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A Single-Center, Double-Blind Placebo Controlled Study to Evaluate the Efficacy of Kre-Celazine®, an Oral Buffered Creatine-Cetylated Fatty Acid Compound, in its Ability to Reduce Site-specific Inflammation and Pain

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KEY WORDS

Kre-Celazine,® buffered-creatine compound, fatty acids, joint and muscle inflammation.

ABSTRACT

In order to determine whether an oral, alkali buffered-creatine – cetylated fatty acid compound was capable of reducing site-specific chronic joint and muscle related inflammation/pain with equal effectiveness, 35 subjects, each fulfilling the entrance criteria, were divided into 2 groups – Group A ("Test Compound" group) and Group B ("Placebo group"). Each participant took the same number of capsules irrespective of their group assignment, for 30 consecutive days. Efficacy was based on the final evaluation of pre and post blood tests, physical examinations (entrance and exit) and participants' "Pain Journal" comments. Results indicated that approximately 100% of ankle/foot pain, 80 - 85% of neck/ shoulder/elbow/wrist and hand pain, 71% of knee pain, respondents in Group A rated their "compound" better than/as good as a prescription product in its ability to reduce/eliminate pain. Hip and back pain scores for Group A were no better than placebo scores. Group A experienced a modest increase in mobility (35%), but no measurable increase in range of motion over and above that experienced in Group B. The alkali buffered-creatine – cetylated fatty acid compound exerted its greatest impact on areas of inflammation/pain in the extremities, as well as in the neck and shoulder region.

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INTRODUCTION

Chronic inflammation and muscle pain affects the body's ability to execute fluid motion. Ensuing joint stiffness restricts range of motion (ROM), which in turn negatively impacts quality of life (QOL). Chronic inflammation is a primary reason for doctor visits and increased costs in our healthcare system.[1] Thousands of "Baby Boomers" born between 1946 and 1950, are now transitioning through age 60 and beyond. Along with the prospect of living to the century mark, comes the reality that osteoarthritis, sports and non-sports related injuries also increase.[2] This year, the Arthritis Foundation has estimated that immune-related joint degenerative conditions are expected to strike more then 27 million Americans during the next decade,[3] with additional untold numbers afflicted with ligament weakness, fibromyalgia, idiopathic pains and muscle trauma.[4-5] Pain reducing medications are utilized daily,

essentially to combat the symptoms of immune-related aging issues. Unfortunately, prescription drugs are not without side effects and many consumers are turning or have already turned to over-the-counter (OTC) substances in the hopes of obtaining pain relief without those side effects.[6]

Cetylated fatty acids (as a group) have been reported to exhibit an anti-inflammatory activity in joint/muscle/ligament regions. These promising results were based primarily on animal study data,[7] while the number of human studies showing any conclusive anti-inflammatory effect is limited.[8-9] Cetylated fatty acids are believed to act by inhibiting the cyclooxygenase pathway in test animals, however, it is unknown whether the same mechanism is functioning in humans.[10]

The National Institutes of Health (NIH) has funded several meta-analyses in the attempt to help identify and validate anti-inflammatory OTC materials.[11] Of the more unexpected findings, unsaponifiables (oils),[12-14] and creatine monohydrate were found capable of modulating certain aspects of cell surface/pro-inflammatory reactant interactions.[15] Creatine monohydrate is a supplement primarily used by athletes who are engaged in high-energy demand activities.[16] It has been extensively researched for its safety and ergo-dynamic supportive function. Until recently, however, very little attention has been paid to its ability to influence cell surface interactions.

Based on research data, we hypothesize that a compound composed of a buffered creatine in combination with cetylated fatty acids might result in a safe, effective form of OTC pain relief.

MATERIALS AND METHODS

Test Subjects

Prospective participants were recruited from Billings Montana and the surrounding suburbs through local advertisements. Respondents who indicated they had chronically (>6 months) experienced at least one area of localized pain/stiffness, underwent an extensive pre-screening process that included a preliminary interview, comprehensive questionnaire and blood tests, before being admitted to the study. A total of 35 subjects (21 males, 14 females) ranging from ages 23 to 88, were admitted. Participants experiencing at least one and occasionally multiple isolated areas of chronic joint/muscle inflammation/pain, were divided into 2 groups designated "Group A" (n = 24) and "Group B" (n = 11). Individuals in Group A were assigned four capsules of an oral, alkali buffered-creatine – cetylated fatty acid compound called the "Test Compound" (product name: Kre-Celazine,® manufactured by All American Pharmaceutical and Natural Foods Corporation, Billings, Montana) daily, Group B, an equal number of placebo capsules daily. The capsules were prepared by the manufacturer in a manner so as to preclude either the physicians or the participants from identifying the contents. The investigator, examining physicians, testing laboratory staff and the participants did not know to which group an individual had been assigned. Each individual's participation lasted 30 consecutive days. Only complete data from those who were considered "100% compliant" was considered "valid." To be considered compliant during this period, each participant was required to take the assigned capsules, comply with the blood draws and examination schedule, fill out a "Pain Journal" according to the protocol provided, and return the original bottle with any remaining capsules, after the last day of their participation.

Study Material Preparation

The "Test Compound" was a proprietary oral preparation consisting of an alkali-buffered creatine – cetylated fatty acid compound, called Kre-Celazine®. Capsules and bottles for the study were prepared in such a manner as to preclude any participant, study physician or blood lab technician from knowing which individual was receiving either material. The identity codes for the participant assignments were kept confidential until after the study.

Blood Sampling

Blood sampling was done at a Laboratory Corporation of America blood collection lab according to standard protocols.

Study Protocol

The entire study was conducted over a period of 90 days. Applications were accepted from both men and women, ages 21 years or older. Prospective subjects were pre-screened according to the following protocol:

- A recruitment Inclusion/Exclusion Criteria form.
- A fasting blood draw completed for creatinine and AST (SGOT) and C-reactive protein.

To be eligible for inclusion in the study, prospective participants were required to fulfill the following inclusion criteria prior to admission:

- Have normal fasting serum levels of creatinine (<1.3mg/dl F; <1.6 mg/dl M), and AST(SGOT) (<41 IU/L - M/F).
- Be at least 21 years of age or older.
- Sign an Informed Consent form.

Prospective participants were excluded from participation if they fulfilled any one or more of the following exclusion criteria:

- Serum creatinine level of >1.5 mg/dl M; >1.2 mg/dl F.
- Serum AST (SGOT) level >41 IU/L.
- Pregnant or breastfeeding.

- Digestive-related or fat-malabsorption disorder.
- Taking a lipid-absorbing drug (excluding a statin).
- Chronic disease state (i.e. hepatitis, cirrhosis, diabetes, cancer, organ failure).
- Taking multiple medications for numerous medical conditions.
- Steroid anti-inflammatory usage.
- Current methotrexate usage.
- Smoker.
- Alcoholic.
- Multi-cups (coffee or tea) drinker daily.
- Taking numerous nutritional supplements.
- Having a medical condition that would preclude participation.

Each study participant was provided with an instruction sheet. After completion of the entrance examination by a study physician, participants were instructed to self-administer the capsules, two in the morning and two in the late afternoon-evening, on an empty stomach, swallowing each capsule with water. No other liquid was permitted for use in swallowing the capsule. Participants were reminded to avoid caffeinated drinks for at least five hours after taking any capsules, and score pain in a Pain Journal. At the end of the study (day 30), participants were required to have a repeat blood draw and complete an exit examination prior to returning the bottle to the company with the remaining capsules. In order to insure compliance with the capsule administration portion of the protocol, each participant had a specific excess number of capsules in his or her bottle. Only data from those participants who were considered 100% compliant was used.

Physicians' Entrance/Exit Exam Protocol

All participating physicians were provided with an examination protocol to be completed, which included the following information:

- Participant Number.
- Gender.
- Blood Test Results [Creatinine; AST/(SGOT); C-Reactive Protein].
- Comment section for blood tests results.
- General Health Assessment section.
- Location and extent of joint or muscle related pain.
- Arthritis or fibromyalgia related pain (specify if possible).
- Define limits of mobility (a joint/or limb).
- Range-of-motion test (ROM).
- [Exit Exam Question] Has this participant's pain changed (better/worse) since the entrance exam?
- [Exit Exam Question] General mobility assessment – what has changed since the initiation of the study?

RESULTS

Participant compliance was high. Complete data from a total of 31 of the original 35 participants was available. Dropouts occurred only in "Group A" and were the result of loss of interest (two persons), adverse/untoward reactions rated significant/serious (edema/pain in one person), final blood data lost at the lab (one person). All 31 participants returned bottles with the correct number of capsules. The gender distribution changed for "Group A" due to the withdrawal of 3 female participants and the loss of data for one male participant. Adverse reactions, rated mild/minor (gas/upset stomach) were reported by both groups (Group A = 20%; Group B = 9%). The participants' lab and questionnaire data are shown in **Table 1**. Final evaluation of any changes in mobility, ROM and inflammation/pain were scored during the exit exams and is shown in **Table 2.**

DISCUSSION

With the prospect of longevity well beyond the 90 year range, the search for anti-inflammatory pain relief that is without the burden of serious side effects, grows more urgent. Cetylated fatty acids (as a group) are under consideration as a substance having potential anti-inflammatory properties with the ability to suppress pro-inflammatory cytokines. Prior to this study, much of the supporting anti-inflammatory data was based on a limited number of human studies and animal data. Equally interesting is creatine monohydrate – a fairly new contender to the anti-inflammatory field. Research suggested that in its phosphorylated form, creatine supplementation may be capable of positively affecting endothelial permeability, thereby inhibiting potentially inflammatory stimulating molecules from adhering and expressing their action on endothelial cells.

Our findings indicate that an oral buffered-creatine monohydrate and cetylated fatty acid compound is effective in improving pain/stiffness and mobility scores in the extremities, as well as in the shoulder and neck region. This finding is of particular interest. While cetylated fatty acid formulations, both topical and oral, have tentatively been cited for their potential to improve knee related stiffness/pain, there has been no significant mention of substantial improvement to those additional areas positively impacted by the formulation used in this study. If the purported anti-inflammatory activity for the cetylated fatty acid family (cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laureate, cetyl plamitate and cetyl oleate) is primarily directed toward (or confined to) the

Table 1. Participants' Lab and Questionnaire Data.

		Group A (Kre-Celazine®)		**Group B** (Placebo)	
Participants:	Initial	24		11	
	Completing	20		11	
Gender		**17 males/3 females**		**4 males/7 females**	
Age		**23 – 88 years**			
Dropouts (M/F)		**3 F**		**0**	
Entrance blood tests:		**Overall average**			
Creatinine		0.9 mg/dl		0.8 mg/dl	
AST(SGOT)		23 IU/L		22 IU/L	
C-reactive Protein		4.1 mg/L		6.2 mg/L	
Exit blood tests:		**Overall average**			
Creatinine		0.9 mg/dl		0.8 mg/dl	
AST(SGOT)		25 IU/L		21 IU/L	
C-reactive Protein		4.2 mg/L		5.1 mg/L	
Pain Relief: (Percentage of participants rating their treatment**,** "as good as" or "better than" their usual OTC or prescription pain reliever)		**Per Area:**			
	Ankle/Foot –	100% (2/2)		0%	
	Knee (and Leg) –	71+% (5/7)		0%	
	Hip –	33% (1/3)		33% (1/3)	
	Back –	50% (5/10)		0%	
	Neck/Shoulders –	85+% (6/7)		33% (1/3)	
	Elbow/Wrist/Hand	80% (4/5)		33% (1/3)	
No Pain Relief: (Percentage of participants rating their treatment, "not as good as" or "didn't work" compared to their usual OTC or prescription pain reliever)		**Per Area:**			
	Ankle/Foot –	0%		100% (3/3)	
	Knee (and Leg) –	29% (2/7)		100% (5/11)	
	Hip –	67% (2/3)		66% (2/3)	
	Back –	50% (5/10)		100% (1/1)	
	Neck/Shoulders –	15% (1/7)		66% (2/3)	
	Elbow/Wrist/Hand	20% (1/5)		66% (2/3)	
Personally said they experienced reduced pain/increased mobility		**Overall Average**			
		Yes	**No**	**Yes**	**No**
		60% (12/20)	40% (8/20)	27% (3/11)	73% (8/11)
Experienced an adverse event:					
Minor or mild (gas/upset stomach)		20% (4/20)		9% (1/11)	
Significant/serious (edema/pain)		4%* (1/21)*		0% x	
Blood Pressure:		**Overall Average**			
		Systolic/Diastolic		**Systolic/Diastolic**	
Entrance		**127/83**		**129/82**	
Exit		**125/75**		**119/77**	

* Due to an adverse event, this participant withdrew before the end of the study.

Table 12. Physicians' Reports.

	Group A (Kre-Celazine®)	**Group B** (Placebo)
ROM:		
Increase	20% (4/20)	18% (2/11)
Decrease	10% (2/20)	36% (4/11)
No Change	75% (15/20)	45% (5/11)
Mobility:		
Increase	35% (7/20)	9% (1/11)
Decrease	5% (1/20)	36% (4/11)
No Change	15% (3/20)	—
Data not Reported	45% (9/20)	54% (6/11)
Pain:		
Decrease	90% (18/20)	36% (4/11)
No Change	10% (2/20)	55% (6/11)

Information for Physicians' Reports was obtained during examinations/interviews.

knee region, this would suggest that the additional neck/shoulder/extremity areas, positively impacted by Kre-Celazine® may have resulted from the additional buffered creatine compound in the mix.

Anecdotally noted and of interest, is the small decrease in diastolic blood pressure over that observed for the placebo. This effect on blood pressure has not heretofore been mentioned in creatine or cetylated fatty acid studies, and may warrant further investigation.

CONCLUSION

The findings presented in this study suggest that Kre-Celazine® is a moderately effective non-prescription material for the reduction of pain and stiffness of the extremities, neck and shoulder regions in humans. It should be noted that the study group was small in number and additional studies are needed to confirm the results from this initial study.

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The first author is the founder, principal investigator and research director of the All American Pharmaceutical and Natural food Corporation and the patent holder of Kre-Celazine.®

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The last author, Wendy Jones, works for Royal Knight Incorporated, a research consulting company, which was retained by All American Pharmaceutical Company to assist in the planning, execution and technical writing of their studies and data.

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