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A naturally-inspired, curcumin-based lecithin formulation (Meriva® formulated as the finished product Algocur®) alleviates the osteo-muscular pain conditions in rugby players

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Abstract. – OBJECTIVE: Curcumin is one of the most investigated phytochemical products because of its low toxicity and its broad spectrum of bioactivity, including anti-inflammatory and analgesic properties. A new delivery form of curcumin, resorting to phosphatidylcholine (Meriva®, formulated as the finished product Algocur®) has been developed to increase its bioavailability. In this study, we tested the efficacy and safety of a Meriva®-based product in rugby players suffering by different osteo-muscular pain conditions

PATIENTS AND METHODS: In this pilot study, 50 male rugby players with osteo-muscular pain due to traumatic injuries, physical overload or acute episode of chronic pain were recruited and treated with conventional analgesic drugs (n = 25) or Meriva®-based product (n = 25) for a maximum of 10 days. The pain perception and the functio laesa were evaluated at baseline and after 1, 3, 6, 10 and 20 days from the initiation of the treatment protocol. Treatment tolerability, compliance, and adverse events were also reported.

RESULTS: During the study, the analgesic effect decreased in both treated group compared to baseline, starting from the third day of treatment. Similarly, the impaired physical function evaluated after 3, 6, 10 and 20 days improved in Meriva®-based product treated group and in subjects treated with conventional analgesic drugs, compared to the baseline condition. The percentage of excellent adherence to treatment or tolerability was higher in the Meriva®-based product treated group. Only 1 (4%) subject treated with Meriva®-based product experienced adverse events whereas 4 (16%) subjects treated with conventional analgesic drugs reported gastric pain as an adverse event.

CONCLUSIONS: Despite the small sample size and the group heterogeneity, this study suggests that the naturally-derived, curcumin-based delivery form, Meriva® (formulated as the finished product Algocur®), could represent a promising safe, analgesic remedy in painful osteo-muscular conditions associated with intense, high impact, physical activities.

Key Words:
Curcumin, Meriva®, Bioavailability, Analgesic, Algocur®, Pain.

Introduction

Curcuma longa is a member of the *Zingiberaceae* (ginger) extensively cultivated in Asia, India, China, and other countries with a tropical climate. Its rhizome is usually processed to obtain a yellow powder, the turmeric spice, largely used in Asian food. Furthermore, turmeric powder has been traditionally used in Chinese and Ayurvedic medicine, particularly as an anti-inflammatory and for the treatment of flatulence, jaundice, menstrual difficulties, hematuria, hemorrhage, and colic[1]. Curcumin, also called diferuloylmethane, is the most abundant, natural polyphenol, found in the rhizome of *Curcuma longa* (turmeric) and others *Curcuma* species. Typically, monomolecular curcumin is present with other so called minor

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curcuminoids (demethoxycurcumin – DMC, bisdemethoxycurcumin – BDMC) and their mixture is generically referred to as curcumin in the biomedical literature.

Several studies investigated the beneficial effects on health of this polyphenolic compounds, showing that curcumin (i.e. natural curcumin, the mixture of curcuminoids) possesses various biological and pharmacological properties such as antioxidant, anti-inflammatory, hepatoprotective, anticarcinogenic, and antimicrobial properties; in addition curcumin plays a role in cardiovascular disease, respiratory disorders, neurological and gastrointestinal disorders[2]. In particular, curcumin modulates the inflammatory response in different ways. Curcumin decreases the production or inhibits the pathway of the primary mediator of inflammation, tumor necrosis factor-α (TNF-α), by affecting the methylation of its promoter, by regulating its histone acetyltransferase-dependent chromatin transcription, by binding its ligand and by directly forming inhibitory interaction with this molecule[3]. Beside TNF-α, curcumin also inhibits the activation signaling of inflammatory nuclear factor (NF-kB), a transcription factor that controls the expression of various cytokines and the major histocompatibility complex genes[4,5]. Therefore, the anti-inflammatory effects of curcumin include also all mechanisms mediated by NF-kB, such as the down-regulation of factors that mediate matrix degradation, prostanoid production (cyclooxygenase-2), apoptosis (Bax and activated caspase-3), and stimulation of cell survival (Bcl-2)[5]. Recent *in vitro* and *in vivo* studies on transient receptor potential ion channels also provided the biologic rationale for the use of curcumin as analgesic[6,7]. Regretfully, the beneficial properties of curcumin are greatly hindered by its instability at physiological pH, low solubility in water and rapid clearance resulting in a low oral bioavailability. To overcome these limitations, a phytosomal formulation of curcumin (a solid state dispersion of curcumin with phosphatidylcholine) has been developed and tested in several clinical trials[8].

The use of natural, tolerable and safe anti-inflammatory and antalgic approaches to alleviate the pain should be an important priority, in particular in young subjects frequently exposed to intense physical activities, injuries and traumatic events such as athletes engaged in high impact and ball sports[9]. In this light, the efficacy and safety of a phytotherapeutic oral formulation containing phytosomal curcumin (Algocur®, PharmExtracta Srl, Pontenure, Piacenza, Italy) were evaluated in rugby players suffering by different osteo-muscular pain conditions. Particularly, in this pilot study, the analgesic properties of this Meriva®-based product, as well as its tolerability, were compared with those of conventional drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs).

Patients and Methods

In this pilot study, 50 male rugby players with osteo-muscular pain due to traumatic injuries, physical overload or acute episode of chronic pain were recruited. According to the Declaration of Helsinki, all patients signed a written informed consent before entering into the study. The study protocol was approved by the Ethic Committee of Ausl Piacenza. Algocur® has received notification n. 70748 from Italian Ministry of Health on the 5th June 2014.

Enrolled subjects received conventional analgesic drugs for 3, 5 or 10 days according to physician's choice, or 1 tablet of Algocur® every 12 hours for 5 or 10 days (each tablet of Algocur® containing 1 g of Meriva®). Concomitant standard management, as well as intensive management with additional anti-inflammatory or analgesic drugs, were also allowed.

The following parameters were evaluated at baseline and after 1 (T1), 3 (T3), 6 (T6), 10 (T10) and 20 (T20) days from the initiation of the treatment protocol:

- Pain perception, estimated according to the visual analog scale devised by Scott-Huskisson (from 0 = none to 10 = intolerable)
- *Functio laesa*, scored by an arbitrary scale ranging from 0 = complete physical function to 10 = maximum impairment of physical function.

Treatment tolerability (ranked as very poor, poor, fair, good or excellent), compliance (ranked as very poor, poor, fair, good, very good), and adverse events were also evaluated.

Statistical Analysis

Data were described by using descriptive statistics (mean and standard deviation for continuous variables; percentages for categorical variables) and exploratory comparisons were performed by applying the non-parametric one-way ANOVA on ranks test or Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of participants and treatment details are shown in Table I.

No differences between subjects in the Meriva®-based product group (n = 25) and conventional analgesic drugs group (n = 25) were observed in term of concomitant additional therapy received during the study.

The analgesic effect scored by the VAS significantly decreased compared to baseline in both treated group, starting from the third day of treatment (T3) (Figure 1). Similarly, the impaired physical function evaluated at T3, T6, T10, and T20, resulted significantly improved in subjects treated with Meriva®-based formulation and in subjects treated with conventional analgesic drugs, compared to the condition at baseline (Figure 2). Noteworthy, the number of subjects showing an excellent adherence to treatment was higher in the group treated with Meriva®-based product (24, 96%) compared to conventional analgesic drug-treated group (15, 60%) (exploratory *p*-value = 0.005) (Figure 3). Moreover, the tolerability was scored as excellent by 24 (96%) subjects who received Meriva®-based formulation, and by 14 (56%) subjects treated with conventional therapy (exploratory *p*-value = 0.002) (Figure 3). Among participants undergoing Meriva®-based treatment only 1 (4%) experienced diarrhea as an adverse event; on the other hand, 4 (16%) subjects treated with conventional analgesic drugs reported gastric pain as an adverse event.

Discussion

Curcumin is one of the most investigated phytochemical products because of its broad spectrum of bioactivity and the very low oral toxicity. Unfortunately, the low absorption and poor systemic bioavailability of curcumin have strongly limited its therapeutic applications. Several new formulations and delivery systems have been developed and tested to overcome these issues, including the use of adjuvants and nanoparticles, liposomes, micelles and phospholipid complexes[8,10]. Phytosome®, a phospholipid based delivery system, is a patented technology to finely disperse phytochemicals into phospholipids such as phosphatidylcholine[11]. Several studies investigated the safety and efficacy of phytosomal curcumin in the treatment of various human disorders, including osteoarthritis[12-16]. Overall, these studies suggested that phytosomal curcumin (Meriva®) can be used as a complementary treatment in the management of osteoarthritis, particularly to relieve pain and increase the motor functions[12-14]. Recently, a pilot comparative study on the analgesic properties of phytosomal curcumin (Meriva®) – when administered at a higher dosage than the one typically used for the chronic complementary treatment of osteoarthritis (1 g/day) – and two conventional analgesic drugs in subjects suffering from recurrent acute pain episodes, showed a similar antalgic action in all treated group, reporting less gastric symptoms in Meriva®-treated subjects[17].

Table I. Baseline characteristic of the study groups and treatment details.

	Algocur® (n = 25)	Conventional analgesic drugs (n = 25)
Age, years		
Mean ± SD	27 ± 7	30 ± 72
Range	17-52	18-40
Type of pain, n. subjects		
Traumatic injuries	4 (72%)	5 (20%)
Physical overload	3 (12%)	14 (56%)
Acute episode of chronic pain	18 (16%)	6 (24%)
Treatment duration, n. subjects		
3 days	0 (0%)	17 (68%)
5 days	23 (92%)	6 (24%)
10 days	2 (8%)	2 (8%)
Concomitant additional therapy, n.subjects		
Standard management	9 (36%)	6 (24%)
Intensive management	3 (12%)	0 (0%)

SD: standard deviation.

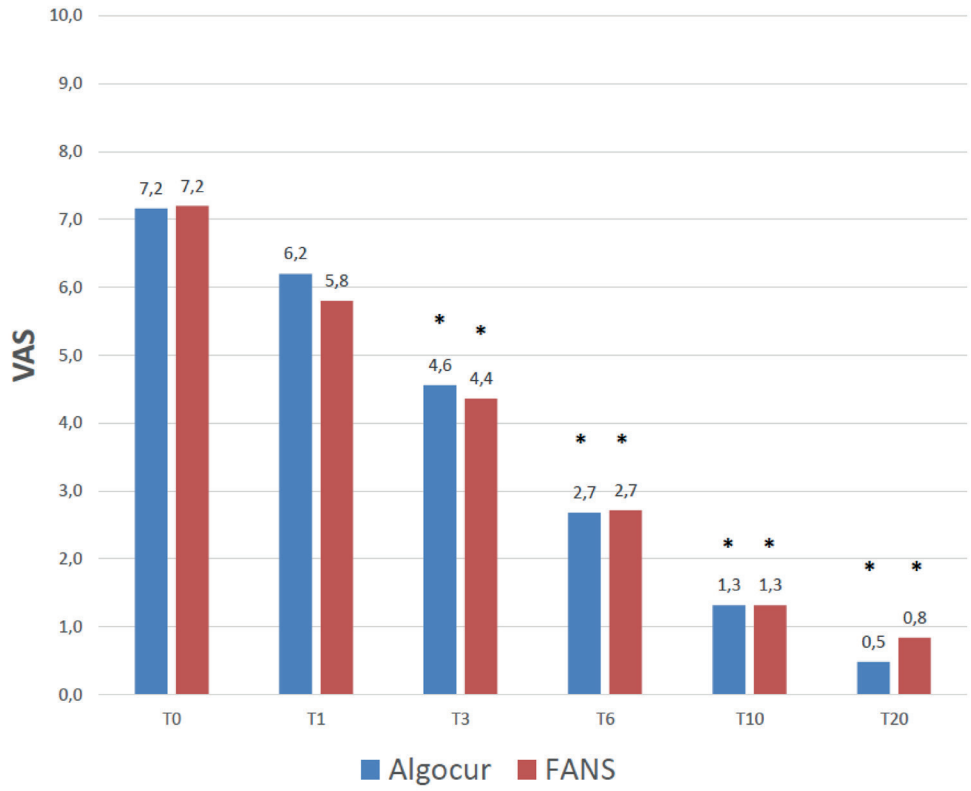

Figure 1. Evaluation of pain by a visual analogue score (VAS) at different time points. *Indicates $p \leq 0.05$.

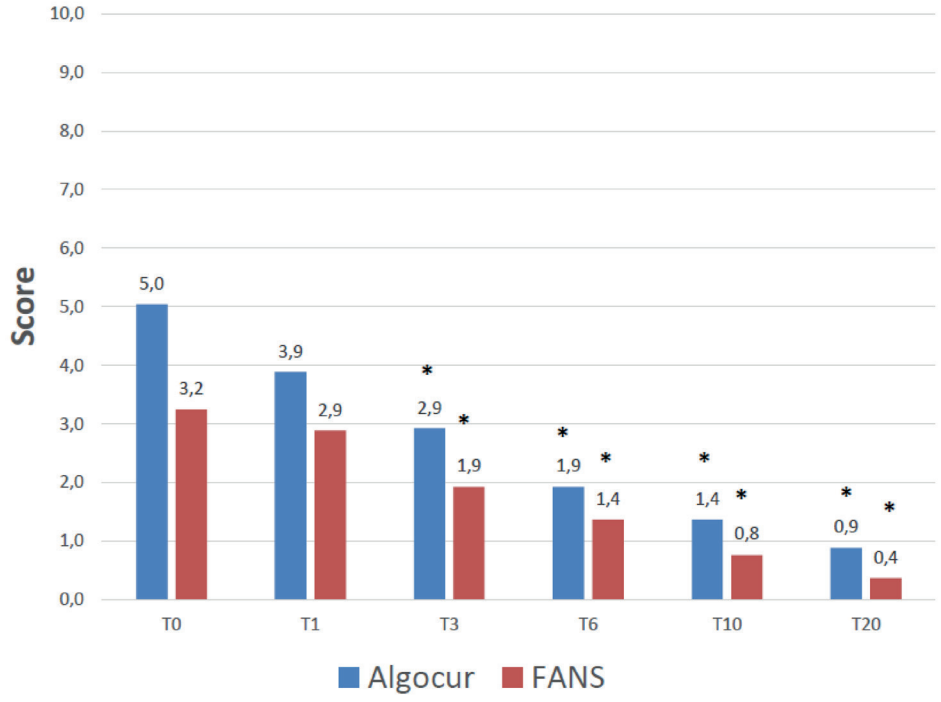

Figure 2. Impaired physical function (functio laesa) assessed at different time point. *Indicates $p \leq 0.05$.

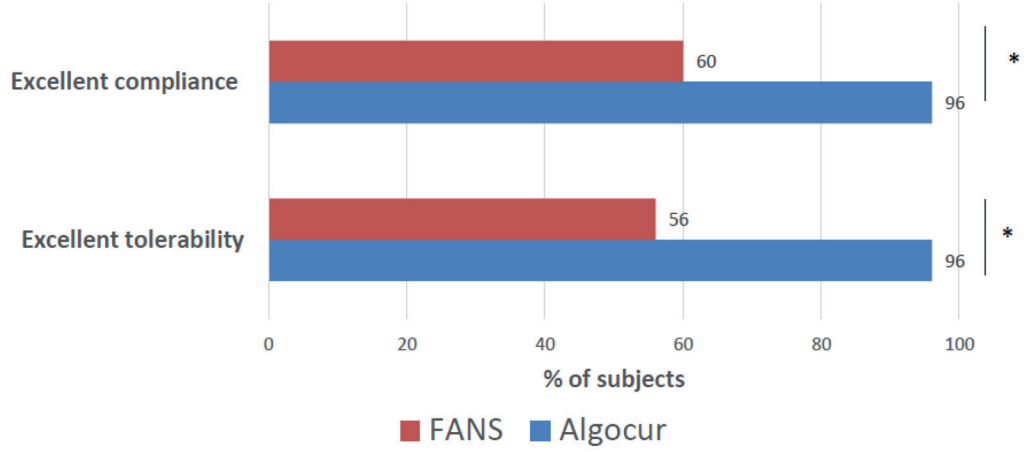

Figure 3. Percentage of subjects with excellent tolerability or excellent compliance to treatments. *Indicates $p \leq 0.05$.

Similarly, we found that the treatment with a Meriva®-based formulation, Algocur®, decreased pain and improved the impaired physical functions in rugby players suffering by different osteo-muscular pain conditions even with a short-term treatment. It is worthy of note that subjects treated with Algocur® experienced less gastrointestinal adverse events than the other treated group. Therefore, in this study, we confirm that a Meriva®-based product, even when administered at higher dosages than the typically suggested for chronic treatment of osteoarthritis, is a safe and tolerable agent that might prevent the common gastric side effects associated with the use of many anti-inflammatory and analgesic drugs.

In our study, impaired motor and physical functions following traumatic injuries and physical exercise overload were also totally recovered in subjects treated with Algocur®. Similarly, recent studies also showed that Meriva® improved strength and physical performance in elderly subjects[18] and reduced the delayed onset muscle soreness (DOMS) due to eccentric muscle activity[19]. These effects are likely associated with the reduction of pain perception as well as with the anti-inflammatory and anti-oxidative properties of Meriva®.

However, our results should be considered preliminary and larger trials on subjects with homogeneous osteo-muscular pain conditions and with a homogenously-treated control group should be planned to better characterize the effects of curcumin.

Conclusions

The naturally-derived, lecithin-based delivery form of curcumin, Meriva® (formulated as the finished product Algocur®), could represent a promising safe, analgesic remedy in painful osteo-muscular conditions associated with intense, high impact, physical activities, exerting its beneficial effect even with a short term treatment.

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Conflict of Interest

ST is an employees of Indena S.p.A. LG is a consultant for Indena S.p.A. The other Authors declare no conflicts of interest.

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