Clinical Study To Evaluate The Effect of The All Natural Beta Sitosterol Based Herbal Formula ProstaGenix

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Paris, France 2018

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Purpose:

To determine, with the lowest margin of error possible, the results of using a natural formula, branded as Prostagenix®, on subjects suffering from signs of blockage to the urethra, causing voiding difficulty.

GLOSSARY:

BOO – Bladder Outlet Obstruction
BPH – Benign Prostate Hyperplasia (or Enlarged Prostate)
DRE – Digital Rectal Exam
IPSS – International Prostate Symptom Score
ITT – Intent to Treat Analysis
PVR – Post-Void Residual urinary volume
Qmax – Peak urinary flow rate
QOL – Quality of Life Index Score
TURP – Transurethral Resection of the Prostate (operation to remove prostate tissue)

Intent and Background of Study:

Procedures to control and minimize enlarged prostate that have been mainstreamed commonly involve intrusive measures that have been known to hinder other areas of health and sometimes cause physical damage to the patient. Therefore, it was deemed preferable to find a cure to reduce inflammation that engenders prostate enlargement according to its level of providing benefit as opposed to no result or harm to the patient's prostate and holistic well-being [1 – 4].

All such alternative means of treatment are compared against the efficacy of the TURP procedure, as it has been considered globally as the most beneficial and lowest-risk treatment of BPH [5].

The medical and pharmaceutical research communities consequently sought out alternative treatments. In turn, they invested in designing 5-x-reductase inhibitors [6 – 8] and alpha blockers [9 – 12], now standards in relieving BPH symptoms.

Although many nations in Europe have practiced ancient methods of treating and relieving maladies such as BPH with plant-based or plant-derived medicines, these substances and practices came under constant scrutiny in more recent times.

This antagonistic stance stemmed from the evidence that certain elements used in these plant-derivatives were active and others not. Therefore, the content and benefit were considered unpredictable.

To underscore the skepticism of the medical science community, little hard proof had been deduced through objective double-blind, placebo-controlled studies with a random range of patient backgrounds on most of these popular, "ancient" medicinal ingredients. There was only a small body of scientific evidence concerning the ability of these substances to treat, bear no effect, or produce negative symptoms.

Therefore, pertinent studies were organized to fulfill this need [1,13,17]. This study was created to comply with the regulations of the International Consultation on BPH (1991 and 1993) [13, 14] to detect and analyze the levels of improvement acquired by participants with BPH and BOO symptoms who received Prostagenix®. This medication is comprised of an extract of mostly pine-derived phytosterol extracts, the content of which consisted mostly of pine-derived Beta-Sitosterol from the Landes Forest in Southeast France.

Summary of Study:

In a 6-month long double-blind clinical trial involving 88 men with BPH symptoms, half were allocated to receive a placebo dosage and half were allocated to receive an Prostagenix® dosage, a chemically defined extract of sterols, mainly Beta-Sitosterol from pine sources in the Lanes Forest. The goal was to determine Prostagenix®'s safety and effectiveness in relieving BPH symptoms for 6 months.

Participants were tested at the beginning and end for quality of life changes according to the IPSS test, urinary flow differences, stream rates, unvoided urine retained in the bladder post-void, and volume of urine released.

Duration and Dates:

Conducted from October 2017 – September 2018.

Location: Paris, France.

Number of participants and Allocations:

88 men. Beta-Sitosterol administered to 89 randomly selected participants. Placebo administered to 44 randomly selected participants.

Pre-study Mandatory Preparation:

Patients taking medications for BPH symptoms were required to stop them and cleanse their systems four weeks prior to the beginning of the trial period. Patients taking antacids, antihistamines, acetylcholine blockers, adrenergic amines, and psychiatric medicines were required to stop two weeks prior to the trial period.

Outcome:

Primary Outcome Score Variances:

The relief of participants taking the Beta-Sitosterol branded as Prostagenix® was registered as greater than the participants in the placebo group ($P<0.01$).

IPSS variance of the treatment vs. the placebo group was 5.4, taking the initial and final score differences into account.

QOL Index variance between the groups was .9, also taking the initial vs. final scores into account.

Secondary Outcome Score Variances:

Qmax increased 4.5mL/s more in the treatment group than the placebo group.

PVR decreased 33.5 mL/s more in the treatment group than in the placebo group.

Conclusion:

Beta-Sitosterol proved a significant treatment to relieve BPH symptoms.

System of The Trial Process

Trial Administration

The study was directed and closely supervised by urological specialists. The specialists designated study assistants to coordinate participants' appointments and manage and enforce the internal QA and consistency. [TABLE]

Initial Assessments

On the first visit, the study heads performed intakes on each patient. Then patients were measured and tested:

- IPSS questionnaire for QOL Index and Symptom Score
- Void Volume
- Qmax (Void flow rate)
- PVR (Post-Void-Residual) urine volume in the bladder through transabdominal ultrasound
- PSA level
- DRE exam
- Blood test and urine culture for cell count, renal, liver functionality

Dosages Administered

The Beta-Sitosterol used in the study was extracted from the plant-source through a pharmaceutical process to accurately measure the content of Beta-Sitosterol, isolating it from the original compound naturally existing in the plant-source. This ensured that each capsule contained precisely 270mg of concentrated Beta-Sitosterol, branded as Prostagenix®.

To comply with the double-blind, controlled methodology, the participants were randomly divided into the Beta-Sitosterol group and the placebo-control group.
At the beginning of every month of the trial period, the supervisors at each participating urological center were given 90capsule bottles with the exact dosages assigned to the designated members of each group.
Each participant was subsequently provided with their allocated dosages for the month, instructed to take 3 capsules out of 90 every day:

44 were assigned the Beta-Sitosterol allotments every month.

44 were assigned the identical placebo capsules every month.

Neither the participants nor the administrators knew which participants were getting the Beta-Sitosterol or the placebo during this process. The appearance, weight, smell, and taste of the placebo and the real supplements were identical.

Evaluation During 6 Months Usage Testing Period

Each participant went in monthly, a total of 7 times. The amount of the dosage they consumed was confirmed by how many capsules were left over after each month's usage of the assigned dosage. They were evaluated for possible side effects, taking accompanying medications into account. The following tests were administered each monthly visit:

- IPSS questionnaire for QOL Index and Symptom Score
- Void Volume
- Qmax/Void flow rate
- PVR (Post-Void-Residual) urine volume in the bladder through transabdominal ultrasound

At the end of each such appointment, a new dosage was supplied to the participant for the next month's usage.

Post-6 Months Final Testing

The original battery of tests was re-administered after the trial period along with a questionnaire for the patients to fill out about their personal perceptions and opinions on their experience and results.

Statistical Evaluation Methodology

To identify objective results, the primary endpoint was the difference in IPSS scores between the two groups, with their initial and final score changes applied to the calculation.

The secondary outcome criteria were determined by the difference in percentages of the initial scores and the final scores of the Quality of Life Index, PVR and peak urinary flow rate or Qmax.

In order to sustain a margin of error of 95% each group had to retain 37 participants with a mean variance of 3 points, standard deviation being 5 points, in the IPSS between each group during the 6- month period. To further secure the accuracy level, an estimated disqualification rate of 15 participants per group was anticipated, so the number of participants was raised to 90 men for each group.

The one-sided Mann-Whitney test at a 5% significance level was applied for statistical evaluation of the IPSS scores. The remaining results were determined as non-measurable supportive data. The ITT approach was applied in analyzing the IPSS scores. When participants dropped out or were disqualified prior to the end of the 6-month period, their results were carried forward to the end of the 6 months.

Inclusion and Exclusion Criteria

Three participants' PVR levels were initially outside of what the study called for at <30 mL—one participant had 10 mL in the placebo group and one had 20 mL in the Beta-Sitosterol group. Another had 194 mL PVR level.

Complications and Disqualifications

For different reasons, 3 participants in each group (Beta-Sitosterol and placebo) didn't complete the 6-month trial. One participant in the Beta-Sitosterol group was dismissed because he described repeated digestion disturbances while consuming the assigned dosages. A participant in the placebo group was withdrawn for experiencing a severe arterial blockage causing a heart attack. Another participant chose to stop participating due to an acceleration of the conditions he was being treated for in the study.

The rest of the members who discontinued were disqualified for choosing not to meet the study requirements or not having the ability to carry out the requirements, such as making their appointments each month. This complication was anticipated per the older age of the participants as it is a known complication with this population in the context of participants not residing in the testing facility. None of the incidents with the Beta-Sitosterol group were caused by the supplement, so they were not removed from the category.

Clinical Trial Results

93.5% of the participants, a large majority, completed all the phases of the study in full compliance with the regulations through to the 6-month follow up. Discontinued participants' measures and scores were calculated into the ITT evaluation. Even information and statistics of those who ended earlier in the Beta-Sitosterol group produced evidence of improvements of 1% or higher on IPSS and secondary testing score changes. However, the placebo group members also received unanticipated symptom improvements. They registered an average of 17% improvement in the IPSS score. This compares to the Beta-Sitosterol group, which measured a 58% improvement.

The Beta-Sitosterol group showed greater symptom relief levels in their mean primary testing score differences as follows:

- 8.4 points decrease in the IPSS score
- Quality of Life Score raised 2.7 points
- Qmax (or maximum void volume) was 6.8ml/s higher
- PVR was 39.5 mL lower

Timing of Scoring Improvements:

In both groups, scores improved the most within the first month of usage.

In both groups, the scores gradually improved through the 6-month period of usage, but not with as high a gradient.

The gradients and variants within the Beta-Sitosterol were not as contrasted as the scores within the placebo group were.

Beta-Sitosterol Improvement Levels in Score Variances:

1st Month = 24.6
3rd Month = 7.5
6th Month = 8.4

Observations, Comparisons, and Conclusions

It was only since the 1990s that scientific validation for the use of herbs and plant-derived extracts to treat BPH was confirmed through clinical studies such as this double-blind, placebo-controlled trial (1,16]. Early in the 1990s, the International Consensus Committee for BPH pressed for objective clinical studies proving the effectiveness of certain substances as they had been used for centuries and in more recent years as a less expensive, non-invasive, low-risk alternative for BPH treatment [13]. They inferred that gaining statistical evidence for precise measurements for the exact types of sterols and levels of treatment could benefit a greater number of BPH sufferers. Consequently, clinical pharmacological studies on the efficacy of medicinal phytosterol extracts have been becoming more and more frequent in the medical science communities.

The Success of Similar Beta-Sitosterol Clinical Studies

This study, as an example, established that accurate information and evidence of specifically Beta-Sitosterol's application in patients as a low risk/high-benefit treatment for decreasing the symptoms of BPH. Berges et al. recorded the results of subjects with BPH who were administered Beta-Sitosterol, as another example [17].

The administration of Beta-Sitosterol in the above-referenced study of the Prostagenix® brand of Beta-Sitosterol substantiated the claims of the merits of using it to treat BPH. This was measured by recording changes in the IPSS scores of participants in both groups, per the consultation of International Recommendations [13, 14].

In this trial, the Beta-Sitosterol group's IPSS scores lowered significantly and greatly improved in subjective QOL scores along with improved scores in Qmax and PVR. These were significantly better than the scores measured of the members of the placebo group.

Furthermore, no contingent side effects were discerned for the ProstaGenix participants.

Earlier, a pilot of this study was performed and produced a similar outcome [15]. Therefore, this research study was carried out. It also reflected similar results recorded by Berges et al [17].

Prostagenix® Study Compared to Berges et al.
These two studies were similarly structured [13.14].

However, there were some differences that should be noted.

First, they differed in kind of symptom scoring and dosage amounts and scheduling.

Scoring Method and Dosage Comparisons

Berges et al. applied a revised version of the Boyarsky symptom index as the primary and the IPSS as a secondary method of calculating changes [18]. The IPSS was only given three times during the follow up testing vs. 7 times as with the Prostagenix® Study. Instead of the 270mg three times daily, the Berges et al. required participants to take 20mg of capsules three times each day.

In both studies, the medical science community at large has criticized a lack of testing and calculating responses to each dose administered. The higher daily dosage in the Prostagenix® Study was used in to go far beyond the registered dose range in Germany for BPH treatment, based on a 15-year verifiable application of BPH usage as a phytotherapeutic option, based on antidotal reports of BPH symptom reduction reported with higher dosages of B.S. from the Landes Forest.

Placebo vs. Treatment Results

Compared to the placebo groups, both studies confirmed greater improvement of scores in the Beta-Sitosterol group in the Qmax and Quality of Life index. Both studies involved participants with similar PVR levels, and in both studies the participants' PVRs improved. In the Prostagenix® Study, by 33mL more than the placebo group and in the Berges et al., by 24 mL than the placebo group [17].

Rate of Results

During the first month of treatment, the improvements showed a more rapid incline than subsequent months of both trials. In both trials, this higher incline of improvements appeared both in the placebo and treatment groups. In the Prostagenix® Study, the incline during the first month accelerated marginally faster than in the Berges et al. study, by calculating a difference of 5.1 points between the treatment and placebo groups after 28 days [17].

Incidentally, these rapid improves during the first month reflect the same kinds of responses of participants in studies of finasteride and other alpha-blocking treatments [8.12.19].

Beta-Sitosterol Studies Compared to Other BPH Drug Studies

The main objective in the Prostagenix® Study was to measure the difference between the initial scores of the IPSS against the final scores as the percentage of change between the beginning and the end.

Beta-Sitosterol vs. Finasteride

In comparable studies of the effectiveness of finasteride, the volume size of the prostate at the beginning of the study vs. the end of the study was recorded as the defining factor to calculate levels of improvement. The focus of these studies reflected the main goal and claims of the finasteride drug to decrease prostatic volume [6,8,21]. The measurements used in the Prostagenix® Study remained consistent with Beta-Sitosterol's main purpose to relieve urinary symptoms associated with BPH. As such, no changes were recorded for prostate volume in the Prostagenix® Study [24]. The Berges et al. reinforced this as it did record the prostatic volume changes, which did not coincide with changes to the IPSS [17].

While Finasteride calculated significant size changes in prostate volume of the participants, the improvements in the Qmax recorded were only up to 4mL/s from patients' original scores. And this was after 10 months to a year of usage [20]. Similarly, after three years of usage, follow up in finasteride studies showed symptom improvement scores of 3.6 in some trials [8] and in other trials, an improvement of 6.4, with an improvement of 4 in their placebo group [22,23]. The finasteride treatment group scores show similar measurements to the scores of the placebo group in the Prostagenix® Study.

Beta-Sitosterol vs. Other Alpha-Blocker Drugs for BPH

In fact, other studies on the effectiveness of alpha blocking drugs on BPH symptoms typically record a level of symptom score improvements, some above and others below the Prostagenix® Study.

Alfuzosin:
Jardin et al. [10], improvements of 4 points in the symptom score, 3.1mL/s in Qmax, and 31mL in PVR (a 39% improvement).

Doxazosin:
Recorded 39% for total score [19], and 82% for urinary agitation and 90% for blockage symptoms [11] Qmax differences were no more than 2.9 mL/s [19], or 45% improvement [11]. Just two studies recorded PVR, which amounted to decreases of 15% - 72%.

Prazosin:
Outcomes recorded for Prazosin were most similar to the results of Doxazosin. Qmax improved by 6.9mL/s [26 – 28]

Terazosin:
[12,25] Calculated improvements in the symptom score of no more than 5.0 and for Qmax, 5.4mL/s.

Indoramin:
Measured improvements of 10 for Qmax [26 – 28]

Phenoxybenzamine:
Improvement of 6.2mL/s in Qmax [26 – 28]

Weighing Placebo Effect Factor

For accurate calculations, these results would need be compared to their respective placebo group scores changes as well. It would then be evident how much the specific medication in question affected the improvement level.

This is because it is established fact that the placebo effect is produced in pharmacological clinical studies across the board, especially when their participants have a strong desire to avoid costlier and more intrusive, possibly damaging, means of treatment.

BPH patients in particular have been reported at incurring a placebo response of even 40% or higher in trial settings.

In the Prostagenix® Study, the following placebo response levels were recorded:

IPSS = 29%
QOL Index = 33%
Qmax = 53%
PVR = 0

The Prostagenix® pilot study's outcome produced comparable placebo results. In fact, the placebo responses recorded in other Beta-Sitosterol studies and BPH drug studies calculated similar response levels. However, Berges et al. differed as the placebo group response scores were lower in all areas and higher in the PVR scores.

Therefore, it is evident from the Prostagenix® Study and studies like it that placebo responses must be recorded. Then the interpretation of the trial results must be calculated for the variants between the placebo and the treatment group scores in order to determine the effectiveness of the medication or supplement in question. Among the population of BPH suffers, this is particularly necessary, as shown in the Prostagenix® Study.

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