A HERBAL REMEDY DERIVED FROM SUBSPECIES OF ROSA CANINA, IMPROVES THE IMMUNE RESPONSE, WORKING CAPACITY AND WELL-BEING OF DOGS? A PARALLEL, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED STUDY

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Purpose: LitoVet a standardised powder made from subspecies of rose-hip (rosa-canina), produced by Hyben-Vital, Langeland, Denmark, has shown anti-inflammatory properties and improves the flexibility of joints and well-being in humans with osteoarthritis as well as in racing horse. It has also been demonstrated that the present powder improves the quality of human cartilage cells. The present study aimed to test whether the same powder might improve the immune response, working capacity and well-being of dogs.

Methods: Eighty six Greyhound dogs represented by both sexes mean age 4.25±1.75 years and weight 30.95±4.0 kg were randomly allocated to either LitoVet or placebo treatment for a three-month period. The animals were randomized in blocks of three with two dogs given LitoVet 10 gram daily as a dry powder added to the food and one dog given the same amount of placebo powder with a similar taste, odour and colour. Both groups were then treated for a three-month period.

The anti-inflammatory capacity was estimated as chemotaxis of peripheral blood neutrophil leucocytes using a Boyden chamber and opsonized zymosan as a trigger and by estimating the total leucocyte counts. Anti-oxidative capacity was estimated by using chemiluminescence. Working capacity, endurance, motivation for different activities including training, litheness, speed, mood and quality of the fur was evaluated by the staff training the dogs by using standardised questionnaires after 6 and 12 weeks, respectively. In addition speed was estimated as meter/second in hounds during competition. LitoVet and placebo treated dogs were compared using Mann-Whitney. A p value of 0.050 or less was regarded as statistically significant.

Results: In vitro studies on neutrophils indicated a dose-dependent anti-inflammatory and anti-oxidative capacity of LitoVet (p<0.048). Anti-inflammatory and anti-oxidative properties were also detected in vivo when the dogs had been treated for twelve weeks with LitoVet (p<0.046 and p<0.010, respectively). The questionnaires developed a consistent pattern. After 6 weeks treatment only litheness showed significant improvement in favour of active treatment (p<0.017). After 12 weeks of treatment a significant change in favour of LitoVet treatment as compared to placebo was seen in the following parameters: working capacity p<0.021, endurance p<0.047, motivation for different activities including training p<0.014, litheness 0.002, speed p<0.027, mood p<0.026 and quality of the fur p<0.045. The improvement observed in the questionnaires was supported by the estimation of speed in competing dogs. There was no significant change in appetite or weight.

Conclusions: The present data suggest that LitoVet exhibits anti-inflammatory properties in dogs and works as a strong antioxidant. This can explain why the actively treated group of dogs showed an improvement in so many different activities as working capacity, litheness, speed and quality of the fur.

HEALTH STATUS OF PATIENTS WHO RECEIVED TAPENTADOL PROLONGED RELEASE DURING AN OPEN-LABEL EXTENSION STUDY

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Purpose: Health status was assessed using the EuroQol-5 Dimension (EQ-5D) questionnaire in a 1-year open-label extension study of tapentadol prolonged release for the management of moderate to severe chronic pain (ClinicalTrials.gov Identifier: NCT00487435).

Methods: Patients were eligible for enrollment in this study if they completed 1 of 4 phase 3 studies (2 studies that evaluated the efficacy of tapentadol prolonged release and oxycodone controlled release compared with placebo in patients with osteoarthritis pain [NCT00421928] or low back pain [NCT00449176], a crossover study that evaluated dose conversion between tapentadol immediate release and tapentadol prolonged release in patients with low back pain [NCT00594516], or a 1-year study that evaluated the long-term safety of tapentadol prolonged release compared with oxycodone controlled release in patients with osteoarthritis or low back pain [NCT00361504]). Patients who completed either of the efficacy studies, the crossover study, or who received oxycodone controlled release in the 1-year safety study were titrated to their optimal therapeutic dose of tapentadol prolonged release (100-250 mg bid) during a titration period of up to 4 weeks, and all patients continued on their optimal dose during a maintenance period of up to 48 weeks. Patients who received tapentadol enhanced access in the long-term safety study continued on their optimal dose determined during that study. Average pain intensity during the past 24 hours was recorded every 4 weeks during the maintenance phase; mean pain intensity at endpoint was calculated using the last observation carried forward for values missing after early discontinuation. The EQ-5D measures health status using 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [3 possible levels: no problems, some problems, or extreme problems], as well as a health status index; patients completed an EQ-5D questionnaire at the end of treatment as well as at Months 1, 2, 3, 6, 9, and 12. Treatment-emergent adverse events (TEAEs) were recorded throughout the study.

Results: Patients (N = 1154) reported mean pain intensity scores of 3.87 at baseline and 3.65 at endpoint. At endpoint, the percentages of patients (regardless of prior treatment) who reported the most positive response to treatment were as follows: no pain or discomfort, 41.9%; no problems with mobility, 43.8%; no problems in self-care, 82.9%; no problems with performing usual activities, 46.6%; no pain or discomfort, 17.2%; and no anxiety or depression, 71.7%. Mean (standard error) changes from baseline on each dimension were as follows: mobility, -0.0 (0.01); self-care, -0.0 (0.01); usual activities, -0.0 (0.02); pain or discomfort, -0.1 (0.02); and anxiety or depression, -0.0 (0.01). The mean (SE) change from baseline in health status index was 0.0 (0.01). The most common (≥10%) TEAEs reported during the study were headache (13.1%), nausea (11.8%), and constipation (11.1%).

Conclusions: The efficacy of tapentadol prolonged release for the management of moderate to severe chronic pain and improvements in health status with tapentadol prolonged release treatment have been demonstrated and reported previously in phase 3 studies. Treatment with tapentadol prolonged release (100-250 mg bid) for up to 1 year in this open-label extension study maintained pain control and health status for patients with moderate to severe osteoarthritis or low back pain. These results support the long-term use of tapentadol prolonged release for the management of moderate to severe chronic pain.

SCREENING, RECRUITMENT AND BASELINE CHARACTERISTICS OF THE LONG-TERM EVALUATION OF GLUCOSAMINE SULPHATE (LEGS) STUDY PARTICIPANTS

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Purpose: Clinical trials evaluating potential ‘disease-modifying’ agents for osteoarthritis are required to demonstrate both symptomatic and structural benefit. Ideally, to reduce ceiling or floor effects, study participants are required to have at least moderate pain, yet retain sufficient tibiofemoral joint space to allow the measurement of narrowing over time. To describe study recruitment procedures and baseline demographics of people with symptomatic knee osteoarthritis participating in the Long-term Evaluation of Glucosamine Sulphate (LEGS) study (NCT00513422).

Methods: The LEGS study is a 2×2 factorial design randomised placebo-controlled clinical trial allocating participants to glucosamine sulphate (1500mg) and chondroitin sulphate (800mg) or matching placebo for two years. Participants are required to attend annual clinic assessments (including radiographs, knee MRI) and complete a bimonthly 7-day Participant Diary collecting prospective data on pain, physical activity, analgesia and work disability. Participants were recruited by small advertisements in local and national newspapers or directly from general practice. The LEGS study utilized a three stage screening process: 1. Telephone screening,
2. X-ray screening, and
3. Two week run-in period

Telephone screening was comprehensive and included questions on age, seafood allergies, co-morbidities (RA, bilateral knee replacements, unstable diabetes, recent lower limb surgery or intra-articular injections), intention to undergo joint replacement in next year, opioid use, informed that knee is ‘bone-on-bone’, willingness to be randomised, willingness to adhere to study procedures and level of knee pain ‘at its worst’ in the past week. The subsequent radiographic screening required evidence of predominant medial tibio-femoral joint disease but retaining at least 2 mm of medial joint space width in a sufficiently symptomatic (≥4 out of 10) knee. If still eligible, a two week ‘run-in’ period required adherence to study treatment capsules and return of a completed Participant Diary.

Results: From an initial 2,682 telephone enquiries, 605 people were randomised (October 2007-2009). The main barrier to recruitment was unwillingness to be randomised to placebo (Figure 1).

![Figure 1. Recruitment flowchart.](image)

Fifty percent of the radiographic ineligibility was due to complete loss of medial tibio-femoral joint space. A further 13% withdrew from participation during the ‘run-in’ period. The baseline demographics of the LEGS study cohort (Table 1) demonstrate the required screening pain of ≥4 out of 10 was not maintained at the subsequent baseline assessment (WOMAC) or 7-day Participant Diary by many participants.

<table>
<thead>
<tr>
<th>N=605</th>
<th>n, %</th>
<th>Pain and disability</th>
<th>Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (sd)</td>
<td>60.3 (8.2)</td>
<td>WOMAC pain (0-100)</td>
<td>33.2 (17.6)</td>
</tr>
<tr>
<td>BMI mean (sd)</td>
<td>28.9 (5.8)</td>
<td>WOMAC function (0-100)</td>
<td>32.4 (18.2)</td>
</tr>
<tr>
<td>Female</td>
<td>339, 56%</td>
<td>SF-12 PCS</td>
<td>41.3 (9.5)</td>
</tr>
<tr>
<td>Obese</td>
<td>214, 35%</td>
<td>SF-12 MCS</td>
<td>52.8 (10.0)</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>73, 12%</td>
<td>Mean pain over 7-days (0-10)</td>
<td>3.5 (1.8)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>195, 32%</td>
<td>Max pain over 7-days (0-10)</td>
<td>4.6 (2.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>138, 23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach problems</td>
<td>67, 11%</td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>62, 10%</td>
<td></td>
<td></td>
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<tr>
<td>Heart Disease</td>
<td>55, 9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>35, 6%</td>
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<tr>
<td>Paracetamol for knee pain</td>
<td>211, 35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs for knee pain</td>
<td>119, 20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: A comprehensive telephone screening reduced the burden of radiographic screenings. The two week ‘run-in’ of study procedures further reduced the number of participants likely to drop out soon after randomisation. It is difficult to identify people with knee osteoarthritis that have at least moderate ongoing pain, yet retain medial tibio-femoral joint space width >2mm.

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**NOVEL LIPOSOMAL GEL OF AN ANTI-INFLAMMATORY AGENT: RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL FOR EVALUATION OF THE EFFICACY AND SAFETY IN PATIENTS WITH SIGNS AND SYMPTOMS OF OSTEOARTHRITIS OF THE KNEES**

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**Purpose:** Non-steroidal anti-inflammatory drugs (NSAIDs) are the “Gold Standards” in the treatments of various pain and inflammation related disorders like arthritis. However, their oral administration and use of newer selective COX-2 NSAIDs known to induce severe intolerance in patients. Thus, the present work aims to compare the efficacy and safety of a diclofenac applied diclofenac in novel liposomal gel vis-à-vis marketed gel and placebo for relief of signs and symptoms in osteoarthritis (OA) of knee.

**Methods:** This was a randomized, double-blind, controlled trial on 36 patients with knee osteoarthritis. They were randomly assigned to liposomal gel, marketed gel and placebo, twice a day for 6 weeks. The patients were assessed by primary efficacy outcome measures included the changes from baseline to end of study on the WOMAC (Western Ontario McMaster Universities) Osteoarthritis Index. The radiographic imaging of OA in the knee was also performed for Kellgren-Lawrence criteria. Safety of the gel was also assessed by evaluating adverse events, vital signs, and irritation at the application site.

**Results:** In liposomal gel treated group, the pain, stiffness and difficulty performing routine activities showed statistically significantly improvements on 6 weeks of treatment compared to the other tested gels. While, all the treatments were found to be well tolerated with no observed adverse event.

**Conclusions:** Diclofenac in liposomal gel is superior to other tested formulations viz. marketed gel and placebo in the relieving the symptoms of OA of the knee. Hence, it can be concluded thatdiclofenac in liposomal gel can be a rational alternative to oral diclofenac formulations for management of various pain and inflammation related ailments including osteoarthritis.

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**OSTEOARTHRITIS DUE TO SURGERY FOR KNEE INJURY IN YOUNGER ADULTS**

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**Purpose:** The literature suggests ACL injuries and meniscal lesions are associated with the development of knee osteoarthritis (OA). There is limited evidence that surgical repair of these lesions diminishes future development of knee OA. A review of the long-term consequences of these injuries suggests that some 50% of those undergoing meniscectomy will develop OA between 10 to 20 years after the surgery. Estimates from the literature indicate that 10% to 90% of individuals with ACL injury develop OA within 10 to 20 years of the lesion. This raises the question as to what proportion of all knee OA cases might be associated with previous arthroscopic surgery.

**Methods:** A study to estimate the proportion of individuals who will develop OA after having arthroscopic surgery was designed by juxtaposing data form different sources. (a) Data on the age- and sex-specific rates of arthroscopic surgery (closed repair of the knee which includes meniscectomy and ACL repairs) in Ontario, Canada for the population aged 5-45 years, (b) data on the age and sex incidence of OA estimated from physician billing data in British Columbia, Canada, (c) Population data for Canada, and (d) estimates of the proportion of individuals with arthroscopic surgery who develop OA were combined to calculate estimates of the number of incident OA cases likely due to arthroscopic surgery at the end of a 10 year period. The rates of arthroscopic surgery were applied to the population to estimate the number of individuals with this type of surgery. OA incidence rates were also applied to the population to estimate the number of new OA cases every year. The following scenarios for the proportion developing OA over a period of 10 years were used: 10%, 20%, 30% and 40%. The main assumptions made were: constant arthroscopic rates and incidence rates of