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A Randomized Comparative Pilot Study of a Topical Herbal Analgesic for the Management of Chronic Musculo-Skeletal Pain

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Abstract

Background: Chronic musculo-skeletal pain is relatively common in all age groups and may be the result of various traumas and the natural aging process. Pharmaceutical agents including non-steroidal anti-inflammatory drugs, opioids and other drugs are frequently used to treat the resulting pain in such patients. Because of the potential adverse effects associated with most of these drugs, the use of complementary and alternative therapies is relatively widespread among patients with chronic musculoskeletal pain. And topical analgesics can produce a local clinically effective concentration without the attendant systemic effects.

Objective: We performed a pilot study comparing the topical analgesic effects of a purified coconut based topical analgesic with diclofenac ointment and jasmine oil in participants with chronic musculoskeletal pain.

Study Design: Comparative pilot study.

Setting: St. Lucia Pain Institute, St. Lucia.

Participants: A randomized comparative pilot study was done with Fidapin (Test drug), Diclofenac ointment (FDA-approved NSAID) and Jasmine oil, after approval by the Ethics Board. One hundred and ninety six (196) participants were enrolled and randomized to the 3 groups using the nQuery Advisor version 7.0 software protocols.

Measurements: The primary outcome measure was the reduction in pain across the three groups. Follow up was by telephone contact at weeks 2 and 12, and a clinic visit at week 4.

Statistical Analysis: The 3 randomized treatment groups were compared with non-parametric Kruskal-Wallis rank tests

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due to the non-Gaussian nature of the data distributions. Categorical characteristics were compared with chi-squared tests. All analyses were based on an alpha of 0.05 and a power of 80%.

Results: All groups showed a significant decrease in pain and there was no statistical significance between the 3 groups.

Conclusion: This study suggested that fidapin, a topical analgesic with coconut oil as a base ingredient provides satisfactory analgesia comparable to topical diclofenac.

Keywords: Musculo-skeletal pain; Complementary and alternative medicine; Topical analgesics; Essential oils

Abbreviations: NSAIDs: Non-steroidal Anti-Inflammatory Drugs; ADHD: Deficit Hyperactive Disorder; NPRS: Numerical Pain Rating Scale.

Introduction

Chronic musculo-skeletal pain is relatively common in all age groups and may be the result of trauma and the natural aging process. Risk factors include age, gender, smoking, diet, limited education, low physical activities, low social economic status, psychological status and manual work. The direct and indirect costs are quite high on the individual as well as the society. Pharmaceutical agents including Non-steroidal anti-inflammatory drugs (NSAIDs), opioids and other drugs are frequently used to treat such patients. None of these most commonly prescribed conventional treatment methods for pain are sufficient to eliminate pain or to have a major effect on physical and emotional functioning in most patients with chronic non cancer pain. The best evidence for pain reduction averages only about 30% in about half of the treated patients, and these pain reductions do not always occur with concurrent improvement in function [1-8].

All of these pharmacological agents have potential side-effects and complications, some of which may include death. Acetaminophen, which is commonly used for musculo-skeletal pain may cause irreversible hepatic disease in some patients and has also been associated with Attention Deficit Hyperactive Disorder (ADHD) in children of parturients who took that drug during gestation. Non-steroidal anti-inflammatory drug (NSAIDS) were quite popular a few years ago but the resultant gastrointestinal complications, including severe hematemesis associated with costly hospitalization and even death have curtailed their use. Hepatic and renal complications may also occur with this group of drugs [9-12].

In recent times, the consequences of inappropriate use of opioid analgesic drugs have become so serious in the USA that both State and Federal Governments are taking active and definitive measures to deal with the associated health effects. Drug addiction, dependency, abuse, misuse, diversion and overdose are all common and the resulting challenges are major national, social, legal, cultural and economic issues of this decade. In many instances, patients who die from an overdose initially began using opioids for relatively trivial musculo-skeletal or myofascial lesions and then progressed to more potent drugs and larger doses [13-17].

The realization of these major problems in the USA, and the rest of the world has been another catalyst for the search for alternative agents to alleviate pain without these serious side effects. If a safe and affordable analgesic can be found to effectively treat chronic musculo-skeletal pain, this finding would not only offer many patients a satisfactory alternative to managing their chronic pain conditions, but would also reduce these national and global morbidity and mortality associated with current conventional analgesic agents.

Topical analgesics can produce clinically effective concentrations at a local site without the attendant systemic effects and associated adverse effects. There is good evidence for the use of topical diclofenac or ibuprofen in acute soft tissue injuries or chronic joint related conditions. Topical NSAIDS are more effective compared to placebos with a relative risk of 1.9 (95% CI 1.7 to 8.2) and an NNT of 4.6 (95 CI 3.8 to 5.9) in the short term [18-20]. However, studies of topical herbal products or their use in general musculoskeletal conditions are rare [7]. The general impressions that many herbal products have been used relatively safely for years and that these compounds have relatively few side effects, have been known for a long time, although there can be important clinical drug interaction. However, topical agents have mostly local effects. Thus, if the right combination of the active agents from these natural products could be produced in an acceptable format and consistency, then a topical analgesic can be offered as a safe and effective analgesic for the management of chronic musculo-skeletal pain.

Based on an in-depth chemical analysis of many plants, herbs and their oils, known locally to have analgesic

properties carried out in the country of Saint Lucia, their chemical composition and subsequent properties were determined and a topical analgesic agent (fidapin) was developed and approved by the National Board. It is a locally-produced, topical analgesic, which is made from natural and essential oils with coconut oil as a base ingredient [21]. The major ingredients include refined coconut oil, methyl salicylate, mineral oil (Drakeol 7 NF), Eucalyptus Oil, Nutmeg Oil, Camphor and another essential oil. Biodegradation, biostability and compatibility of the various components of Fidapin were also analyzed. Fidapin was produced locally using production protocols approved by the Bureau of Standards of the Ministry of Commerce in St. Lucia, the country where the study was done. The major objective of this pilot study was to compare the analgesic effects of fidapin with topical diclofenac and jasmine oil.

Methods

The study plan was reviewed and approved by the Committee for the Protection of Human Subjects of the Saint Lucia Pain Institute, the ethics committees of the Ministry of Health and the St. Lucia Medical/Dental Association. St. Lucia was chosen as the study site for a number of reasons: the population is relatively opioid-naive; chronic musculo-skeletal pain is quite common and most patients tend to use topical analgesics for musculo-skeletal pain management. Statistical power calculation using a confidence level of 95%, power of 80%, population variance of 1000, and a hypothesized difference of 10 indicated that 196 participants would be sufficient for the study.

Recruitment was via television, radio and newspaper announcements and interviews announcing the study. Participants were initially evaluated by two investigators after the initial triage screening by the Study Coordinator. At that screening visit, the participants were assessed using the inclusion and exclusion criteria. The inclusion criteria for the study were:

a. Chronic musculoskeletal pain of more than 6 weeks

b. Chronic axial musculoskeletal back pain affecting the cervical, thoracic, lumbar and sacral regions

c. Ages between 18 and 75 years

The exclusion criteria for the study were:

a. Patients receiving opioid or NSAIDs medications in the past 7 days.

b. History of spinal surgery.

c. Spinal Stenosis, active cancer or spinal cord lesions.

d. Uncontrolled Hypertension (BP>180/110) and/or severe Diabetes (hemoglobin AIC > 7.0).

e. Allergy to NSAIDs.

f. Gastro-intestinal disorders in the past 12 months.

g. Recent application of any topical agents to the affected area (in the past 7 days).

h. Allergy to any oils.

i. Active skin lesions or skin diseases or cutaneous manifestations of any systemic illnesses.

j. History of heart attack, stroke or thromboembolic phenomena.

k. Female subjects of childbearing age with a positive pregnancy test

Of the participants evaluated, 6 were excluded from enrollment for various reasons relating to the exclusion criteria. One hundred and ninety-six (196) participants were enrolled in the study and were subsequently randomized using a pre-determined computerized protocol (Figure 1). The randomized protocol used was the query Advisor version 7.0 software. The participants were assigned to one of three groups: the jasmine oil group; the Fidapin group and the Diclofenac group. Diclofenac, a well-known FDA-approved and commonly used Non-Steroidal Anti-Inflammatory drug was used as a topical ointment while both the Jasmine oil and the study drug (Fidapin) were dispensed in liquid form in a blue bottle (to prevent drug degradation by sunlight) with a pump-spraying device attached. Jasmine oil was used in the study due to its proven effects as an essential oil for stress disorders and analgesia. The Diclofenac ointment was dispensed in a tube labelled “study medicine”. All the medications including jasmine oil were dispensed in 5-ounce sizes which barring spillage or wastage would last for several weeks [22,23].

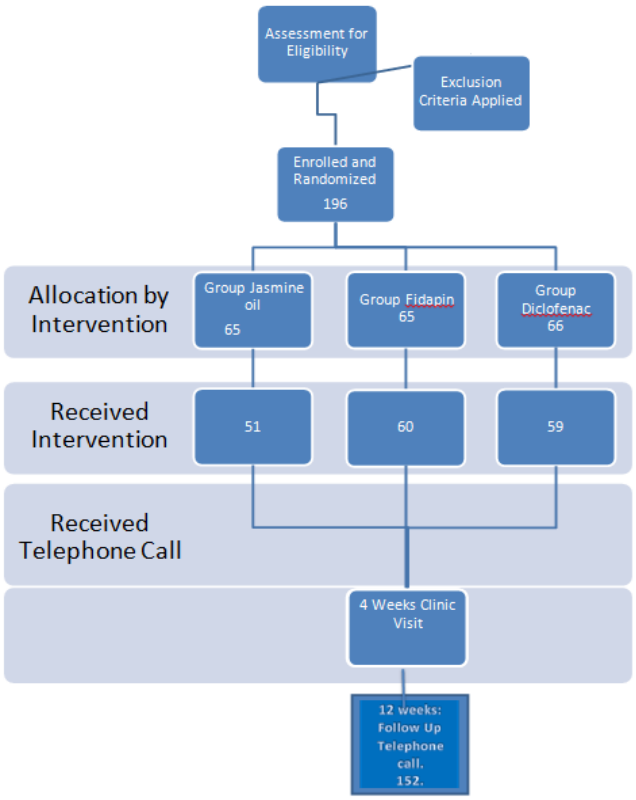

Figure 1: Study Flow Chart.

Participants were instructed in the technique for application and use of the various medicines to the painful site. Application was twice daily for 4 weeks. All participants signed Study Consent Forms. They received other precautionary warnings regarding the use and handling of the medicines including protection for the eyes. They were also given telephone numbers of the Study Coordinator and Principal Investigator to be used in case of an emergency.

All participants were contacted by the Study Coordinator after 2 weeks and pain score, satisfaction with the drug, satisfaction with the overall study and the presence of adverse effects were determined. Then, 2 weeks later (4 weeks after study commencement), participants were asked to return to the study office for follow-up clinical evaluation and determination of pain score, adverse effects and related data. All participants were paid a predetermined $50.00 EC (equivalent to about 18.50 US dollars) to cover the total costs of transportation to and from the study office for the duration of the study.

A 3 months follow-up telephone interview was conducted. Of the original 196 participants, 152 responded to the follow-up call which addressed continued pain and pain score, use of the various study drugs and subsequent satisfaction with the individual study agent.

Statistical Methods

The primary outcome measure was the analgesic responses to the 3 treatment agents as defined by the change in reported pain score from baseline. Numerical Pain Rating Scale (NPRS) was determined for each patient using a scale of 0 (no pain) to 10 (the maximum possible pain, for example, immersion of the hand in boiling water). That raw score was multiplied by 10 to obtain a percentage score. For example, if a patient was not precise and indicated that the pain was between 6 and 7, the patient was assigned a score of 65%.

The 3 randomized treatment groups were compared on these and other numeric outcomes with non-parametric Kruskal-Wallis rank tests due to the non-Gaussian nature of the data distributions. Categorical characteristics (race, gender) were compared with chi-squared tests. All analyses were based on an alpha of 0.05 and a power of 80%. A sub-analysis was carried out on the set of participants with lumbar pain, and a confirmatory

multivariable regression was performed to check the association of treatment and changes in pain after adjusting for baseline pain, type of pain (lumbar vs other) and prior duration with pain.

During the study, there were 11 protocol violations, which was immediately corrected. All analyses were conducted both on Intention-to-treat basis (as assigned) as well as on the basis of the actual treatment group.

Results

Demographics

196 participants were randomized to three groups; 26 did not respond, or were unavailable for follow up. 14(54%) of these non-responders were in the jasmine oil group, while 7(27%) were in the diclofenac group and 5(19%) were in the Fidapin group. 3 participants discontinued therapy. Two of these were related to pregnancy (one in the diclofenac group, and one in the Fidapin group). The third was due to allergy to diclofenac. Two participants in the diclofenac group dropped out of the study before participation began.

Overall, the mean (SD) age was 52 (12.7) years; within groups, it was 50.5, 53.3 and 52.2 for jasmine oil, Fidapin and Diclofenac groups respectively (no statistically significant differences between the groups). Sixty three percent were females and 37% were males. There was no significant difference between the treatment groups with respect to race (P=0.4548), gender (P=0.6170), age (P= 0.4538) or baseline pain (P=0.4538). Table 1 shows the baseline data and outcome results.

Effects on Pain

The average NPRS score at enrollment was 65, 69 and 68 % for Jasmine oil, Fidapin and Diclofenac groups respectively. The median NPRS score at enrollment was 65, 70 and 70 on the same scale for Jasmine oil, Fidapin and Diclofenac respectively. There was no statistically significant difference between groups on magnitude of pain scores or any change in pain scores, and this was the case in both the as-randomized analysis and the as-treated analyses (Kruskal-Wallis P=0.3243). All 3 groups showed significant decreases (Table 1) in pain scores from baseline to 12 weeks. Table 2 shows the reduction in severe pain at 2 weeks and to 4 weeks.

Group	Jasmine oil	Diclofenac	Fidapin	Stat. Significance
Age (years)	50.5	52.2	53.3	P=0.454 (NS)
Pain Location (% lumbar)	72.3	65.7	71.9	P=0.648 (NS)
Median Duration of pain (years)	4.0	7.5	8.25	P=0.151 (NS)
Average NPRS at enrollment (%)	65	68	69	P=0.324 (NS)
Median % pain reduction(3 months	40	30	37.5	

Table 1: Baseline characteristics and changes in pain and duration of use of study agents.
NS: Not significant.

Severe pain (>70/100)	Jasmine oil	Diclofenac	Fidapin
Initiation	34/65	33/64	31/65
At 2 weeks	14/65	10/64	8/65
At 4 weeks	12/65	14/64	9/65

Table 2: Proportion of participants in each group with severe pain (> 70/100).

The median duration of pain prior to commencing the study for all participants was 6.0 years. There was no significant difference between groups in the duration of prior pain with group medians of 4.0, 8.25 and 7.5 years for jasmine oil, Fidapin and Diclofenac groups respectively (P=0.1511). There was no good correlation between the magnitude of the pain and the duration of prior pain (P =0.1237).

All participants' musculo-skeletal pain was classified initially by main anatomical location: Cervical (14), Thoracic (26), Lumbar (137) and Sacral-coccygeal (14). A few others also had pain in the extremities, and some participants had pain in multiple locations. Lumbar pain was the dominant type of pain and the percentage was closely similar among the 3 treatment groups; 72.3% for the jasmine oil group; 71.9% for the Fidapin group and 65.7% for the Diclofenac group (p=0.6482). Since over two thirds of the enrolled participants had lumbar musculo-skeletal pain, there was a sub-analysis of that subset which showed no significant difference among groups on the magnitude of pain scores or change in pain scores. All 3 groups showed significant decreases in pain from baseline to 2 weeks and to 4 weeks (p<0.0001).

None of the participants taking Fidapin experienced any adverse effects. Four participants in the Diclofenac group and two in the jasmine oil group developed mild

superficial skin rashes which receded without therapy when the drug was discontinued. One patient in the Diclofenac group admitted that she was obtaining satisfactory pain relief from the application but after 5 days, she developed progressive radicular pain and paresthesia which were intensifying. These sensations subsided when the medication was discontinued but promptly reappeared when the Diclofenac was re-introduced. The study was discontinued in that patient after 8 days. The medication was not reintroduced for this participant for safety reasons. None of the participants who developed adverse effects required any medical interventions for the treatment of these effects.

Only 152 subjects from the originally enrolled participants were available for telephone contact for the 3 month post-study telephone interview. 54 participants in the Fidapin group, 53 in the Diclofenac group and 45 participants in the jasmine oil group responded. There was no difference among treatments in the 3-month post-study average pain score or in the current pain score.

Median change in pain from baseline to 3 months showed a decrease of 37.5%, 30% and 40% on the 100 point scale for Fidapin, Diclofenac, and jasmine oil groups respectively. This decrease was not statistically significantly different between the groups.

Discussion

Musculo-skeletal pain and myofascial pain are very common in most societies and in most countries. The pain is usually secondary to traumatic injuries, inflammatory lesions, and various arthritic and degenerative processes. While chronic Pain syndromes and their associated management have dominated the medical landscape for the past decades, there is no outstanding drug that reliably relieves pain without unacceptable complications and/or adverse effects. This is particularly true in the management of chronic musculo-skeletal pain syndromes [24,25].

In this pilot study, the study drug (fidapin) showed significant decrease in pain score in the participants that were comparable to topical Diclofenac. Participants in the jasmine oil group also showed significant decrease in pain, making the overall decrease in the study drug groups not statistically significant compared to jasmine oil. There are many possible reasons for this lack of statistical significance in the results. First, this was a relatively small study number (196 subjects). That number was influenced by the limited funding available for the project. In addition, jasmine oil in this study has an antispasmodic quality, and is often used over the counter for pain and as an aphrodisiac. The jasmine oil group in this study had pain for a median duration of 4 years prior to participation (compared to 8.25 years for the study drug and 7.5 for diclofenac). It is possible that this could have also contributed to the relative improvement compared to the other groups [23,26]. This could also have favored the jasmine oil and help to explain why there was no statistically significant difference compared to the trial agent. There was also no statistically significant difference between diclofenac which is an FDA approved analgesic agent and the study drug, or the jasmine oil.

However, continued use of agents among participants favored the study drug (fidapin) much more than the jasmine oil much more than diclofenac. The side effects profile also favored the study drug.

Diclofenac was dispensed in a tube. This was different from the pump spray device used for the study drug and jasmine oil. These differences in the study vehicles could have contributed to the results. But such differences in the carrier vehicle may not be important unless participants were able to meet and compare the study medications–which were very unlikely since they were recruited from all over the country and were not confined to a restricted geographical area.

Conclusion

The frequency of chronic musculo-skeletal and myofascial pain is high enough to justify the search for safe and effective analgesics. The currently available oral analgesics may provide some pain relief in some patients but the resulting complications may be very high. The many significant side effects warrant a continued search for an analgesic that may control chronic pain without major side effects or complications. This comparative pilot study showed that the study drug was similar in effectiveness to topical diclofenac, but has minimal side effects. It is also similar in effectiveness to jasmine oil. The number of participants in each study group was relatively small and therefore more expanded randomized, double-blind, placebo-controlled studies will be needed to confirm these findings.

Essential oils and herbal preparations have been around for decades. Properly prepared, their analgesic effects may be comparable to FDA approved agents, and with fewer side effects.

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