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Flexofytol® (A Belgian Curcumin Extract) for the Treatment of Aged Patients with Osteoarthritis and Comorbidity

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Abstract

Introduction: Currently, the therapeutic arsenal of osteoarthritis includes several extracts of Curcuma including Flexofytol®, a bio-optimized extract of *Curcuma longa*. However, in older patients, indications for treatment might be limited by comorbidity and polymedication. Therefore, we aimed to assess the benefits and risks of Flexofytol®, in an older population with comorbidities. **Patients and Methods:** This retrospective observational study included 31 patients over age 70 years (medianage: 77 years, range 71 - 81) that were treated with Flexofytol for painful osteoarthritis of the knee or lumbar spine. These patients were initially weakened by diabetes (48%) and/or renal insufficiency (71%), or they were taking anticoagulants (35%). The effects of Flexofytol®, were evaluated at 0, 6 and 12 weeks with visual analog scales for pain and disability and the SF-12 Quality of Life questionnaire. Adverse effects and drug interactions of Flexofytol®, were evaluated. In particular, we evaluated renal function, diabetes parameters and coagulation tests. The data were analyzed with Kruskal-Wallis and Wilcoxon-Mann-Withney non-parametric tests. **Results:** Patients with Flexofytol®, showed significant improvement: pain improved by 50% (p = 0.0002) and functional disability improved by 33% (p = 0.0075). A series of quality of life parameters improved within the first 6 weeks of treatment and up to 3 months of treatment without impacting renal function, metabolic parameters or coagulation tests. We observed no significant adverse effects. **Conclusion:** In conclusion, our results suggested that Flexofytol®, may be useful in the management of painful osteoarthritis, particularly in older patients that are fragile due to comorbidity and polymedication. These initial results must be confirmed in future studies.

1. Introduction

When ageing, although the individual variations are important, our functional capacities decrease including cardiovascular, cerebrovascular and musculoskeletal functions as co-morbidities evolve. With age, managing comorbidities becomes increasingly more complicated and drug prescriptions grow in number (3.6 times more than in young individuals). These conditions lead to a high risk of drug-drug interactions and undesirable effects [1] [2].

The functional degradation that accompanies aging is aggravated by osteoarthritis. The prevalence of osteoarthritis also increases to above 37% after age 60 years. Its cardinal symptoms are pain and the associated reduction of physical capacity [2] [3].

As with younger patients, older patients with osteoarthritis are managed with anti-inflammatory drugs and analgesics. These drugs are given at increasingly powerful doses as the condition becomes more severe. Consequently, the prescriptions cause disturbances in postural balance and alterations in consciousness which lead indirectly to more frequent falls and loss of autonomy [4].

Among musculoskeletal disturbances associated with age, low back pain is common. It can be severe (56 ± 20 mm on a visual analogue scale of pain between 0 and 100 mm) in older patients (mean age 73.6 years) and it is sometimes quite disabling. Low back pain is relatively supportable during walking, but it becomes increasingly severe during prolonged sitting, more troublesome during physical activities and more disabling during prolonged standing [5].

Another musculoskeletal disturbance associated with aging is knee pain. Knee osteoarthritis occurs rarely before age 30 but it becomes very common after age 60 years. Its prevalence was estimated at 15% in women aged 70 years and 30% after age 85. Moreover, the pain associated with knee osteoarthritis increases dramatically with age [6].

Management strategies of osteoarthritis in older individuals aim to preserve the best possible functional independence and quality of life. This aim explains the increase in prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics [7]. On the other hand, these prescriptions increase the risk of severe side effects. Moreover, these drugs have been linked to cartilage degradation [7] [8].

Epidemiological studies have shown an increasing incidence of renal insufficiency with age, particularly after 70 years. This is partly due to the high prevalence of chronic diseases in older people, especially diabetes, and cardiovascular diseases. Renal insufficiency is associated with high mortality [9].

The risk of renal insufficiency is particularly high in patients with pre-existing

renal disease and in patients that take NSAIDs chronically [9]. Thus, NSAIDs administration should be avoided particularly on a continuous basis, and alternatives should be proposed [9] [10].

In addition, the American Geriatrics Society (Recommendations 2015), has also recommended avoiding NSAIDs in older patients because, in addition to their gastrointestinal toxicity, they can induce water retention and heart failure [4].

Many older patients require chronic anti-coagulation with anti-vitamin K or new oral anticoagulants, to reduce the risks of heart rhythm disorders, stroke and thromboembolic disease. Although these patients do not require commonly biological monitoring, they are at risk of drug-drug interactions.

Gastrointestinal, renal and cardiac risks as well as anticoagulation are each a relative contraindication for NSAIDs. These concerns have increased the interest in proposing other treatments for osteoarthritis.

The polypathologies and polymedications associated with age carry a major risks of side effects. Ageing is often associated with changes in physiology that affect pharmacokinetics and pharmacodynamics [1].

Consequently, because aged patients with osteoarthritis are often fragile and multi-treated, they could benefit from a management strategy that controls pain and functional disability without adverse effects and without drug-drug interactions.

However, the efficacies of "chondroprotective agents" in the management of osteoarthritis such as glucosamine, chondroitin, etc. remain unclear [10].

Approximately 3000 to 4000 years ago, curcumin was extracted from the root of *Curcuma longa* and became part of the therapeutic arsenal used in Ayurvedic medicine.

Curcumin is effective in many indications such as wound healing, joint pain, digestive disorders, breathing difficulties. It also has anti-inflammatory and antioxidant properties, which are potentially interesting for treating osteoarthritis.

In previous clinical studies, curcumin was tested for treating osteoarthritis. Different formulations of curcumin were compared to anti-inflammatory drugs, placebo, chondroitin and glucosamine. Treatment lasted from 4 weeks to 8 months and outcomes also included cytokine assays and oxidative stress tests. In most studies, curcumin was found to be superior to placebo for improving pain, joint flexibility, walking and quality of life, and the use of painkillers. For markers of inflammation, collagen degradation and oxidative stress, curcumin was equivalent to non-steroidal anti-inflammatory drugs. Several previous studies have indicated that curcumin played a protective role in renal function particularly in diabetic nephropathy. In addition, its anti-inflammatory and antioxidant effects decreased insulin resistance in diabetes [8] [11] [12] [13] [14].

Flexofytol•, a bio-optimized extract of Curcuma, is obtained by a process that improves the assimilability of curcumin. Flexofytol• has been shown to reduce markers of collagendegradation, oxidative stress, and inflammation. Probably as

a consequence, patients treated with Flexofytol• for osteoarthritis reported decreased pain, improved joint flexibility, and improved quality of life by the sixth week of treatment [15] [16]. The efficacy of curcumin in osteoarthritis can also be illustrated by its protective effect against cartilage degradation measured with the Coll-2-1 marker [17].

Apart from diarrhea which occurs with high dose, Flexofytol• appears to cause no adverse effects.

Based on those findings, curcumin, particularly Flexofytol•, might hold a special place in managing older patients with osteoarthritis due to its a beneficial effect on pain and functional disability, and its lack of adverse effect. It may even have a chondroprotective effect and improve renal function and carbohydrate metabolism.

Conversely, curcumin is also capable of inhibiting the generation of thrombin or factor X in vitro, it may affect prothrombin time (PT) and the activated partial thromboplastin time (aPTT), and cause hemorrhage [18] [19].

This study aimed to assess the effect and tolerance of Flexofytol• in old patients with chronic comorbidities suffering from osteoarthritis.

2. Patients and Methods

The study was approved by the Hospital-Faculty Ethics Committee of the Erasmus Hospital on October 22, 2015 (CCB Reference: B 406201525621).

This study included 31 patients (11 men, 20 women; mean age 76 ± 8 years, median age of 77 years (71 - 81) (EIQ) with painful osteoarthritis of the lumbar spine or knee. After providing written informed consent for study participation, patients were treated with Flexofytol• (2 - 4 capsules daily) for 12 weeks by a geriatrician or rheumatologist

We collected data on clinical information before and after treatment, including the severity of pain (0 to 10 on an analogue visual scale), functional disability (0 to 10), the SF-12 Quality of Life questionnaire [20], adherence to treatment, the clinical response and tolerance to treatment. We also recorded changes in concomitant therapies.

The patients either had diabetes or carbohydrate intolerance (defined as fasting glucose greater than 100 mg/100mL and a ratio of glycosylated hemoglobin / haemoglobin ratio greater than 40 mmol/mole) [21], (n = 15) and/or defined renal insufficiency (creatinine clearance lower than 60 mL/min among MDRD formula) [22]. Renal insufficiency was defined as laboratory values of urea and creatinine that were above normal range. Eleven patients, 11 were also taking anticoagulants (anti-vitamin K, antithrombin or antiXa drugs).

Non-Gaussian continuous variables (Wilk-Shapiro test) are expressed as the median with interquartile range (EIQ, percentile 25 - percentile 75). Repeated measurements (time 0, 6 weeks and 3 months) were analyzed globally with the nonparametric Kruskal-Wallis test and the comparisons 2 to 2 by Wilcoxon-Mann-Withney nonparametric test. To avoid elimination of patients when

missing data for repeated measures were present, we did not use a test for repeated measures but a test for independent measures (Kruskall Wallis). This test was less sensitive and thus leaded to less significant results. The outliers data were kept in the analysis.

Categorical variables are expressed in percentages and compared with the Chi² test. P values <0.05 were considered significant.

3. Results

3.1. Clinical Benefits of Flexofytol®

As shown in Figure 1, pain decreased by 50% in the first 6 weeks of treatment (p = 0.0002). This analgesic action persisted for 3 months (p = 0.0004).

During the first 6 weeks of treatment, this effect was accompanied by a 33% reduction in functional disability (p = 0.0075), which also persisted for at least 3 months (p = 0.0056; Figure 2).

Several patients experienced issues in performing quality of tasks listed in the SF-12 which required moderate efforts such as moving a table, vacuuming, playing balls ... (question 2a), or climbing a staircase (question 2b) due to their general health condition. Those patients did not feel any difference in performance after Flexofytol® treatment.

On the other hand, due to their physical state under the influence of the treatment, patients felt less limited in doing things they desired (question 3a and 3b, p = respectively 0.012 and 0.004 to 6 weeks and p = 0.007 and 0.003 to 3 months) (Figures 3-5).
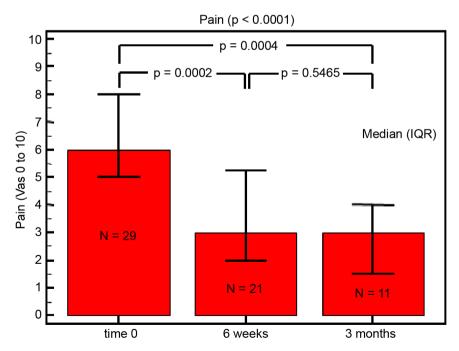

Figure 1. Pain reduction during Flexofytol treatment. Pain was measured on the visual analogue scale (VAS) where 0 was no pain and 10 was the mostpain imaginable. P-values were evaluated with the Kruskal-Wallis test.
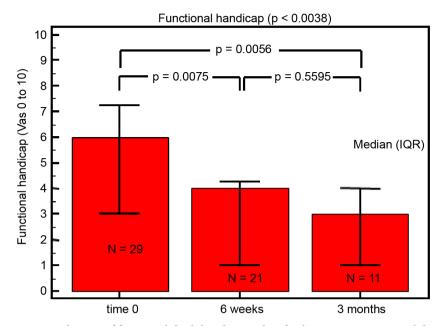
Functional handicap (p < 0.0038)

Figure 2. Reduction of functional disability during Flexofytol treatment. Functional disability was measured on a visualanalogue scale (VAS) where 0 was no disability and 10 was complete loss of function. P-values were evaluated with the Kruskal-Wallis test.
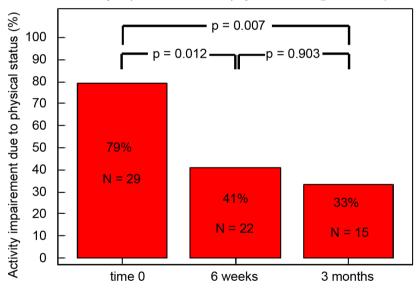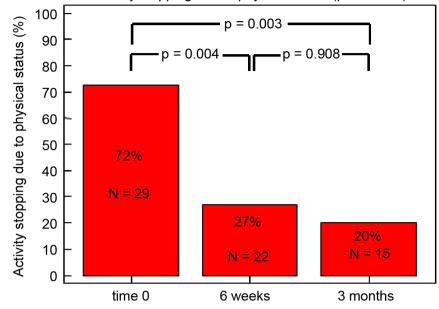
Activity impairement due to physical status (p = 0.0014)

Figure 3. Improvement of impairments in activity during Flexofytol treatment P values were evaluated with the Chi^2 test.

Discomfort due to physical pain during work or domestic activities found in question 5 was reduced at 6 weeks (p = 0.0063) and at 3 months (p = 0.0032).

No significant changes were noted during treatment for other SF-12 items. For example, patients retained their general perception of the health status (question 1) and their more emotional perceptions such as doing less than they wanted or performing with as much care or attention as they wanted (question 4). Moreover, they reported no changes in feeling embarrassed with others

Figure 4. Reduction due to Flexofytol treatment of activity stopping because of physical condition (SF12 question 3b).

Figure 5. Decrease of activity impairment during Flexofytol treatment. (P-value was evaluated with the Kruskal-Wallis test).

(question 6) feeling calm and relaxed, overflowing with energy, or feeling sad or dejected (question 7).

Treatment tolerance was excellent. No significant adverse effects were reported ($p = 0.4512$).

Other medications taken by patients were not modified during the study period ($p = 0.7706$).

3.2. Absence of Flexofytol Effect on Blood Parameters

In all patients, none of the diabetes variables was significantly modified during treatment such as blood glucose (p = 0.9886) and glycosylated hemoglobin (p = 0.5508). Moreover, renal function parameters remain unchanged including urea (p = 0.7305), creatinine (p = 0.7395) and uric acid (p = 0.5907). The coagulation tests showed no change in PT (p = 0.3233) or aPTT (p = 0.2655).

The lack of effects on blood indicators of renal, hepatic and metabolic functions and on coagulation tests was confirmed when groups of patients with diabetes or renal insufficiency were studied separately (Table 1).

Table 1. Absence of effect of Flexofytol treatment on blood parameters of patients with diabetes and renal insufficiency.

DIABETE (n = 15)		Before			After			p-value
		N	median	IQR	N	median	IQR	
INR	Units	7	1.02	(0.97 - 1.17)	9	1.00	(0.937 - 1.085)	0.4581
Prothrombin ratio	%	8	25	(24.5 - 29.55)	9	25.6	(24.7 - 55.15)	0.6298
Urea	mg/dl	14	41.5	(37.5 - 50.75)	12	41.5	(31.25 - 55.5)	0.7771
Creatinine	mg/dl	14	1.2	(0.95 - 1.49)	13	1.1	(0.85 - 1.3)	0.3679
Uric acid	mg/dl	13	5.7	(4.75 - 8.25)	8	5.5	(4.42 - 7.52)	0.7172
GOT	IU/L	14	22	(15 - 28.25)	13	23	(18.5 - 28.5)	0.3302
GPT	IU/L	14	15.5	(11.75 - 23.25)	13	23	(17.5 - 35.5)	0.0801
GammaGT	IU/L	13	22	(16 - 43.5)	12	26.5	(21.5 - 57.5)	0.4138
Alkaline phosphatase	IU/L	12	57	(55.25 - 74.75)	12	65.5	(53.25 - 76.75)	0.9769
Glycemia	mg/dl	13	110	(101 - 133.5)	9	117	(93.5 - 127)	0.5039
HbA1c	mmol/mol	8	44	(40.25 - 55)	11	45	(40 - 57)	0.8038

RENAL INSUFFICIENCY (n = 22)		Before			After			p-value
		N	median	IQR	N	median	IQR	
INR	Units	8	1.01	(0.945 - 1.59)	11	1	(0.92 - 1.03)	0.4308
Prothrombin ratio	%	10	25.65	(24.275 - 31.55)	11	26.3	(25 - 43)	0.3239
Urea	mg/dl	19	44	(38 - 65)	15	50	(35 - 72)	0.7286
Creatinine	mg/dl	19	1.2	(1 - 1.4)	16	1.1	(0.985 - 1.377)	0.6659
Uric acid	mg/dl	16	6.15	(5.125 - 8.275)	11	6.1	(4.2 - 8)	0.6214
GOT	IU/L	17	21	(16.5 - 25)	15	22	(17 - 27)	0.8497
GPT	IU/L	17	18	(13 - 23)	15	20	(14 - 26)	0.6634
GammaGT	IU/L	15	23	(17 - 29)	14	24	(17.5 - 31.25)	0.8785
Alkaline phosphatase	IU/L	14	56	(51.5 - 87.75)	13	54	(53 - 98.5)	0.884
Glycemia	mg/dl	15	109	(94 - 119)	12	122	(92.75 - 131)	0.3536
HbA1c	mmol/mol	8	42.5	(38.5 - 49.25)	13	45	(40 - 54)	0.6631

4. Discussion

This preliminary observational prospective study reported results from a reallife experience of Flexofytol® treatment in older patients (median age 77 years) with risk factors. Although limited in terms of number of patients, our results suggested that this treatment could make a difference in pain, functional disability, quality of life and functioning in everyday life, particularly for patients weakened by diabetes and/or renal insufficiency.

Flexofytol® treatment was well supported: no adverse effect was observed over the treatment duration (6 weeks to 3 months). These findings suggested that Flexofytol® holds promise as an alternative to NSAIDs which are known for their side effects and contraindications, particularly in older patients and those with renal and/or anticoagulation disturbances. Flexofytol® treatment did not change any biological parameters in terms of improvement or degradation and it had no impact on coagulation.

These findings must be interpreted with caution. The study limitations were its observational design, the small number of patients (n = 31) and the short follow up duration (3 months). Therefore, we could not draw any definitive conclusions.

A placebo effect might have contributed in part to the reported good effects of the treatment on pain and functional disability. However, the placebo effect could not entirely explain the treatment mode of action because Flexofytol® did not have any impact on the emotional or relational aspects of daily life as reflected in the SF12 questionnaire results.

Our study must be confirmed with controlled and randomized studies to determine whether Flexofytol® holds promise as an alternative to anti-inflammatory drugs.

A survey conducted in 2016 by general practitioners had previously shown that Flexofytol® provided multiple benefits due to its favorable effects on pain, flexibility, quality of life, anti-inflammatory drugs consumption and clinical tolerance in general population of adults with osteoarthritis of the knee and hip [12]. The present study confirmed those results in older patients with multiple chronic conditions (77 years median). Moreover, we showed that Flexofytol was welltolerated in a population with fragile health due to comorbidities such as renal insufficiency and/or diabetes and/or coagulation/haemorrhagic risks.

Research on the mode of action of curcumin has suggested that the extract is likely capable to improve renal function and carbohydrate metabolism, which was not confirmed in our study. Yet, the lack of improvement may be due to a duration of treatment too short and/or a too limited number of patients.

Other studies have suggested that curcumin could prolong prothrombin time and aPTT. This property was not confirmed in the present study with Flexofytol. However, again, the study design (number of patients, duration of drug exposure…) may have limited our power of detection. Moreover, new anticoagulants that do not modify these parameters may have contributed to the lack of detec-

tion [18] [19].

5. Conclusion

In conclusion, the results of this preliminary study suggested that curcumin and its derivative Flexofytol might be useful in managing the symptoms of osteoarthritis in older patients and/or patients in fragile conditions due to co-morbidities and polymedication. These findings are subject to confirmation in future studies.

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