



HUMAN CLINICAL STUDY

Evaluating The Efficacy and Safety

of

An Herbal Topical Pain Relief Cream

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1.0 STUDY PURPOSE

The purpose of this randomized 10-day study was to evaluate an all-natural topical pain relief cream (Investigational Product, or IP) with respect to alleviating chronic arthritis pain and other symptoms using human subjects with a documented history of arthritis.

2.0 INTRODUCTION

Extracts from many dozens of plants from around the world have been applied to the relief of various symptoms we know as arthritis throughout the history of mankind. Previous studies have shown that a proprietary mixture of extracts of Juniper, Goldenrod, Dandelion, Meadowsweet and Willow is particularly effective in this area when ingested. The major pharmacologically active ingredients of these herbs include terpenenes, flavonoids, salicylates and complex glycosides, among others. The relief of pain and inflammation is via blockade of the production and release of certain prostaglandins and cytokines. They also act by blocking the production and/or metabolism of certain neurotransmitters and by affecting excess water removal. The mechanisms of action are similar to those of commonly prescribed anti-arthritic drugs, but without side effects known to the prescription products.

3.0 OBJECTIVES

This study was undertaken to determine if a topical preparation of these same herbal extracts and incorporating a common active ingredient, menthol, could provide effective relief from the arthritis symptom suite.

The primary objective is to assess the effectiveness of the IP for the relief of moderate to severe arthritis pain, the subjective effects of pain on daily living and the quality of life, and range of motion in affected joints used as target localities for application of the IP. The secondary objectives are to assess the safety and tolerability of the IP by monitoring the occurrence of adverse events, and to monitor reductions in the discretionary use of oral analgesic drugs for pain relief.



4.0 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the guidelines set by the World Medical Assembly (Declaration of Helsinki, 1964) and in accordance with good clinical practice guidelines set by ICH E6 (CPMP/ICH/135/95) and the FDA Guidelines for the protection of the persons submitted to clinical research.

All subjects for this study (or a legally acceptable surrogate) will sign an Informed Consent after having been fully informed of the nature and methods of the clinical trial and be given a signed copy. The subject's signature will be obtained prior to any study-related procedures being performed. HIPAA authorization will be obtained from all subjects.

5.0 STUDY DESIGN

This is a 10 day treatment study designed to investigate the effectiveness of the IP in the treatment of chronic muscle and/or joint pain and other symptoms of arthritis.

There were 83 subjects initially enrolled in the study and who were examined initially, received the IP in an unmarked tube, and were given instructions as to its proper application. Subjects were instructed to apply the cream to a target area three times per day, at approximately the same time, for ten days. Subjects enrolled at the screening / baseline visit (Day 1) were examined by a clinician to establish a baseline condition, received a follow-up phone call at Day 3, and returned at Day 10 (Final Visit) for an exit interview and clinical evaluation, and to return self-evaluation (Quality of Life) diaries. This study was performed and supervised by clinical research staff at Palm Beach Research Center, West Palm Beach, Florida.

5.1 SAFETY ENDPOINT

Clinical assessments and reported adverse events will be closely followed and reported.



5.2 FLOW OF EVENTS

| | Screenin g/ Baseline (Day 1) | Day 2 and Days 4-9 | Day 3 [±2 days] | Day 10 [±2 days] |
|--|---------------------------------------|--------------------------|--------------------|---------------------|
| Telephone Contact | | | X | |
| Informed Consent, Medical History, etc. | X | | | |
| Physical Exam | X | | | X |
| Vital Signs | X | | | X |
| Urine Pregnancy | X | | | |
| Concurrent Medications | X | X | X | X |
| Pain Self-Assessment* | X | X | X | X |
| Subject's Opinion | | | | X |
| Dispense Diary | X | | | |
| Dispense/Apply Study Drug | X | X | X | X |
| QoL Questionnaire | X | | | X |
| Record Adverse Events | X | | | |
| Global Assessment of Efficacy | X** | | | X |
| Collect Diary | | | | X |
| Collect Study Drug | | | | X |

***Recorded in Diary**

****5 minute post treatment evaluation**

5.3 INVESTIGATIONAL PRODUCT

The IP is a blend of active and inactive ingredients. The active ingredient is menthol. The inactive group is comprised of water, methyl glucose sesquistearate, proprietary herbal extract blend (juniper, goldenrod, dandelion, meadowsweet, willow), oil of wintergreen, avocado oil, stearic acid, aloe, grape seed oil, cyclomethicone, shea butter, steareth-10, phenoxyethanol methylparaben, cetareth-20, and steareth-2. Except for the herbal extract blend and oil of wintergreen, the inactive group elements are commonly used in the health and beauty aids industries as skin penetrants and skin softeners. Previous experience with preparations containing these ingredients has indicated that they pose no known adverse reaction threat.



5.4 SUBJECT SELECTION

The study enrolled 83 Male and female subjects at least 18 years of age experiencing chronic moderate to severe muscle pain and/or joint pain. Acceptable joint pain areas are areas that the subject can reach with their hands. Hand pain is unacceptable because of need to wash hands immediately after using the Investigational Product Cream to prevent eye injury. Generalized muscle pain was treated as long as the subject could self-apply.

5.5 Inclusion Criteria

1. At least 18 years of age.
2. Presently experiencing moderate to severe chronic pain in muscle and/or joint: Any area that subject can reach with a score of 50 or greater on a visual analog pain scale (1-100).

OR

Score 60 or greater on a visual analog pain scale (1-100) that is measuring their pain within the past 4 days of the baseline office visit (Day 1).

3. Female subjects must use an adequate method of birth control.
4. Female subjects of child bearing age must be willing to have a urine pregnancy test performed, and must have a negative result to continue.
5. Subject must be willing and able to sign the Informed Consent and to follow the study directions.

5.6 Exclusion Criteria

1. Females who are pregnant or lactating.
2. Surgery of any type within the past four months.
3. Joint implant or joint tissue replacement in any joint in the past 1 year.
4. History of active drug addiction within the past 3 months.
5. Subjects who are taking opioid analgesics for any reason.
6. Subjects diagnosed with any type of active cancer.



7. Subjects diagnosed with any other serious medical condition that, in the opinion of the investigator, would jeopardize the safety of the subject or affect the validity of the study.
8. Subjects who have used an investigational agent or device within the last 30 days.

6.0 DATA ANALYSIS and DEMOGRAPHIC

The experimental design for the major endpoints of this study is a single group repeated measures experiment with two observations per subject performed by clinicians at baseline and at 10 days. Interim data points at days 2-9 are primarily used to describe the time-course of the changes observed from baseline to study termination. The analyses assessed the change in subjective measures of pain, range of motion, and the effect of pain on the quality of life. These measures will be treated as continuous variables from visual analog scale measurements. Changes in the physiological parameters of inflammation, swelling, range of motion (ROM), and crepitus (joint stiffness) were measured on a five-point scale ranging from Very Severe to Very Mild by clinicians at intake and exit examination. The variables of height, weight, and gender were investigated for their utility in adjusting the major outcome variables.

The statistical models for the analysis of the continuous outcome variables will include repeated measures Analysis of Covariance (ANCOVA) using height, weight, and gender as covariates for each target variable. The variables measured on the 5-point scale were analyzed using the appropriate categorical models for testing whether the baseline and 10-day marginal frequencies are the same (this is similar to the repeated measures analyses for the continuous variables). Finally, a multiple Regression/Correlation analysis investigated relationships among all measurement variables. All statistical tests were performed at the $p \leq 0.05$ level of significance.

Ancillary (*ad hoc*) analyses were performed to assess the time-to-onset of any meaningful change in outcome variables. The time-to-onset was then correlated with 10-day levels and overall changes. These analyses were data-driven, and thus not be used for specific tests of efficacy.



6.1 Subject Demographics

There were 83 subjects initially enrolled into the study. Daily applications were completed by 78 subjects. The demographics of these subjects are shown in Table 1.

Table 1. Demographics

| | |
|----------------------|--------------------|
| Age | 38.6 ± 1.78 |
| <u>Race</u> | |
| Black | 55 (70.5%) |
| Caucasian | 21 (26.9%) |
| Hispanic | 2 (2.6%) |
| <u>Gender</u> | |
| Female | 53 (55.1%) |
| Male | 35 (44.9%) |

7.0 Results and Discussion

The pain experienced by each subject was indicated by the subject on a visual analog scale (VAS) ranging from 0 to 100. Higher VAS scores indicate more severe perceived pain. The product was applied three times a day for ten days with a VAS score being recorded at each application. A final VAS score was recorded at the end of the study. These data were analyzed in a repeated measures Analysis of Covariance (ANCOVA) for change in pain (pre to post) adjusting for age, gender, and race. The change in VAS score was statistically significant at $p < 0.0001$. There were no differences in the reduction of pain by age, gender, or race.

At the initial visit all subjects were examined by a clinician for the presence (yes or no) of inflammation, swelling, joint stiffness (crepitus), muscle pain, arthritis, and the extent of range of motion (poor to excellent). For this analysis ROM was categorized into two categories poor-fair-good versus very good-excellent. The percent of subjects getting statistically significant relief for these variables are shown in Table 2, below. Each variable was tested for statistical significance



using the McNemar Chi-Square test for change. There was a statistically significant reduction in the frequency of the presence of all of the physiological variables and a significant improvement in ROM from initial to final observation. Although the subjects recorded their own daily records for pain, etc., the noted reductions of swelling, inflammation, joint stiffness, and the noted increase in range of motion were observed by clinicians at the Palm Beach Research Center where the study was conducted.

Table 2. Percent of Subjects with Significant Condition Relief, by Condition and Time

| | % | p |
|----------------------------|----------|----------|
| Inflammation | 94.1 | < 0.0001 |
| Swelling | 63.0 | < 0.0001 |
| Joint stiffness (Crepitus) | 100.0 | = 0.0008 |
| Muscle Pain | 100.0 | < 0.0001 |
| Arthritis | 94.1 | = 0.0002 |
| Range of Motion | 93.8 | < 0.0001 |

These results represent statistically significant changes in patient condition. Fig.1, on the next page, shows this data expressed another way.

Fig. 1

Fig.1 shows that by the end of the study:

- 94.1% of study subjects got significant relief from each of arthritis and inflammation
- 63% of study subjects got significant relief from swelling
- 100% of study subjects got significant relief from each of muscle pain and joint stiffness
- 93.8% of study subjects got significant increase in range of motion in affected joints

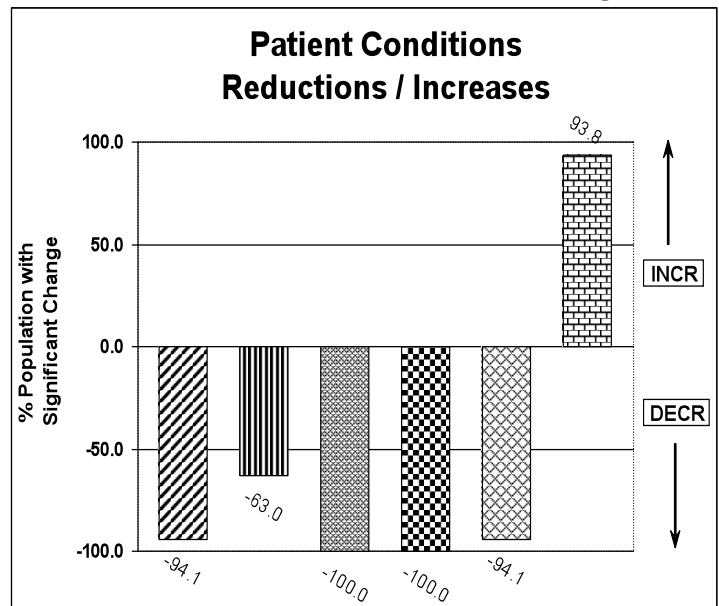


Fig. 2

Fig.2 shows that at the start of the study, before applying cream:

- 27.5% of study subjects had pain scores of 50-69
- 45.1% of study subjects had pain scores of 70-89
- 6.3% of study subjects had pain scores of 90 or higher

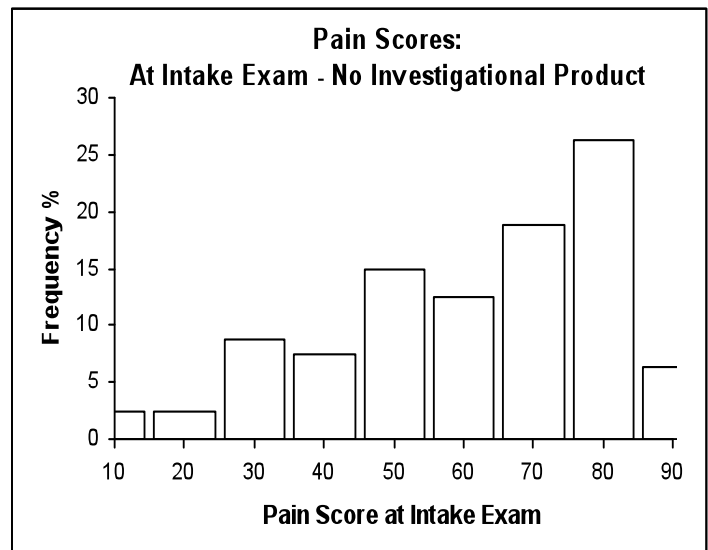


Fig.3 shows how the pain score distribution changed **within 5 minutes** after applying the IP.cream: **It is important to note that this figure represents the % amount of pain reduction, not pain scores.**

- 22.5% of study subjects got 50-69% relief from pain
- 41.3% of study subjects got 70-89% relief from pain
- 26.3% of study subjects got 90-100% relief from pain

This pattern of dramatic relief upon application of the IP held firm all through the study. The data shows that this IP does more than provide short-term relief. Each application of IP cream gave another burst of post-application high rate pain reduction shown in Fig.3.

Fig.4 shows the percent of **persistent** pain reduction present at the end of the study compared to the intake exam. These are the mean pain reductions in study subjects at the end of their between-dose time cycles and before the next dose of the IP cream.

Fig. 3

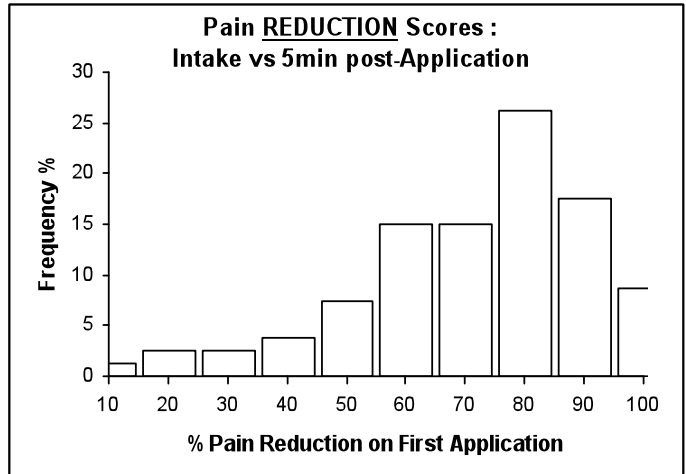


Fig. 4

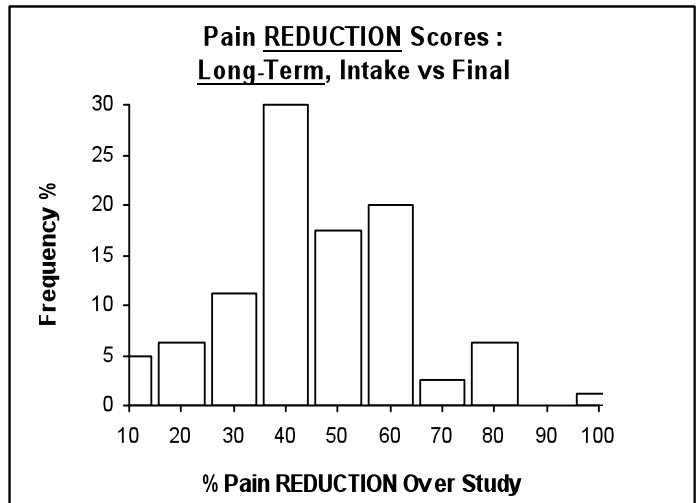


Fig 4 shows this residual relief level as:

- 41.3% of study subjects had 30-49% chronic pain relief
- 17.5% of study subjects had 50-59% chronic pain relief
- 20% of study subjects had 60-69% chronic pain relief
- 10.1% of study subjects had 70-95+% chronic pain relief



Daily mean pain scores among all study subjects showed a continuous decline during the study with no apparent plateau value, indicating that pain relief resulting from the application of the IP doesn't dissipate, but continues to accumulate as chronic relief. This is illustrated by the difference in frequency distributions of Fig.2 vs Fig.4. Since the decrease in daily mean pain scores across all study subjects did not plateau, we can conclude that the study did not show an end value as to how far pain relief would have gone. The causative mechanism of this observation is that the symptom relief provided by the herbal extracts driven into the sub-dermal tissues continues to increase as unmetabolized herbal extracts accumulate in those tissues because the cream is re-applied each day. This tells us that the cream not only addresses the issues of immediate relief, but it also provides ongoing chronic relief for symptoms which are undoubtedly chronic in nature.

8.0 SUMMARY

This study shows that:

- 60-95% of subject's pain was relieved in 73.8% of the study population in the first 5 min after application
- 67.5% of study subjects also experienced ongoing chronic pain reductions of 40-69%.
- 94.1% of subjects got significant relief from each of arthritis and inflammation
- 63% of subjects got significant relief from swelling
- 100% of subjects got significant relief from each of muscle pain and joint stiffness
- 93.8% of study subjects got significant increase in range of motion in affected joints

9.0 CONCLUSIONS

By all measures the treatment statistically significantly reduced pain, inflammation, swelling, joint stiffness (crepitus), muscle pain, and arthritis, and increased range of motion uniformly over time. The trend over time did not reach a plateau, which indicates further benefit would be obtained by longer treatment



or continuous use. The lack of adverse side effects when using this preparation indicates that it provides a suitable alternative to prescription drug therapies for these symptoms.