A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy of a Citrus Bioflavanoid Blend in the Treatment of Senile Purpura

Joshua M. Berlin MD,[a] David P. Eisenberg MD,[b] Mindy B. Berlin RN,[a] Robert A. Sarro MD,[a] Douglas R. Leeman PA-C MPH,[a] Howard Fein MD[c]

[a]Dermatology Associates, PA, of the Palm Beaches, Boynton Beach, FL
[b]University of Connecticut Health Center, Farmington, CT
[c]Palos Verdes Dermatology Associates, Inc., Palos Verdes, CA

ABSTRACT

Background: Senile purpura is a common, chronic skin condition affecting more than 10 percent of individuals over the age of 50. Despite being a benign condition, the continual development of purpura lesions in afflicted patients is frequently a source of significant visual and social concern. To date, there are no known effective treatments for this condition.

Objectives: To evaluate the efficacy of a novel nutraceutical citrus bioflavonoid blend in improving the skin's appearance in patients with senile purpura.

Methods: A six-week, randomized, multicenter, placebo-controlled, double-blind study was conducted to determine whether a uniquely formulated, oral citrus bioflavonoid supplement could treat active lesions of senile purpura while preventing new lesions from arising. Seventy patients with senile purpura were enrolled and 67 completed the study. Subjects were randomized into two groups receiving either a citrus bioflavonoid blend or placebo medication, which was taken orally twice daily for six weeks. Clinical evaluations were performed by blinded investigators at two locations.

Results: A statistically significant reduction in the number of new purpura lesions in the skin area undergoing clinical study was documented. At the end of six weeks, the citrus bioflavonoid blend treated group showed a 50 percent reduction in purpura lesions from baseline. Patient self-assessment of the effectiveness of the medication echoed the results of an investigator global assessment with a statistically significant improvement in the skin's appearance noted by the patients receiving the active medication. No adverse effects were noted by either the patients or investigators.

Conclusion: This new treatment appears to both safely and effectively diminish skin bruising in patients with senile purpura.

J Drugs Dermatol. 2011;10(7):718-722.

INTRODUCTION

Senile or actinic purpura was originally described by Bateman in 1817.[1] In his original treatise, the morphology of purpura was described as dark purple blotches of an irregular form and various magnitude. Although this original description still remains true, a treatment for this problem has remained elusive for nearly two centuries. It has been estimated that up to 11.9 percent of people over the age of 50 are afflicted with senile purpura.[2] The condition appears to be more prevalent with increasing age as a recent study found senile purpura in 29.3 percent of elderly patients examined in a long-term care facility.[3] Despite the fact that there are no long-term health sequelae associated with senile purpura (SP), the lesions are often cosmetically disturbing to patients as they tend to occur in visible areas of the body, such as the extensor surfaces of the forearms, legs and hands. The goal of this study was to determine the effects of a novel citrus bioflavonoid blend (CBB) as a potential treatment for SP

METHODS

Study Design

This multi-center, randomized, double-blind vehicle-controlled study was designed to evaluate the efficacy and safety of a proprietary CBB relative to a placebo in the treatment of SP when administered daily for six weeks. The study was approved by the institutional review board of Concordia Clinical Research. Thirty-two male and thirty-eight female participants

with a mean age of 74 years enrolled in the study with 67 successfully completing all phases. Of the 67 patients, 35 patients completed the active treatment while 32 patients finished the placebo treatment. Study participants received orally either two capsules of CBB daily or two capsules of placebo (calcium carbonate) daily over a six-week period. A representative area of skin bruising located on either the right or left forearm, hand, or leg was selected from each patient and its appearance documented with a high-resolution digital photograph. All participants were monitored at two-week intervals for the number and size of purpura in the study region by a blinded investigator. Furthermore, subjects were asked to keep a diary for their own assessment regarding the appearance of their skin.

This new treatment appears to both safely and effectively diminish skin bruising in patients with senile purpura.

Eligibility Criteria

Eligible participants had between three and 27 purpura lesions in the clinical study region at baseline. The mean number of purpura lesions was 9.75 in the CBB-treated group and 9.43 in the placebo-treated group at baseline. Participants were permitted to take coumadin, clopidogrel, or aspirin during the study if they were already on these medications. A two-week supply of either CBB or placebo was supplied at the initial visit and at two-week intervals through the course of the study.

Dosage and Administration

All study participants in the treatment arm orally ingested two tablets daily, morning and evening. Each tablet contained a proprietary blend of citrus bioflavonoids and minerals. Participants in the non-treated group orally ingested two placebo tablets of calcium carbonate daily. To monitor compliance, participants returned every two weeks for six weeks to receive further medication and for bi-monthly efficacy assessment. Participants were interviewed about compliance and any missed doses.

Efficacy Assessment

The primary efficacy endpoint was the change in the total number of purpura lesions in the study region from baseline to week 6. The secondary endpoints were a measurement of the speed of healing, as measured by the two week average percentage change in purpura and a reduction in IGA score compared to baseline after six weeks. Participants were assessed by the blinded investigator at baseline, two weeks, four weeks and six weeks for changes in the number of purpura lesions and IGA scores. Investigators counted the total number and assessed the size of purpura lesions in the clinical study region. Photographic assessment was conducted at each visit. In addition, participants completed a weekly diary to assess their own opinion of the efficacy, satisfaction with medication and side effects.

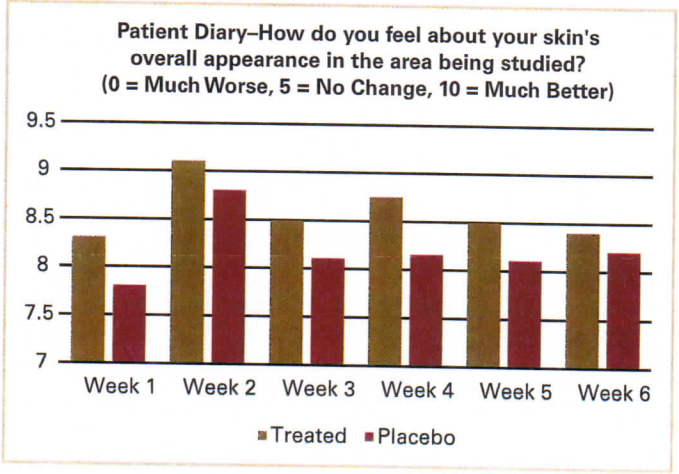
Safety Assessment

The trial medication contains a combination of readily available dietary supplements which have been extensively and safely used in various OTC nutritional products for more than 70 years. The medication is primarily composed from citrus extracts and also contains *Arnica montana*. Further, several of the active ingredients were shown to be safe in long-term use as part of the Multicenter Ophthalmic and Nutritional Age-Related Macular Degeneration Study in the United States.[4] Similar safety findings were also observed in the present study as no adverse effects were noted by either the subjects or the investigators.

Statistical Methods

All statistical analysis was performed using JMP® 7.0.4 for the Microsoft® Windows® XP operating system. Unless otherwise stated, statistical significance was based on two-tailed tests of the null hypothesis resulting in *P*-values of 0.05 or less. Analyses were performed on the intent-to-treat (ITT) population and per protocol (PP) population.

FIGURE 1. Citrus bioflavonoid blend treated patients always feel their bruises look better.



RESULTS

Seventy patients were randomized into two groups receiving either placebo treatment (calcium carbonate) or a proprietary CBB containing rutin, citrus bioflavonoids, ascorbic acid, hesperidin, eriocitrin and *A. montana*. Patients in both groups were instructed to take the study medication orally twice a day for a period of six weeks. Sixty-seven patients completed the study with three patients in the placebo group discontinuing treatment: two patients were lost to follow up and one patient stopped the medication due to a perceived lack of efficacy. Each patient was evaluated at baseline, two weeks, four weeks, and six weeks. Throughout the course of the trial, patients were instructed to maintain a periodic self-assessment diary. As part of the self-assessment, patients were asked to quantify on a numerical scale their perceived improvement in skin appearance

FIGURE 2. Citrus bioflavonoid blend treated patient at **a)** baseline, **b)** week 2, **c)** week 4 and **d)** week 6.

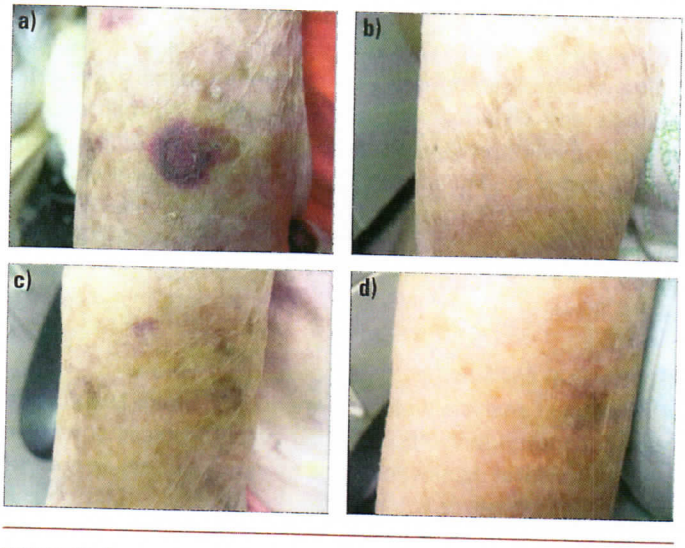
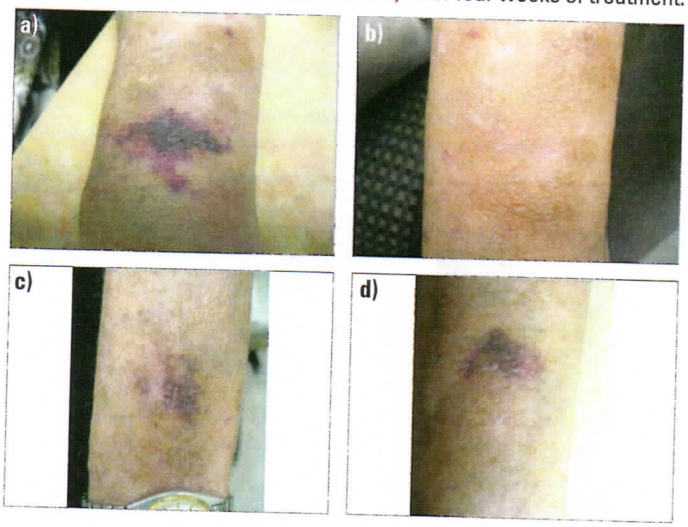


FIGURE 3. Comparison of citrus bioflavonoid blend treated patient **a)** before treatment and **b)** after four weeks of treatment; and placebo treated patient **c)** before treatment and **d)** after four weeks of treatment.



with the number zero corresponding to the appearance being significantly worse, five representing no change, and 10 being significantly better. A statistically significant difference was observed in the patients treated with CBB compared to placebo with CBB-treated patients feeling that their skin had improved in appearance over baseline at all study points (Figure 1).

The purpose of the study was to determine the effects of CBB on purpura development and resolution in a pre-selected clinical study area over a six week period. After six weeks of treatment, the CBB-treated group showed a statistically significant higher IGA score of 9.2 versus 7.7 in the placebo group (P=0.03). Some representative clinical examples of purpura lesions undergoing resolution with CBB are shown in Figure 2. Further photographs of CBB-treated patients compared to placebo-controlled

FIGURE 4. Comparison of citrus bioflavonoid blend treated patient **a)** before treatment and **b)** after two weeks of treatment; and placebo treated patient **c)** before treatment and **d)** after two weeks of treatment.

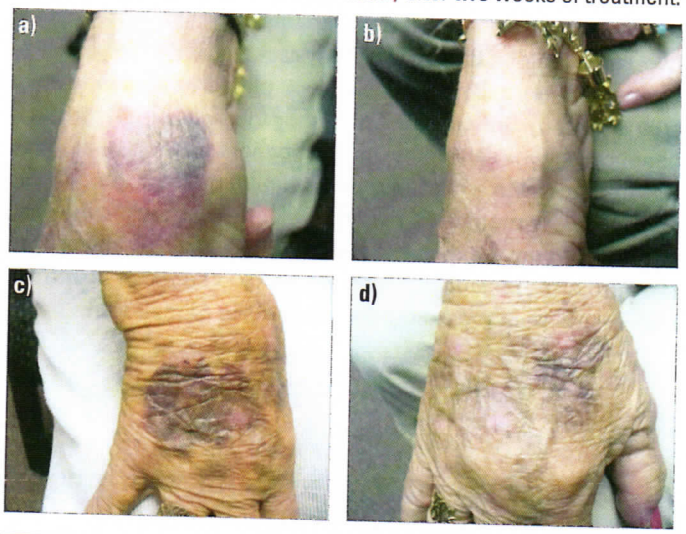
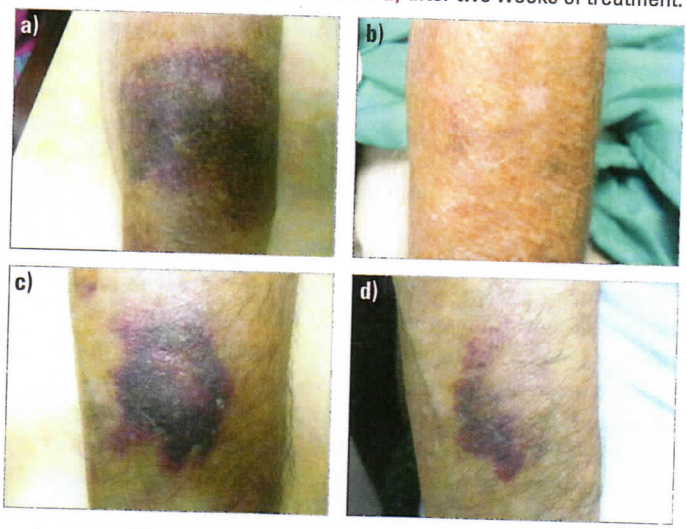


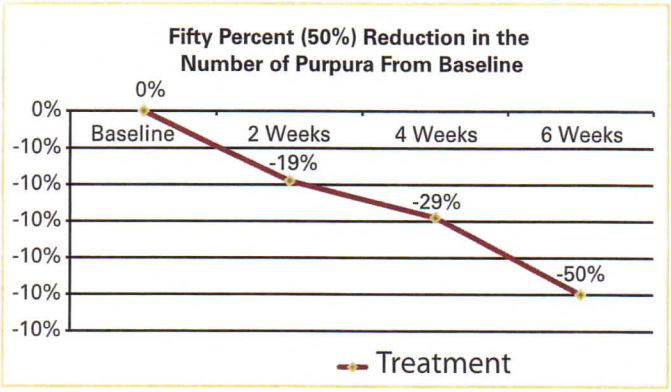
FIGURE 5. Comparison of citrus bioflavonoid blend treated patient **a)** before treatment and **b)** after two weeks of treatment; and placebo treated patient **c)** before treatment and **d)** after two weeks of treatment.



patients are illustrated in Figures 3, 4 and 5. In the clinical study area, there was a statistically significant 50 percent reduction (P=0.02) in the number of purpura lesions over baseline after six weeks of treatment (Figure 6). As illustrated in Figure 6, patients receiving CBB showed a steady decrease in the number of purpura lesions throughout the six week clinical study. For study subjects receiving CBB, there was a 19 percent decrease in the number of purpura lesions at two weeks, a 29 percent decrease at four weeks and a 50 percent decrease at six weeks. At the conclusion of the six-week study, patients in the placebo group showed a nine percent increase in total number of purpura lesions whereas CBB-treated patients had a 50 percent decrease in the number of purpura lesions. The worsening of the placebo-treated patients is likely secondary to the random

and sporadic nature of the condition, with patients developing new lesions in response to various unpredictable internal and external factors such as medications, dietary changes and incidental trauma. However, of note, a similar increase was not seen in the CBB-treated population, which is an indication of the suppressive effect of this nutraceutical combination on the development of new purpura lesions. In summary, CBB appears to both safely and effectively minimize the appearance of purpura in patients afflicted with senile purpura.

FIGURE 6. After six weeks, there is a statistically significant 50 percent reduction in the number of purpura with citrus bioflavonoid blend.



DISCUSSION

Senile purpura (SP) is a common condition among the elderly which presents as irregular, purpuric macules and patches with a characteristic dark purple color. Although significant antecedent trauma is typically not reported, SP frequently arises in areas where minor insults to the skin, such as the extensor surfaces of the forearms, hands and legs, commonly occur. Individual lesions can last for several days to weeks. In some instances, after the purpuric lesions resolve, residual hyperpigmentation due to the deposition of hemosiderin may persist for even longer durations. SP is a chronic, life-long condition often with new purpura lesions developing just as soon as, or even before, existing lesions resolve. Factors such as chronic sun exposure, use of anticoagulant medications such as aspirin, clopidogrel and warfarin, trauma, and long-term use of topical and oral corticosteroids can further exacerbate the condition.

Histologic studies of lesions of SP have shown a thinned epidermis often with significant dermal solar elastosis. A decreased amount of collagen as well as a marked increase in abnormal elastic fibers has also been reported. Extravasated red blood cells and hemosiderin are often seen in the upper dermis in association with a characteristic lack of an inflammatory response. This lack of a phagocytic inflammatory response has been proposed as one reason why the individual lesions of SP can take several weeks to resolve.[5]

There have been many hypotheses regarding the underlying cause of SP. It is postulated that prolonged exposure to ultraviolet radiation results in dermal atrophy and consequent fragility of the dermal blood vessel walls. As a result of the damage to the dermis, the microvasculature becomes more susceptible to minor trauma resulting in extravasation of red blood cells. Clinically, this process results in the appearance of purpura.

The authors believe the ingredients used in the CBB in this study work synergistically to improve the appearance of purpura in patients with SP. Citrus bioflavonoids have previously been shown to reduce capillary fragility and permeability as well as inhibit hyaluronase.[6] *Arnica montana,* which was also included in the CBB, has been reported to decrease capillary permeability which allows for the expedited clearing of extravasated red blood cells.[7] Ascorbic acid is a prerequisite cofactor for collagen synthesis and is generally thought to play a role in maintaining capillary strength.[8] Citrus bioflavonoids, such as hesperidin, help maintain vascular stability and reduce reactive oxygen species generation.[9] Rutoside is a form of bioflavonoid which reduces capillary permeability and inhibits elastase and hyaluronase.[6] Lastly, the CBB is formulated with eriocitrin, a flavonoid glycoside present in lemon fruit with significant antioxidant properties.[9] The collective pharmacologic activities of the various ingredients used in the CBB may explain why the study medication not only cleared existing purpura lesions, but also kept new ones from forming.

CONCLUSION

Although senile purpura is a common benign disorder, it can cause significant psychological distress in patients with this condition. In this study, we report a novel nutraceutical formulation that improves skin appearance in patients with senile purpura. This blend of citrus bioflavonoids and *A. montana* not only speeds the healing of existing purpura but prevents the formation of new lesions as well.

DISCLOSURES

Dr. Berlin has served as a consultant for Pharmaderm, Medicis, Nexgen Dermatologics, Medimetriks and Galderma Laboratories. He is also a member of the Speaker's Bureau for Warner-Chilcott and Galderma Laboratories.

Dr. Sarro has served as a speaker and participated in advisory boards for Amgen and Abbott Laboratories.

Dr. Fein has served as a consultant for Galderma Laboratories, Nexgen Dermatologics and Medimetriks. He is also a member of the Speaker's Bureau for Galderma Laboratories and Medicis.

Dr. Eisenberg, Ms. Berlin and Mr. Leeman have no relevant conflicts of interest to disclose.

REFERENCES

1. Bateman T. In *Delineation of Cutaneous Disease*. London: Langman; 1817.
2. Beauregard S, Gilchrest BA. A survey of skin problems and skin care regimens in the elderly. *Arch Dermatol*. 1987;123:1638-1643.
3. Dinato SL, Oliva R, Dinato MM, Macedo-Soares A, Bernardo WM. Prevalence of dermatoses in residents of institutions for the elderly. *Rev Assoc Med Bras*. 2008;54(6):543-547.
4. Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study – Part 2: Antioxidant intervention and conclusions. *J Am Optom Assoc*. 1996;67:30-49.
5. Kaya G, Saurat JH. Dermatoporosis: A chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology*. 2007;215(4):284-294.
6. Wadworth AN, Faulds D. Hydroxyethylrutosides: A review of its pharmacology and therapeutic efficacy in venous insufficiency and related disorders. *Drugs*. 1992;44:1013-1032.
7. Macedo SB, Ferreira LR, Perazzo FF, Carvalho JC. Anti-inflammatory activity of arnica Montana 6cH: Preclinical study in animals. *Homeopathy*. 2004;93(2):84-87.
8. Murad S, Grove D, Lindberg KA, Reynolds G, Sivarajah A, et al. Regulation of collagen synthesis by ascorbic acid. *Proc Natl Acad Sci USA*. 1981;78(5):2879-2882.
9. Zielinska-Przyjemska M, Ignatowicz E. Citrus fruit flavonoids influence on neutrophil apoptosis and oxidative metabolism. *Phytother Res*. 2008;22(12):1557-1562.

ADDRESS FOR CORRESPONDENCE

Joshua M. Berlin, MD
Dermatology Associates, PA, of the Palm Beaches
10301 Hagan Ranch Road, Suite D930
Boynton Beach, FL 33437
Phone:.....(561) 739-5252
Fax:.....(561) 739-5255