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Measurement of pain relief resulting from administration of *Perna canaliculus* lipid complex PCSO-524™ compared with fish oil for treating patients who suffer from osteoarthritis of the knee and/or the hip joints

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| **Key words:** osteoarthritis, oil from Greenshell Mussel, fish oil.

Abstract

Aim: To compare, from baseline, pain relief, changes in the indicators of quality of life and safety for osteoarthritis patients taking a patented CO₂ stabilised oil from the NZ Greenshell Mussel *Perna canaliculus* (PCSO-524™) compared with patients taking fish oil (containing an industry standard EPA 18% and DHA 12% blend).

Material and methods: 50 patients older than 50 years from the Rheumatology Clinic at the Wrocław Medical University Hospital were administered randomly either Lyprinol® capsules that contained PCSO-524™ or fish oil capsules in a double-blind study. All subjects had a diagnosed history of osteoarthritis of the knee and/or the hip. The patients' characteristics are presented in Tables I and II. At baseline and then after four, eight and 12 weeks of treatment, information was collected using first the visual analogue scale (VAS) for pain; second the health assessment questionnaire (HAQ); and third the patient's own overall assessment of

the progression of osteoarthritis and their health condition. For patient safety control, before enrolment in the study and at the end of the study, patients had a blood cell count, ESR, ALAT and urine analysis.

Results: Patients treated with PCSO-524™ showed a statistically significant improvement of both their pain symptoms related to osteoarthritis and improved quality of their daily lives ($p = 0.05$) (Tables III-IV, Fig. 1-2). No side effects were observed with the patients who took PCSO-524™. Patients treated with fish oil showed significantly less improvement and a greater level of physical discomfort caused by the fish oil during the study.

Conclusion: Reduction of pain was statistically evident at four weeks among the subjects who took capsules that contained PCSO-524™. Practitioners can expect quicker long-term results with less risk of side effects for their osteoarthritis patients when they recommend products that contain PCSO-524™, compared with fish oil.

Introduction

Numerous clinical studies have shown that both *Perna canaliculus* oil (PCSO-524™) and fish oil (standardised to contain EPA 18% and DHA 12%) have anti-inflammatory activity that can contribute to reduced pain and improved joint mobility for patients who suffer from osteoarthritis (OA). It has been observed from the Mickelborough [1] asthma studies that substantially larger doses of fish oil during a longer time period were needed compared with similar studies that used the oil of

Perna canaliculus to note reductions in inflammatory markers. This preliminary study was undertaken to understand and establish the comparative and relative benefits of *Perna canaliculus* oil versus fish oil for subjects diagnosed to have osteoarthritis.

This study builds on the earlier double-blind placebo-controlled trial by Gibson *et al.* (1980) [2] carried out in the Victoria Infirmary in Glasgow and a subsequent double-blind trial [3] carried out in the Glasgow Homeopathic Hospital, which compared the lipid fraction of

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Perna canaliculus with the original freeze-dried preparation. These studies demonstrated significant improvements in making the extracts of *Perna canaliculus*. These improvements were the result of work by researchers in New Zealand, Australia and Japan who developed a stabilisation process that led eventually to a patented CO₂ supercritical extract of the non-polar lipids from the New Zealand Greenshell Mussel *Perna canaliculus*.

Gibson's subsequent research (1998) [3] and case studies (2000) [4] using both the stabilised extract powder and the stabilised lipid oil (now trademarked as PCSO-524™ and available commercially as Lyprinol®) confirmed the effectiveness of the stabilisation process and provided physicians with a new, safe and effective first-line therapy for the treatment of symptoms associated with OA and RA.

This study also follows many of the guidelines in the protocols used in 2004 by Professor CS Lau, Department of Medicine at the University of Hong Kong, Queen Mary Hospital, who conducted and published an extensive double blind placebo controlled study on the treatment of knee osteoarthritis using Lyprinol®, which contains PCSO-524™ [5].

Fish oil studies that have shown a reduced inflammatory response are also numerous and well documented. These studies covered asthma, exercise-induced inflammation and arthritis. Positive results usually require large doses of up to 20 g of fish oil to achieve a therapeutic dose. It is well known that fish oil should be used under medical supervision by people who bruise easily, have a bleeding disorder, or take blood-thinning medications. Large doses of omega-3 fatty acids may increase the risk of bleeding. It is also well known that fish oil can cause gas, bloating, belching and diarrhoea. Due to the known side effects of fish oil, and the fact that our subjects were elderly, we decided to conduct this preliminary study using smaller dosages of fish oil with comparable intake as would be prescribed for *Perna canaliculus* oil.

The significance of the study is comparative. Patients often use well-known analgesics such as paracetamol or ibuprofen for treating pain related to osteoarthritis. In the long term, analgesics may cause pain in the gastro-intestinal system and also affect the kidneys adversely. PCSO-524™ has been shown to be an effective complementary or alternative active ingredient for the treatment of OA and studies that are listed in the references have shown an absence of side effects. Large doses of fish oil are known to act as platelet aggregation inhibitors. If a smaller dose of *Perna canaliculus* oil can achieve the same anti-inflammatory benefits as larger doses of standardised fish oil this would provide practitioners with a safer first-line alternative without the risk of haemorrhage. It may also enable reduced usage of analgesics.

Material and methods

Characteristics of the group of patients involved in the study

The subjects were recruited from existing patients who attended the Rheumatology Clinic at the Wrocław Medical University Hospital. The inclusion criteria were restricted to clinically diagnosed knee and/or hip osteoarthritis patients older than 55 years, male or female and not currently taking anti-inflammatory prescriptive medication. These patients also had radiographic evidence of osteophytes or confirmation by medical image. Patients were excluded who had concurrent rheumatoid arthritis, other connective tissue disorders and those on prescription medication. Patients who took anticoagulants were automatically excluded from the trial.

Initially, there were 50 subjects in the study group. Twenty-five subjects were assigned randomly into one of two groups. Group A received capsules that contained PCSO- 524™ under the Lyprinol® brand. Group B received capsules that contained a minimum of 18% EPA and 12% DHA in fish oil.

There were 44 women and six men enrolled in the study. The group was diverse in terms of age, though the patients had to be more than 55 years old (average age in Group A was 65.58 years and in Group B it was 66.72 years).

The average weight of the patients in Group A was 78.2 kg and in Group B it was 75.7 kg.

The patient characteristics, comparing the two groups at baseline, did not show a statistically significant difference with regards to age, gender, weight, height, BMI, systolic blood pressure and diastolic blood pressure.

Nor was there a bias in one group with regards to the type of afflicted joint or type of joint pain as per Table I and Table II.

Randomisation

Randomisation was obtained by coded labelling of packs. Both preparations were filled into 150 mg capsules and had similar appearance and odour. Subjects were divided into groups A and B. Neither the patients nor the physicians who assessed the results knew which of the preparations had been allocated. The capsules and the dosing instruction (four capsules, 150 mg each, two times per day, i.e. 1200 mg of preparation per day) were given to the patients by the physicians in packages that were assigned randomly. It was unknown to all parties which of the preparations was given to Group A and which to Group B. The current treatment was not changed and no other drugs, except paracetamol as rescue medication, were introduced during the three-month study period for each subject.

Table I. Comparative characteristics of osteoarthritis subjects by type of the afflicted joint for group A and B

Type of Joint	Group A (PCSO-524™)			Group B (fish oil)			Row total
	Number	group A (%)	groups A + B (%)	Number	group B (%)	groups A + B (%)	
Only both knees	13	52	48.15	14	56	51.85	27
Only hip joints	4	16	57.14	3	12	42.86	7
Hip joints and spine	1	4	100	0	0	0	1
Both knees and hips	0	0	0	1	4	100	1
Nonspecific	7	28	50	7	28	50	14
Total	25	100	50	25	100	50	50

Table II. Comparative characteristics of osteoarthritis subjects by joint pain type for group A and B

Joint pain location	Group A (PCSO-524™)			Group B (fish oil)			Row total
	Number	group A (%)	groups A + B (%)	Number	group B (%)	groups A + B (%)	
Pain-related restriction of joint mobility	17	68	48.57	18	75	51.43	35
Nonspecific	7	28	58.33	5	20.83	41.67	12
Restriction of mobility of knee and hip joints	1	4	50	1	4.17	50	2
Total	25	100	51.02	24	100	48.98	49

Intervention treatment

The interventions used were:

- Lyprinol® (150 mg/capsule) which contained 50 mg of patented CO₂ extracted Greenshell Mussel non-polar lipid oil (PCSO-524™), 99.85 mg of pharmaceutical grade olive oil and 0.15 mg natural vitamin E as a stabiliser, which give total ingredients per capsule of 150 mg;
- fish oil (150 mg/capsule) which contained 150 mg of fish oil produced by Ocean Nutrition and contained total omega-3 (EPA & DHA), 18% EPA and 12% DHA area under the assay curve.

Each patient carried a number in relation to the intervention substance.

- Group A) Lyprinol® x eight capsules daily (four capsules twice a day for 12 weeks)
- Group B) fish oil x eight capsules daily (four capsules twice a day for 12 weeks)

Additionally, all groups received paracetamol as rescue medication. Every analgesic intake was recorded by the patient and assessed by the physician at four-week intervals.

Subjects completing the study

At the end of the study, all 25 subjects from Group A (PCSO-524™) completed the treatment. Only 22 subjects from Group B (fish oil) completed the treatment. Two patients from Group B were excluded because of adverse effects of the fish oil (diarrhoea, nausea, stomach aches, increased arterial blood pressure). One patient was excluded due to vacation commitments. Each subject commenced with a baseline assessment followed by three separate assessment sessions with the physician during a three-month period. The study was conducted during a nine-month period.

Study design

1. Visual analogue scale (VAS) for patient self-assessment of pain

The subjects provided an assessment of their OA pain level using the 100 mm visual analogue scale. This was reviewed with the physician at four-week, eight-week and 12-week intervals.

2. Health assessment questionnaire (HAQ) for patient self-assessment of activity

This questionnaire was designed originally for patients who had inflammatory joint disorders. It covers daily activities that require physical activity and mobility. These included dressing, arising, hygiene, reach, walking, eating, grip and activities. This was reviewed with the physician at four-week, eight-week and 12-week intervals. Improvement in the level of physical activities was considered to be an improvement to quality of life.

3. Improvement of health and disease condition

Both the patient and the doctor provided an overall assessment of health and disease condition. This was reviewed at baseline and at each four-week assessment until completion.

4. Safety

At the baseline and at the end of the study, the analytical testing included blood counts (white blood cells, red blood cells, haemoglobin, haematocrit, platelet count, liver function testing (AspAT, ALAT) and erythrocyte sedimentation rate (ESR).

5. Tolerance of the intervention treatments

At each four-weekly assessment, a doctor enquired about adverse reactions to the intervention treatment.

6. Statistical analysis

The randomised codes were broken by a statistician and the results were analysed independently for statistical significance by a medical statistician. The analysis of differences between two groups were performed by Mann-Whitney U-test in case of non-parametric distribution and by Student's t-test in case of parametric distribution. The differences in variables with regard to duration of treatment were calculated by ANOVA Kruskal-Wallis test in non-parametric distribution variables and ANOVA in parametric distribution variables. The differences in qualitative variables were

assessed by χ^2 test and by the differences between two structure indicators test. All results are presented as a mean \pm SD

Results

1. Visual analogue scale

The patient assessment pain scores for *intervention treatments* showed a significant improvement for PCSO-524™ after four weeks. The longer the period of administration of PCSO-524™, the greater the relief from pain and stiffness associated with the symptoms of osteoarthritis. Patients who were administered fish oil did not show initial improvement during the first assessment. No further improvements were statistically significant in the subsequent assessments for fish oil patients (Fig. 1, 2, Tables III, IV).

2. Health assessment questionnaire index

A definite improvement was observed in all the categories of the index for patients who were administered PCSO-524™. This is presented in the following charts with levels of significance at defined visits.

3. Improvement of health and disease condition

In 96% of patients from Group A, a significant improvement of overall health condition was observed and noted. In contrast, 62% of patients from Group B showed improvement (Table V).

4. Safety

There were no significant changes to blood parameters, liver function tests or erythrocyte sedimentation rate between the groups or during the study. It was observed that the subjects who took PCSO-524™ showed improvement in blood cell count (increase of haemoglobin, haematocrit and erythrocytes). This would need more extensive clinical evaluation in a larger trial.

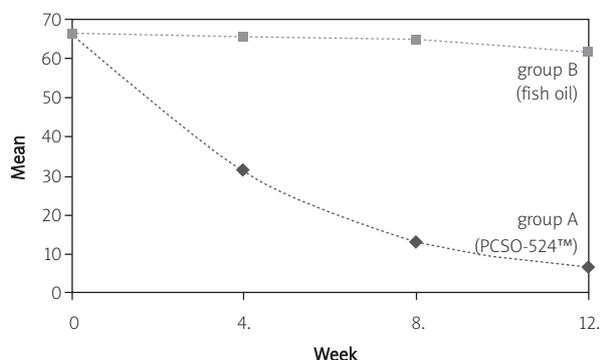


Fig. 1. Graph showing above VAS results for pain only.

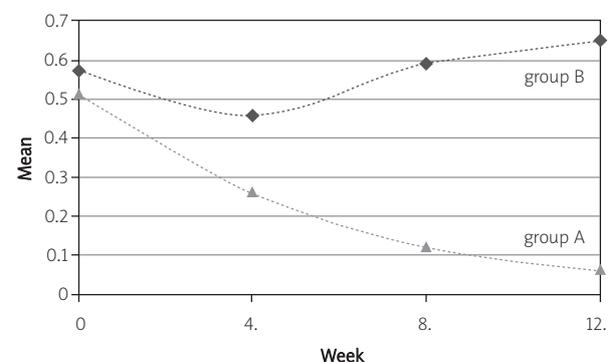


Fig. 2. Graph showing HAQ global score.

Table III. Summary of the visual analogue scale (VAS)

Assessment category	Group A (PCSO-524™)				Group B (fish oil)			
	week				week			
	0	4.	8.	12.	0	4.	8.	12.
Pain	66	31.56	13.28	6.88	66.39	65.46*	64.91*	61.52*
Disease activity	62.64	25.04	11.84	5.84	62.57	62.64*	59.67*	58.81*
General health	62.96	25.52	13.20	6.48	62.96	62.68*	61.10*	59.19*

**p* < 0.05

Table IV. Results of the Health Assessment Questionnaire (HAQ)

	Group	Week				Progression	Significance <i>p</i>
		Baseline	4.	8.	12.		
Dressing	A	0.30 (0.46)	0.10 (0.25)	0	0	-0.39	< 0.05
	B	0.48 (0.60)	0.41* (0.55)	0.43* (0.55)	0.43* (0.60)	0	ns
Arising	A	0.54 (0.63)	0.30 (0.46)	0.10 (0.35)	0.06 (0.30)	-0.38	< 0.05
	B	0.69 (0.62)	0.55 (0.50)	0.64* (0.57)	0.67* (0.62)	0.03	ns
Eating	A	0.32 (0.40)	0.15 (0.19)	0.07 (0.17)	0.04 (0.15)	-0.38	< 0.05
	B	0.29 (0.42)	0.30* (0.39)	0.27* (0.47)	0.29* (0.45)	0.05	ns
Walking	A	0.66 (0.55)	0.34 (0.45)	0.14 (0.27)	0.08 (0.24)	-0.48	< 0.05
	B	0.65 (0.75)	0.52 (0.56)	0.62* (0.71)	0.81* (0.70)	0.09	ns
Hygiene	A	0.47 (0.44)	0.13 (0.27)	0.05 (0.16)	0.07 (0.19)	-0.43	< 0.05
	B	0.47 (0.56)	0.39* (0.47)	0.48* (0.55)	0.56* (0.64)	0.09	ns
Heating	A	0.86 (0.59)	0.62 (0.46)	0.38 (0.42)	0.18 (0.32)	-0.49	< 0.05
	B	0.90 (0.79)	0.84 (0.61)	0.79* (0.77)	1.02* (0.81)	0.06	ns
Grip	A	0.28 (0.36)	0.13 (0.30)	0.05 (0.16)	0.01 (0.07)	-0.37	< 0.05
	B	0.35 (0.44)	0.38* (0.45)	0.42* (0.51)	0.48* (0.48)	0.14	ns
Activities	A	0.68 (0.52)	0.33 (0.36)	0.19 (0.33)	0.06 (0.21)	-0.34	< 0.05
	B	0.86 (0.70)	0.75* (0.52)	0.89* (0.71)	0.97* (0.73)	0.14	ns.
HAQ	A	0.51 (0.34)	0.26 (0.22)	0.12 (0.17)	0.06 (0.14)	-0.52	< 0.05
	B	0.57 (0.51)	0.46 (0.42)	0.59* (0.50)	0.65* (0.52)	0.1	ns
	all	0.54 (0.43)	0.35* (0.33)	0.33 (0.42)	0.34 (0.47)		

*differences between A and B groups – *p*<0.05

5. Tolerance

All 25 subjects in Group A reported 100% tolerance of the treatment without any side effects. In contrast, side effects from the fish oil were noted during the four-

week assessments of eight subjects in Group B. Two subjects had to withdraw and six subjects reported negative side effects. One patient withdrew for a vacation (Table VI).

Table V. Health and disease improvement (yes/no)

Improvement (yes/no)	Group A (PCSO-524™)			Group B (fish oil)			Row total
	Number	groups A (%)	A + B (%)	Number	groups A (%)	A + B (%)	
Yes	22	95.7	62.9	13	61.9	37.1	35
No	1	4.3	11.1	8	38.1	88.9	9
Total	23			21			44

Table VI. Tolerance of treatment

Tolerance	Group A (PCSO-524™)			Group B (fish oil)			Row total
	N	groups A (%)	A + B (%)	N	groups A (%)	A + B (%)	
Good	25	100	59.52	17	73.91	40.48	42
Quite good: constipation and stomach ache during the first month	0	0	0	1	4.35	100	1
Quite good: headaches cramps, pain in the kidney area	0	0	0	1	4.35	100	1
Generally good: nausea during the first day	0	0	0	1	4.35	100	1
Good (Influenza from) 01.10 to 06.10 and frequent pain in the liver area from 06.11 to 23.11	0	0	0	1	4.35	100	1
Bad	0	0	0	2	8.70	100	2
Total	25			23			48

Discussion

The aim of this clinical trial was to evaluate the comparative effectiveness of *Perna canaliculus* oil relative to fish oil for pain relief, quality of life and safety. The efficacy results for *Perna canaliculus* oil are similar to those reported in other studies [2–6].

The patients from Group A treated with *Perna canaliculus* oil showed a statistically significant reduction of pain, improved levels of mobility and activity and 100% tolerance, with no noted side effects. In comparison, patients from Group B treated with fish oil did not show a notable reduction in pain; there was no significant improvement of mobility or activity and 64% tolerance.

The researchers did not expect to observe such a major difference between Group A and Group B. This

result requires further explanation regarding the active substances in the two intervention treatments and the dosage levels.

PCSO-524™ is produced from the New Zealand green-lipped mussel, a common species found in the clean waters around New Zealand. The non-polar lipids are removed from the mussel using a patented CO₂ supercritical extraction process.

Between 2006 and 2008, Dr Theo Macrides led a team of researchers at the School of Medical Sciences, RMIT University, Australia, to analyse and explain the anti-inflammatory mode of action of the oil extracted supercritically from *Perna canaliculus*. [8] Three research papers were subsequently published on PCSO-524™ and help us to understand why this natural ingredient has such a high efficacy towards inflammatory disorders.

In the first paper [8], they analysed and found that PCSO-524™ is a very complex mixture of lipid classes and is unusually high in free fatty acids. Lyprinol® was then compared with fish oil, which was found to be less COX active. They found that fish oil was predominantly composed of triglyceride molecules that are rich in EPA and DHA, while Lyprinol® is more complex, with more than 60 lipid compounds. Seemingly, fish oil results in the release of inhibitory polyunsaturated fatty acids (PUFAs) that give it a similar mode of activity, but with less efficacy than Lyprinol®. The second paper [5] covered a preliminary toxicology assessment. The results showed that the CO₂ lipid extract and its free fatty acid (FFA) components contain biologically significant anti-inflammatory activity in vivo, with no apparent adverse side effects. In the third and most important study [9], the free fatty acid (FFA) class was isolated from the CO₂ lipid extract and the FFA components identified, which included a novel fraction that demonstrated a newly discovered inhibition of inflammatory markers. They actually discovered a new structurally related family of omega-3 PUFAs identified in their most bioactive fractions, which included C18:4, C19:4, C20:4, and C21:5 PUFA. C20:4 was the predominant PUFA in the *Perna canaliculus* oil and was identified as a structural isomer that mimicked arachidonic acid (AA). The novel anti-inflammatory compounds are now understood to compete much more efficiently than other pro-inflammatory fatty acids for the LOX and COX pathways.

Earlier work by Sinclair (2000) [10] shows the mechanism of anti-inflammatory activity to be based on the inhibition of the lipoxygenase pathway, which was responsible for the transformation of arachidonic acid in the cell membrane into leukotrienes. In this way, PCSO-524™ prevented the migration of neutrophils and alleviated the signs of osteoarthritis, such as pain, swelling and stiffness. This is a slow process, which takes usually four to eight weeks to show the first signs of pain alleviation.

In the present study, we observed a surprisingly rapid reduction of clinical symptoms associated with osteoarthritis notable within four weeks and continuous improvement over the 12 weeks of the study. This was in line with previous findings [4] that the lipid fractions of *Perna canaliculus* could achieve significant clinical improvements in less than a month in some patients who had rheumatoid arthritis.

There is much published literature [5] supporting the view that dietary n-3 polyunsaturated fatty acids (PUFA), particularly eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic acids (DHA, 22:6n-3), are important modulators of a host's inflammatory/immune responses. The literature also points to the need for large dosages of n-3

PUFA during a long duration if they are to be potentially useful as therapies for diseases characterised by immune dysfunction. Oliveira established results with fish oil after 12 months. The *Perna canaliculus* oil certainly showed that a quicker and more observable reduction in pain could be achieved with smaller dosages. There were no statistically significant results from fish oil for the administered dosage during the 12 weeks. This could have been due to the low dosage of fish oil and also to the short duration of the trial. However, we would not recommend larger dosages of fish oil for elderly patients.

It was further noteworthy that patients from Group A had less demand for a supportive treatment with paracetamol during the study. In contrast with Group B, only six patients from Group A decided to use additional treatment with paracetamol (36%), while in Group B 64.64% of the patients used additional paracetamol treatment to alleviate pain.

Conclusion

Stabilised *Perna canaliculus* oil is the first known natural inhibitor of LOX, the activity of which has been referenced in numerous clinical trials, with no adverse effects.

The patients from Group A judged the efficacy of PCSO-524™ positively with regard to pain relief within the first four weeks and considered it to be beneficial for their quality of life. Group A subjects continued to measure further reductions in pain during the 12-week period of the study. The benefits of fish oil were not evident during this 12-week trial. Given the potential side effects, large dosages needed and long duration required for fish oil, practitioners could consider stabilised *Perna canaliculus* oil as a safer and faster acting first-line medication for patients who suffer from osteoarthritis.

Subjects who received the fish oil will continue the study under the same protocol as the PCSO-524™ Group A patients. These results will be reviewed with discussion from other interested researchers and also reported.

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