 19.4%, and the percentage of patients with varicocele grade 3 decreased from 21.2% to 4.7%. 13.5% showed normal venous dilation. The rate of testicular hypotrophy with DV < 20% normalized to 11.8%.

Significant changes in the variables indicating sperm quality were observed after 6 months of treatment with Spermotrend® at a dosage of 3 capsules per day. The ejaculate volume significantly improved, as well as sperm motility, compared to the values at 4 months of treatment. Sperm morphology and concentration, as well as pH, also showed significant improvements. After 6 months of treatment and follow-up, 72.9% of patients had normal morphology. 64.1% showed normospermia and 16.5% hyperspermia.

Furthermore, considering the grade of varicocele evaluated through imaging studies, the patients showed an improvement in the grade of varicocele after 6 months of treatment with Spermotrend®. 55.3% of the patients showed normal venous flow and dilation. Only 5.9% of the patients had grade 2 varicocele, and 38.8% had grade 1 varicocele, with no one showing grade 3 varicocele. Regarding testicular hypotrophy, 90.6% of the patients completed the study with norma-

lized testicular volume by recovering normal venous flow. We hypothesized that Spermotrend® may help control oxidative stress at the endothelial level, thus promoting the recovery of venous flow and elasticity. Furthermore, it could be due to restoring the levels of L-arginine, which are reduced by the activity of the arginase enzyme.

Therefore, this study demonstrates that daily supplementation of Spermotrend for a continuous period of 6 months has a beneficial effect on sperm quality and the control of venous flow and dilation associated with varicocele, despite the heterogeneity of altered parameters associated with male infertility. The antioxidants and micronutrients of Spermotrend® help restore proper REDOX balance and sperm metabolism, thus promoting the correct sperm morphology, motility, mobility, and maturation [44].

Recent studies have shown that increased oxidative damage plays a significant role in changes in sperm quality in male patients with infertility, especially those who also have varicocele [24]. In normal situations, cellular machinery and endogenous antioxidants restore the balance of reduction and oxidation (REDOX). However, in situations of excessive oxidants and/or antioxidant deficiency, oxidative damage negatively affects spermatogenesis. This is the case of varicocele where structural anomalies in the pampiniform plexus of the spermatic cord can lead to increased testicular oxidative stress [25] [26]. Thus, antioxidants could therefore play an important role in the proper development of spermiogenesis, especially in patients with associated varicocele. Our study supports the evidence that 6 months of a cocktail of antioxidants in males with infertility may help to improve sperm quality and alleviate venous flow and dilation associated with varicocele that ultimately results in infertility.

Spermotrend® contains important chemical ingredients such as zinc, selenium, and L-arginine with recognized benefits in fertility. Zinc, one of the most commonly used supplements in men suffering from infertility, is an element present in seminal plasma and in the prostate. It is essential for the production of spermatozoa, as well as for their morphology and proper motility. It is also involved in the correct testicular development and the control of steroidogenesis [31] [45]. Selenium is another well-studied and used nutritional supplement in the treatment of male infertility. This element acts as an antioxidant, forming part of the enzyme glutathione peroxidase, and helps control the production of oxidants, especially in sperm DNA. Its supplementation has shown an increase in motility, sperm survival, and reduction of spermatozoa with DNA fragmentation [34] [46]. Human studies suggest that L-Arginine supplementation is safe and effective for men with oligospermia or asthenospermia [37]. L-arginine is a key part of sperm production. It helps in producing nitric oxide and has excellent antioxidant properties. L-arginine coordinates several different functions that are required for booming sperm growth and development. Particularly, its supplementation affects several semen parameters including morphology and motility, which can ultimately enhance male reproductive performance [47].

Combining several supplement nutrients with recognized effectiveness in

male infertility may have synergistic effects on different molecular pathways such as oxidative stress, oxide nitric production, and inflammation, among others, that ultimately might explain the profound benefits seen with Spermotrend® in sperm quality and morphology, although further studies may ascertain this hypothesis.

Finally and given the small sample size of this clinical trial, further large-scale multicenter studies should be conducted to confirm our findings.

In this study, after 6 months of therapy with Spermotrend®, we observed significant beneficial effects on sperm morphology, mobility, and vitality. These results suggest that nutrient supplements play an essential role in maintaining male fertility. Moreover, these results support the significance of formulations that combine several nutrient supplements as a therapy to treat male infertility and recover the functional capacity of spermatozoa. Thus, Spermotrend® could be offered as a functional and effective short-term therapy to improve sperm parameters associated with male infertility, as well as the grade of varicocele, and it helps reduce testicular hypotrophy, restoring the functionality of the affected testicles. Based on the results obtained in this study, daily use is recommended for at least 6 months, although a large randomized controlled trial is warranted to confirm our results.

Ethical Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Clinica Seniors, Managua (Nicaragua) under code **5626** and was conducted in agreement with the Declaration of Helsinki. Written consent was obtained from all patients before study enrollment.

Contribution of the Authors

All authors have contributed equally to the conceptualization, methodology, investigation, writing, preparation, and drafting of the clinical trial manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest. The authors are responsible for the content and writing of the article. The sponsors were not involved in the study design, data collection, and analysis, decision to publish, or manuscript preparation.

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Availability of Data and Materials

The datasets used and/or analyzed during the current clinical trial are available

from the corresponding author upon reasonable request.

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