

Title: A randomized placebo controlled study of a novel pantothenic acid based dietary supplement in subjects with mild to moderate facial acne

Running head: Pantothenic acid dietary supplement for facial blemishes

Key words: pantothenic acid, dietary supplement, facial blemishes, acne

Version: DRAFT 3.1

Abstract: pages 2-3

Manuscript body: pages 4-11

Table 1: page 12

Figures 1-4: pages 13-17

ABSTRACT

Objective

The purpose of this study was to determine the safety, tolerability and effectiveness of of daily administration of an oral dietary supplement containing pantothenic acid on improving skin health in men and women with facial acne blemishes.

Methods

A double blind, randomized placebo controlled clinical study of healthy adults who had been previously diagnosed with mild to moderate acne vulgaris was performed. Subjects were randomized 1:1 to the study agent, a dietary supplement containing pantothenic acid versus an aesthetically matched placebo for twelve weeks. The primary endpoint of the study was the difference between total blemish count and from baseline to the end of the study (12 weeks) in the study agent treatment group versus the placebo group. Secondary measurements included difference in mean non-inflammatory and inflammatory lesions, difference in Investigators Global Assessment and total score of the Dermatology Life Quality Index from baseline to week 12 between the two groups. Investigator assessment of overall improvement at week 12 was also measured and skin photographs were taken. The primary safety and tolerability endpoints were assessment of adverse events utilizing the National Cancer Institute's Common Criteria for Adverse Event Reporting and measurement of serum complete blood count and hepatic function.

Results

Forty-eight subjects were enrolled in the study and forty were evaluable. Analysis of the total number of skin blemishes demonstrated that there was a significant mean reduction

in lesion count following the pantothenic acid group versus the placebo group at week 12. Mean change in lesion count per facial area was also different between the two groups in regard to forehead and cheek lesions. Mean reduction in inflammatory lesions was also significantly reduced in the pantothenic acid group versus the placebo group. Quality of life as measured by total DLQI scores demonstrated significantly lower at week 12 vs. baseline in the pantothenic acid group. The study agent was safe and well tolerated and there were no serious adverse events reported.

Conclusions

The results from this study indicate that the administration of a pantothenic based dietary supplement in healthy human adults with facial blemishes is safe, well tolerated and reduces total facial blemish count versus placebo after twelve weeks of administration. Secondary analysis shows that administration of the study agent significantly reduced area-specific and inflammatory blemishes. Further randomized, placebo-controlled trials are warranted.

MANUSCRIPT BODY

Introduction

Acne is a common disease of the hair follicles in the skin associated with an oil gland. Facial blemishes due to acne can affect up to 80% of people during their lifetime and frequently starts in teens but often persists into adulthood or begins during adulthood. Lesions include non-inflammatory type and inflammatory type facial blemishes. There are many common treatments including drugs, over the counter products and procedures such as laser therapy. There has also been an increasing interest in the use of natural products for skin health such as vitamin C, other antioxidants and omega-3 fatty acids. One agent that has shown promise in reducing facial blemishes is pantothenic acid (vitamin B5). Pantothenic acid is a water-soluble member of the B-vitamin family that is converted into 4'-phosphopantetheine, that is then converted to co-enzyme A (CoA) via adenosine triphosphate (8). Pantothenic acid has been shown to regulate epidermal barrier function and keratinocytes differentiation via CoA metabolism (9). Skin softening ability of pantothenic acid based topical products has been demonstrated in a recent clinical trial (10). A recent feasibility study has also demonstrated that daily oral supplementation of a nutritional agent containing pantothenic acid was feasible and safe. Secondary endpoints of that study demonstrated that there was a reduction in total skin blemishes over an 8-week period (Ref). Therefore the purpose of this study was to further test the pantothenic acid based supplement in a randomized double blind placebo controlled clinical study in order to test the effectiveness of the study agent in reducing global facial blemish count versus placebo over a twelve week period.

Materials and Methods

Subjects

Fifty-one adult subjects (average age) with ≥ 50 non-inflammatory and up to 50 inflammatory lesions were recruited at two dermatology sites. The main exclusion criteria included pregnancy and lactation, known allergy or hypersensitivity to any of the constituents in the study agent and current use of any prescription treatment (oral or topical) for acne (washout). Past use of any procedures including laser therapy, microdermabrasion and other procedures were prohibited if the participant had received it within the past three months. The study was institutional board review approved and written informed consent was obtained from each subjects. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helinski.

Study Design

The study was performed between August 2012 and November 2013. Once informed consent was given, consecutive human subjects with facial blemishes as demonstrated by total blemish count were assessed and randomized 1:1 to either the study agent, a pantothenic acid based dietary supplement herein: study agent (PantohenTM, Avilan Marketing LLC, New York, NY) or an aesthetically matched placebo tablet. The dosage of the study agent or the placebo administered was two tablets taken orally, twice a day with food for twelve weeks. Each four-tablet dose of the study agent contained 2.2 grams of pantothenic acid. The primary outcome of the study was the reduction in total facial blemishes at the study endpoint (week 12) in the study agent (Pantohen) versus (vs.) the placebo group. Secondary outcomes were change in non-inflammatory lesions at specific facial areas, change in inflammatory lesions (total and specific facial areas), change in the

Investigators Global Assessment and change in scores on the Dermatology Life Quality Index (DLQI) from baseline to week 12 between the two groups. The DLQI is a general questionnaire that evaluates quality of life (QOL) in dermatology patients and consists of ten questions about symptoms, feelings, daily activities, type of clothing, social or physical activities, exercise, job or education, interpersonal relationships, marriage relationships, and relationship to dermatologic symptoms. Higher scores indicate a poorer QOL (Ref). Finally we assessed investigator overall improvement as deemed by the study doctor using a 5-point scale: 2=marked improvement, 1=slight improvement, 0=unchanged, -1=worsening, -2=marked worsening at the study endpoint (week 12).

Statistics

The study sample size had 80% power to detect a significant difference in total lesions from baseline to week 12 of the study between the two groups and significance was set at 0.05. The Investigators Global Assessment and Investigator Overall Improvement evaluations was performed on a 5 point scale and transformed to numerical values (0-5) and the mean, standard deviation and percentages were calculated. Differences in DQLI scores were analyzed from baseline to week 12 using a t-test. A last observation carried forward method was prospectively defined and used for missing data if the subjects had data at least for the first two visits. The tolerability and safety outcome was the incidence of adverse effects, complication/illness and/or serious medical events due to the study agent as measured by the National Cancer Institute's (NCI) Common Criteria for Adverse Event Reporting Version 3.0 and by analysis of serum complete blood count and hepatic function from baseline to week 12. Descriptive analyses were performed for

demographics utilizing characteristic measures such as mean, standard deviation, and range.

Results

Subjects

Fifty-one subjects were screened, forty-eight were randomized and forty-one subjects were evaluable. Of those, 6 subjects were lost to follow up, 1 withdrew consent and 1 was dropped for non-compliance. None of the subjects were terminated due to an adverse event (See Figure 1 for study flow). Demographics and baseline characteristics are listed in Table 1.

Efficacy analysis

Primary Endpoint

There was a statistically significant decrease in the number of total facial lesions over the study period in the subjects taking the study agent, Pantothen, versus placebo ($p=0.019$) (Figure 2). Lesion count reduced in the study agent versus placebo group by 68.21%.

Secondary Endpoints

Analysis of the number of non-inflammatory blemishes demonstrated a significant mean reduction in lesion count from baseline to week 12 in the study agent vs. the placebo group ($P=0.016$) (Figure 3). Breakdown of changes in lesion count per facial area also demonstrated significance in numerous categories in the study agent vs. placebo group (Figure 3). Overall efficacy as measured by the Investigators Global Assessment was significantly improved for the Pantothen group versus placebo at week 12 ($P=0.045$) as

42.85% vs 14.28% were downgraded to a grade 1 (almost clear skin, few non-inflammatory lesions and no more than 1 inflammatory lesion). Figures 4A and 4B demonstrates examples of clearer skin in both inflammatory and non-inflammatory blemishes from baseline versus week 12 in subjects in the Pantothen group.

Dermatology Life Quality Index (DLQI) and Overall Investigator Assessment of Improvement

The mean \pm SD DLQI score was lower at week 12 from baseline between the study agent and placebo group (Baseline scores, 7.6 ± 5.3 vs. 9.53 ± 7.69 , $P=0.44$ Study Agent vs. Placebo, versus Week 12 scores, 1.93 ± 1.90 and 5.3 ± 4.8 Study Agent vs. Placebo respectively, $P=0.022$). The overall investigator assessment of improvement at week 12 as measured by a 5-point scale demonstrated that 85.7% of subjects had ≥ 1 rank improvement in the Pantothen versus the placebo group (35.7%).

Primary Safety and Tolerability Endpoints

The study agent was well tolerated. One subject withdrew consent due to complaint that the tablet size was too large. There were no differences in complete blood count or hepatic function as measured at week 12 from baseline in either of the study agent or placebo groups (data not shown). There were two adverse events reported, 1 of fatigue (placebo group) and 1 of shingles (study agent group) that were deemed unrelated to the study agent by the study principal investigator. No serious adverse events were reported during the study.

Discussion

Pantothenic acid (vitamin B 5) is a water-soluble B-complex vitamin. In this study, volunteers with facial blemishes who took a daily oral dose of a pantothenic acid based dietary supplement demonstrated improved skin health versus those who took a placebo tablet. The results of this study further confirmed that it was safe and tolerable for healthy human volunteers to take the nutritional supplement (PantothenTM) containing pantothenic acid for twelve weeks. The results of this study showed that there was a greater than 67% reduction in the number of total facial blemishes after 12 weeks of supplementation. Results also demonstrated that there was a significant reduction in the number of total and some facial areas in non-inflammatory lesions after 12 weeks in the pantothenic acid group, improved scores on the Investigators Global Assessment from baseline to week 12 and improved overall investigators assessment at study endpoint. In addition, subjects in the study agent group demonstrated better quality of life as measured by the Dermatology Life Quality Index; a well-validated quantitative questionnaire that measures the bother of unclear skin on patients' quality of life with regard to social, behavioural and mood indicators. Most importantly, the study agent was well tolerated and safe as demonstrated by minimal adverse events and no changes in serum blood counts.

The mechanism by which this occurs may be due to antibacterial and skin softening activity of pantothenic acid. Pantothenic acid is converted into 4'-phosphoantetein that is then converted to co-enzyme A (CoA) via adenosine triphosphate (ATP) (7-9). Coenzyme A is a critical agent important in lipid metabolism and other cellular processes and it has been shown that pantothenic acid may regulate epidermal barrier function through proliferation and differentiation of keratinocytes via

CoA metabolism (10 and Gaisa 2008). It is possible that the reduction in the amount of global skin lesions in volunteers following oral administration of the pantothenic acid based study agent may function through these mechanisms. However the exact mechanism of this effect is not understood. More recently the association between coenzyme A metabolism and inflammation has also been suggested as it has been shown that the pantetheinase enzyme that recycles pantothenic acid and pantetheinase gene (vanin-1) knockout mice have been shown to be involved in the progression of inflammatory reactions (Nitto 2013). The bioavailability of pantothenic acid has been reported in the range of 40-63 percent and amounts found in 24-hour urine samples have been shown to correlate with intake (11). For example avocados contain a wide variety of essential nutrients including pantothenic acid and essential fatty acids and studies have demonstrated that these correlate with improved health in persons that consume them (Dreher 2013).

In addition to physiologic mechanisms of action our study also demonstrated that volunteers in the Pantothen group that demonstrated clear skin had improved quality of life as measured by a well-validated, quantitative questionnaire. It has been clearly shown that patients with poor facial skin acne have reduced quality of life with regard to dissatisfaction about appearance, social bother and even co-morbid depression. It has also been stressed that assessment of quality of life in studies testing any type of agent for acne are important and strongly correlate with treatment success (15).

Limitations of this study are its short duration time and that our study was powered to detect a difference in total lesions. If we aimed to look at the effects of the study agent in inflammatory lesions, we might need a longer intervention period.

Moreover, we were unable to measure long term use and durability. Given the safety and tolerability of the study agent and the ability of the study agent to improve facial blemishes further randomized, placebo controlled studies of Pantothen are warranted.

Table 1. Demographics

Characteristic	Arm 1: Study Agent	Arm 2: Placebo	P-value
N	19	21	n/a
Mean age, years (SD)	29.7 (7.5)	27.1 (3.8)	
Sex			n/a
Male	3	2	
Female	17	19	
BMI			
All	26.2 (5.7)	26.1 (6.7)	
Race (No. [Percentage])			
White	10 [52.6]	10 [47.6]	
Black	6 [31.6]	4 [19.04]	
Asian	2 [10.5]	4 [19.04]	
Other	1 [5.2]	3 [14.3]	
Ethnicity			
Latino	3 [15.8]	3 [12.3]	
Non-Latino	16 [84.2]	18 [85.7]	
Baseline blemish count [Av (SD)]			
Total- Av (SD)	51.3 (22.4)	71.8 (42.8)	0.071
Non-inflammatory	41.2 (16.7)	48.9 (33.7)	0.374
Inflammatory	15.3 (8.9)	17.3 (14.3)	0.603

Figure 1: Subject Flow

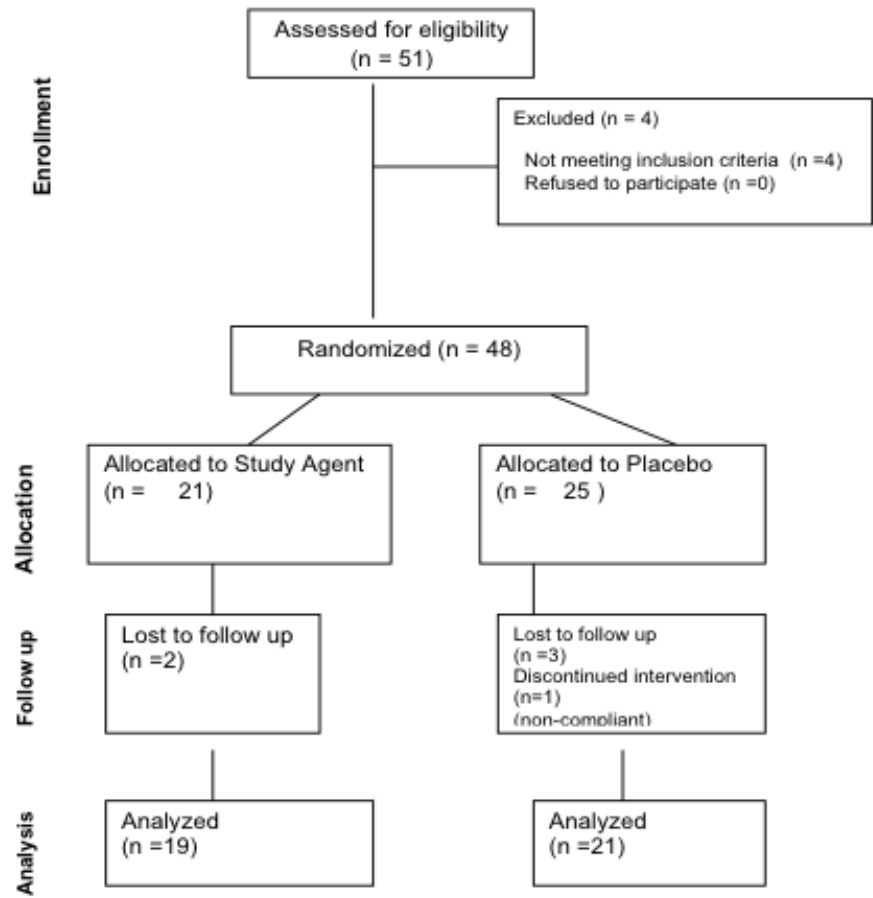


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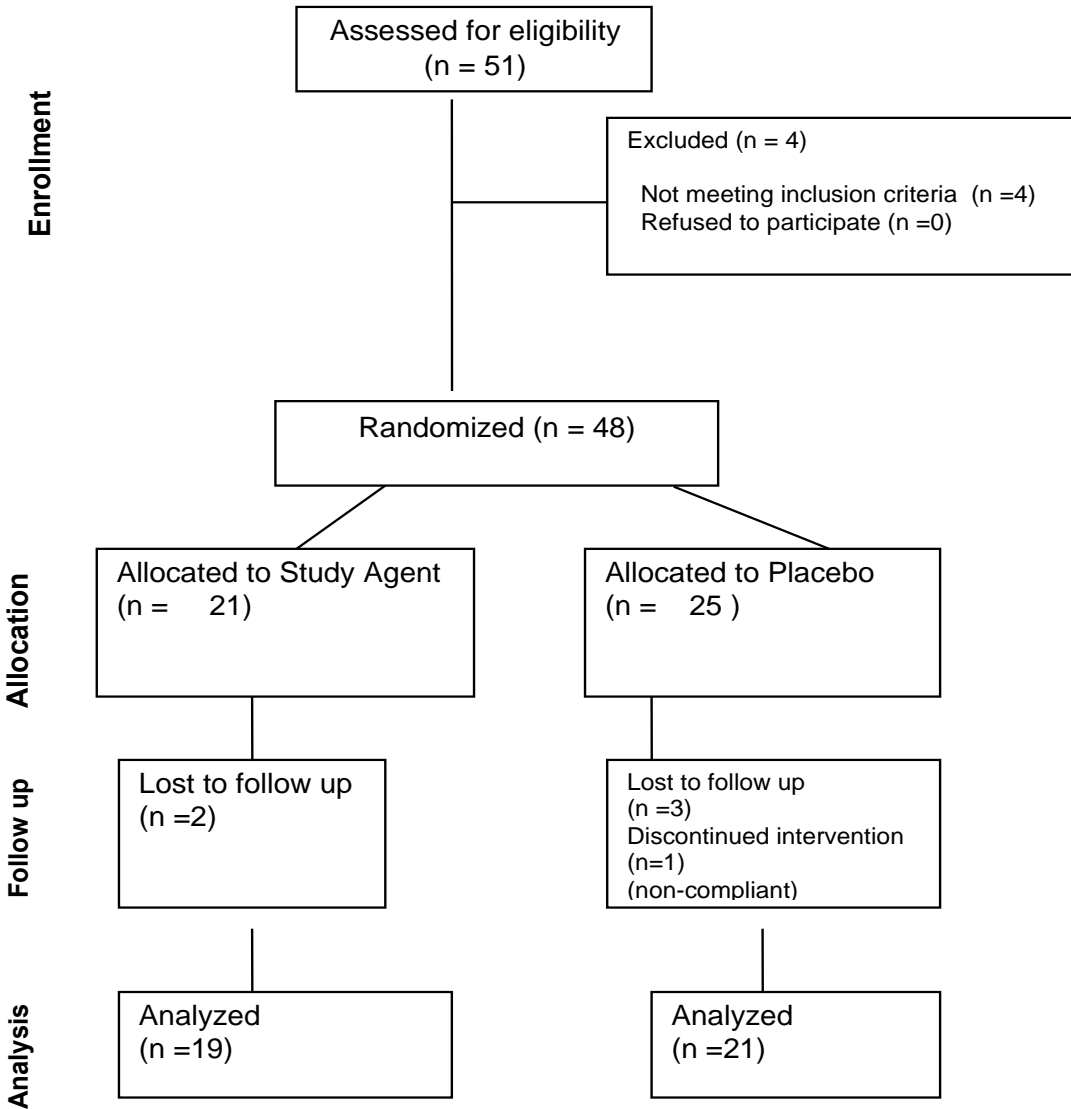
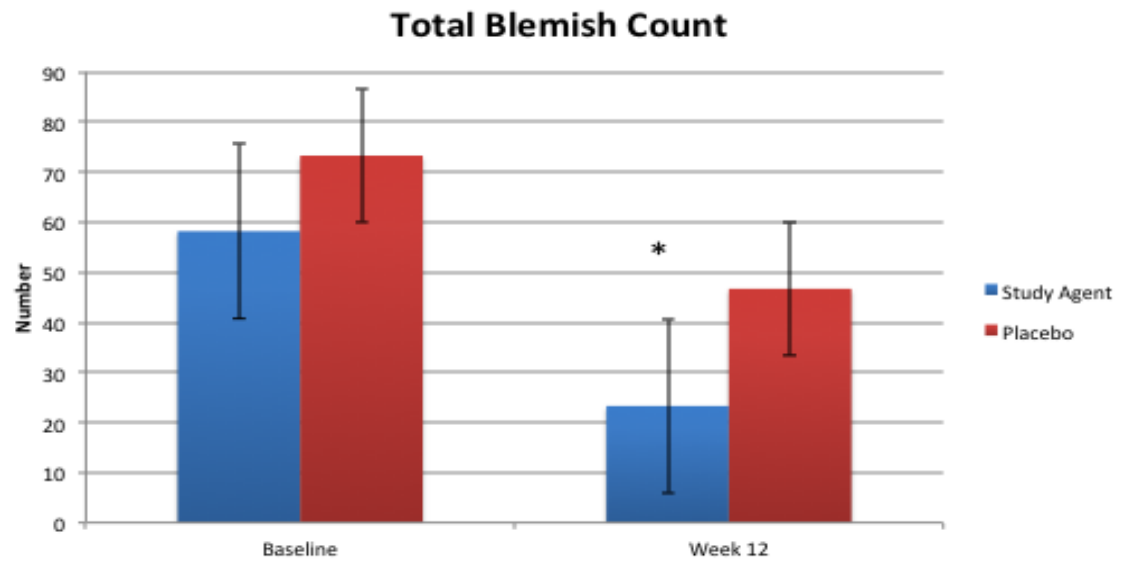
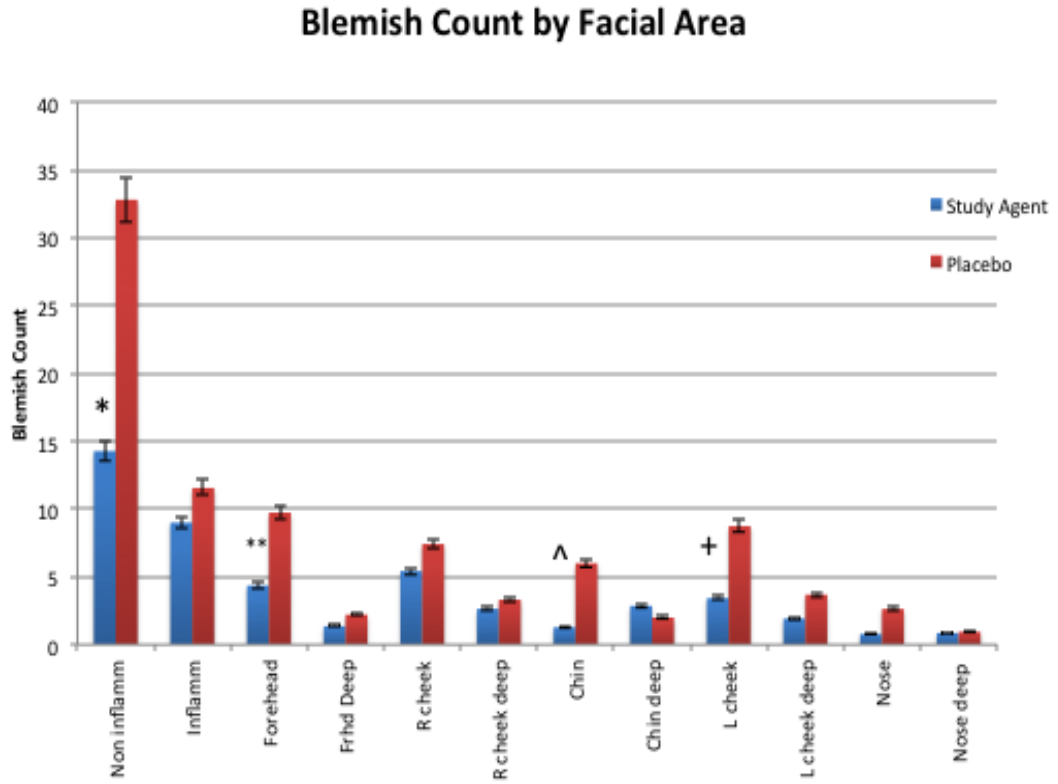


Figure 2: Total Blemish Count at Week 12



*p=0.0197 Study agent versus Placebo at week 12
T-test

Figure 3. Counts at Week 12



*p=0.162, **p=0.018, ^p=0.0024, +p=0.0192

Figure 4A. Forehead Non-Inflammatory



Baseline



Week 12

Figure 4B. Chin and Cheeks: Inflammatory and Non-Inflammatory



Baseline



Week 12