2014

Is Arginine Oral Supplement Effective on Wound Healing in Adult Patients With Stage II, III and IV Pressure Ulcers?

Camilla Chou
Philadelphia College of Osteopathic Medicine, camillach@pcom.edu

Is Arginine Oral Supplement Effective On Wound Healing In Adult Patients With Stage II, III and IV Pressure Ulcers?

Camilla Chou, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the addition of arginine protein supplementation is effective in wound healing of adult patients with stage II, III and IV pressure ulcers.

STUDY DESIGN: Systematic review of three English language primary studies. One observation controlled study and two randomized controlled studies all published between 2010-2012.

DATA SOURCES: Two double blind randomized controlled trials and one observational controlled trial comparing the efficacy of arginine supplementation in wound healing of adult patients with stage II, III and IV pressure ulcers. All research articles were found using Cochrane Library EMB, Dynamed and Pubmed databases.

OUTCOMES MEASURED: Pressure ulcer healing size and time were documented and compared using The National Pressure Ulcer Advisory Panel (PUSH) tool. The PUSH tool measures length x width, exudate amount and tissue type. Patients' nutritional status and intake are also monitored throughout the studying using Subjective Global Assessment (SGA) tool.

RESULTS: Two studies demonstrated significant decline in the ulcer size and healing time with the addition of arginine supplement. Brewer el al. showed patients receiving 9g of arginine daily has a mean healing time of 10.5 ±1.3 weeks compared to the historical group without arginine, which has mean healing time of 21.1±3.7 weeks. Van Anholt et al. demonstrated the intervention group receiving 9g of arginine has a significant decreased PUSH score, and faster healing time ($p \leq 0.012$). The p-value calculated for the intervention group is $p=0.006$ and for the control group is $p=0.016$. Leigh et al. showed similar wound healing size and time for the 4.5g arginine control group and the 9g arginine intervention group. The PUSH score for the 4.5g arginine group is 8.9±0.7, and for the 9g arginine group is 8.1±1.0. There is no significant difference in healing rate overall between the two groups, $p=0.991$. However, the time-to-heal rate decreased by half when compared both groups to historical data group receiving no supplement decreases the healing time.

CONCLUSIONS: All three studies showed that arginine oral supplementation is effective in decrease pressure ulcer healing time and size in adult patients with stage II, III and IV pressure ulcers. And one study showed no significant differences between the different dosing of the supplement.

KEY WORDS: Arginine, pressure ulcers, adults, wound healing

INTRODUCTION

A pressure ulcer is the breakdown of skin, due to localized injuries, such as pressing or rubbing over areas of bony prominence. Common sites are heels, hips, elbows, knees, sacrum, coccyx and ankles.[1,2] Pressure ulcers commonly affect those with medical conditions requiring prolonged immobility, thus hindering their ability to change positions. Once a pressure ulcer develops, it can progress rapidly and prove detrimental to patients. Arginine is an essential amino acid that plays an important role in protein synthesis, collagen deposition, and pressure ulcer healing.[1] This systematic review paper evaluates two randomized controlled trials (RCTs) and one observational controlled trial, while comparing the efficacy of arginine oral supplements for wound healing of pressure ulcers stage II, III and IV in adults.

The use of arginine supplements in treatment plans of patients with pressure ulcers is relevant to patients and physician assistant practice because pressure ulcers can cause serious complications such as cellulitis, sepsis, bone and joint infection. Furthermore, understanding the process of pressure ulcers and healing rate, will increase the likelihood physician assistants can treat patients, thus preventing ulcers. The incidence of pressure ulcers is high in geriatric and bed bound patients. In 1993, 280,000 pressure ulcers were diagnosed in hospital stays, which almost doubled by 2004.[3] The Centers for Disease Control and Prevention (CDC) estimates 11% of long-term residents in nursing homes suffered from various stages of pressure ulcers.[4] Subsequently, the cost of management and prolonged length of stay are problems for the patients and healthcare facilities. Studies have shown that ~15% of geriatric patients develop new pressure ulcers within the first week of hospitalization, with an average charge of $43,180 per stay for pressure ulcer treatment.[3] Pressure ulcers are responsible for frequent emergency room visits and hospital admits. However, generally by the time a patients seeks help, their

condition has exacerbated to more than just topical cream treatment. It has been reported that pressure ulcers account for 2.7% to 9% of acute care settings and 2.4% to 23% in long-term care facilities.[3,5]

The role of protein supplement in pressure ulcer healing is not well studied; however, it is believed that with adequate protein supplements, further breakdown of the soft tissues and muscles can be prevented.[7] As the incidence rate and cost statistics shown above, healthcare providers can improve the health status of patients and reduce hospital costs with early intervention using proper and adequate nutritional supplementation.[8]

Current treatments of pressure ulcers include daily cleansing and positioning of the wound by trained staff. Normal saline is preferred by most facilities, with around the clock repositioning by wound care nursing technicians.[4,5] Dressing and debridement of severe pressure ulcers using wet-to-dry dressing changing every 4 to 6 hours, and whirlpool devices for wounds with thick exudates. For patients with infected wounds, infection management is achieved by using topical antibiotics such as neomycin and bacitracin.[5] Systemic antibiotics should be avoided since most of these patients are on multiple medications and are immunocompromised. Lidocaine-prilocaine cream and NSAIDs are mainstays for pain management. Adjunct therapy, such as nutrition management by adding protein supplements to meet 1.2 to 1.5g/kg/day, is widely used to improve patients' protein status and improve wound healing.[6] Arginine has shown to improve protein malnutrition in pressure ulcer patients, however, there are no structured guidelines and studies for the amount of proteins needed and its effectiveness.

OBJECTIVES

The objective of this selective EBM review is to determine whether or not the addition of arginine protein supplementation is effective in wound healing of adult patients with stage II, III and IV pressure ulcers.

METHODS

A number of criteria was thoroughly considered in the selection of studies. Studies were selected based on population, pressure ulcer stages and the type of intervention. The population was limited to patients > 18 years of age with no signs of malnutrition and diagnosed with at least one stage II to IV pressure ulcer. The intervention was 9g of oral arginine supplements daily.

The randomized controlled studies compared the intervention group to the comparison group that received 9g of arginine supplement daily. The observational controlled group compared the intervention group to the comparison group of 17 historical control patients assessed by a medical history audit. The outcomes were measured to assess the improvement of the overall pressure ulcer and pressure ulcer healing size. Pressure ulcer healing size and time were documented and compared using The National Pressure Ulcer Advisory Panel (PUSH) tool. All three studies were controlled trials, while two of the three studies are double blind randomized controlled trials and one of the three is an observational controlled trial.

A detailed search using Pubmed, Dynamed and Conchrane Library Database was performed using arginine, pressure ulcers, and wound healing as keywords. All three articles used in this review were written in English language and published in peer-reviewed journals between 2010 and 2012. The author of this review conducted the research and the chosen articles were analyzed and selected based on topic relevance and patient oriented outcomes (POEMs). The inclusion criteria were studies that were randomized controlled trials published after 1996 using

arginine protein supplement as the sole intervention. The exclusion criteria were patients < 18 years of age, body mass index <18.5kg/m^2, on oral steroids, and/or receiving palliative care. The statistics reported and used by all three articles include ANOVA and p-value. Demographics of the three final selection are displayed in Table 1.

Table 1: Demographics and characteristics of the selected studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Brewer[1], 2010	Observational, controlled trials	18	50± 10 years	Bedbound spinal cord injury patients with stage 2,3 or 4 pressure ulcers	Patients with PKA, sepsis, chronic renal failure or metabolic disease	1	9g of commercial powdered arginine supplement daily until full healing of the documented pressure ulcers
Van Anholt[4], 2010	RCT, double blind	43	73± 5 years	At least one pressure ulcer stage III to IV receiving stand care and standard diet without prior nutritional supplements.	BMI< 18.5 for patients 18-70 years old, BMI< 21 for patients older than 70 years old. DM ulcers, life expectancy less than 6 mo, palliative care, use of steroids and anyone with dietary restrictions.	11	Intervention group receives regular hospital diet with 9g of Arginaid each day. Comparison group receives regular hospital diet with 4.5g of Arginaid each day.
Leigh[2], 2012	RCT, double blind	23	67± 5 years	Pressure ulcers stage 2, 3, or 4 not showing	Sepsis, acute gastrointestinal surgery, dialysis or	7	One group receive 4.5 of arginine and the other

				signs of healing, on oral diet and has not received any oral supplement.	individuals receiving hydroxyurea or prednisolone or dexamethasone.		group receive 9g of arginine daily.

OUTCOMES MEASURED

The outcomes measured were patient oriented evidence that matters (POEMs), which includes pressure ulcer healing time and size. The initial pressure ulcer size and depth were measured at the time of enrollment and again at the end of the study. Pressure Ulcer Advisory Panel (PUSH) tool measures the length x width, exudate amount and wound tissue type. The PUSH score is used to assess the effectiveness of arginine supplement by measuring the outcomes of pressure ulcer healing size and time. A PUSH total score of 0 indicates completely healed and score of 17 indicated greatest severity.[2] Patients' nutritional status and oral intake were also monitored throughout the study using Subjective Global Assessment (SGA). SGA determines nutritional status of well nourished, moderately malnourished and severely malnourished by assessing patients' recent weight change, dietary intake, signs of muscle wasting and gastrointestinal functional impairs.[1] Van Anholt et al. also assessed the time spent changing the dressing between the intervention and control groups.

RESULTS:

Two double blind randomized controlled and one observational controlled trial were analyzed in this review. All participants in the studies are adults > 18 years of age, hospitalized and receiving care for documented stages II, III or IV pressure ulcers. Participants were followed by the same nursing staff if they were discharged from the hospital. All three studies excluded patients with sepsis, gastrointestinal surgery, on palliative care, history of metabolic disease such

as PKA, body mass index <18.5, and on dialysis. These exclusion criteria were selected due to the interference of arginine absorption and possible metabolic adverse reactions of taking protein supplements.[1,2,9] Patients taking Hydroxyurea or prednisolone were also excluded because these drugs can affect the healing rate of pressure ulcers and wounds.[1,2,9]

In Brewer et al., 26 pressure ulcers documented and healed in the historical control group were used to compare to the 30 pressure ulcers documented and healed in the intervention group. The results indicated the intervention group receiving 9g of arginine daily had significant faster time-to-healing rate than the historical control group receiving 4.5g of arginine daily. The findings proved the time-to-healing weeks were shortened by 50% in the intervention group. Also, the pressure ulcer area (cm^2) is significantly reduced in the intervention group 4.5±1.3 compared to the historical control group 6.7±0.3.[1] The author pointed out that no documentation of baseline stages of pressure ulcers in the historical control group were available, therefore, no comparison can be done between each specific staging category.[1]

Table 2: Time-to-healing of pressure ulcers reported by Brewers, et al.

	Historical control time-to-healing weeks	Intervention group time-to-healing weeks	P value
All pressure ulcer documented	21.1 ± 3.7 (n=26)	10.5± 1.3 (n=30)	0.006
Stage 2	N/A	5.5±1.3 (n=30)	-
Stage 3	N/A	12.5 ±1.9 (n=14)	-
Stage 4	N/A	14.4 ±2.6 (n=6)	-
Paraplegic	19.4 ±4.2 (n=13)	14.7 ± 4.6 (n=26)	0.586
Quadriplegic	22.8 ± 6.2 (n=13)	10.4 ± 2.5 (n=4)	0.311

The nursing staff visits the participants and monitors supplement compliance. Each arginine packet consumed was counted and checked against the amount of arginine the participant is

advised to take. The record showed compliance with the arginine supplement is at least 85% until full healing of the pressure ulcer. 13/18 participants consumed 100% of the arginine supplements provided throughout the study. No tolerance or adverse effects were discussed in this research article.[1]

In Leigh, et al., the study showed no difference in time-to-healing rate between the control group receiving 4.5g of arginine and intervention group receiving 9g of arginine. Both groups took approximately 8 to 9 weeks to reach full healing with a p-value of 0.991.[2] However, there was substantial decrease in PUSH scores over time, $p<0.001$.[2] Table 3 shows the PUSH scores and healing rate for the two groups over the study period, calculated using repeated measure ANOVA. Because it is unjust and unethical to conduct a placebo control group in a hospital in-patient setting, the author compared this study to a historical control group.[2] The historical group participants had similar pressure ulcers and consumed similar amounts of energy and protein each day without the use of arginine oral supplements. The comparison showed that the full healing rate was 15.6 weeks for the historical group, which indicates a "two-fold improvement in both groups"[2] receiving oral arginine supplements, regardless of the dosage.

Table 3: Healing rate of pressure ulcers and PUSH tool reported by Leigh, et al.

	Control group (4.5g Arginine)	Intervention group (9g of Arginine)
PUSH Score at Baseline	9	8
PUSH Score in 3 weeks	5	5.5
Healing Rate	8.7±0.7 weeks	8.4±1.0 weeks

Compliance of the oral supplement was monitored by the nursing staff daily and recorded in the patients' calorie count chart. The record showed the compliance with the oral supplement was 90.3% for the control group and 93.3% for the intervention group.[2] The author reported one

participant dropped out of the intervention group due to gastrointestinal side effects from arginine, but did not describe the presentation or the severity of the side effect.

In Van Anholt et al., the 8 weeks study showed significant decrease in pressure ulcer size in the intervention group, p=0.006. The healing of pressure ulcers was evidence in week 3 of the intervention group (p=0.019) and onward (p≤0.012).[9] In the control group, the healing of the pressure ulcers were smaller compared to baseline in week 5 of the study (p=0.019) and onward (p≤0.008). Furthermore, the PUSH score of the intervention group improved significantly compared to the control group, p=0.011. Specifically, the intervention group had less documented necrotic or granulated ulcers and more closed ulcers than the control group, (p=0.037). Lastly, the time spent on dressing change on each pressure ulcer showed that less time is spent on dressing change in the intervention group, p=0.006.[9]

Table 4: Average numbers of dressing required per wound per week reported Van Anholt et al.

	Intervention Group	Control Group
Baseline dressings	5.5	4.8
# of dressings weekly in week 1	5.8	5.5
# of dressings weekly in week 2	5.5	5.5
# of dressings weekly in week 3	5	5.6
# of dressings weekly in week 4	5	5.5
# of dressings weekly in week 5	4.5	5.5
# of dressings weekly in week 6	4.3	5.6
# of dressings weekly in week 7	4	5.5
# of dressings weekly in week 8	4.3	5.2

The compliance of the supplement was documented each time participants consumed a study supplement along with a questionnaire regarding gastrointestinal tolerance and adverse effects.

The record showed that the compliance rate is 75.8±3.7% and 86.5±2.3% for the intervention and control group respectively.[9] The author reported a total of 13 adverse effects were reported to be related to the study product.[9] Most of the complaints were gastrointestinal intolerance such as diarrhea, dyspepsia and constipation. Diarrhea is found to be more severe in the intervention group, averaging six times a day. Total of two participants from the intervention group dropped out due to tolerability and the taste of the oral supplement.[9]

Table 5: Adverse Events Across Trials (# of participants monitored) [1,2,9]

	Brewer el al. (18)	Leigh et al. (23)	Van Anholt et al. (43)
Total GI AEs	n/a	1	13
Diarrhea	n/a	n/a	8
Constipation	n/a	n/a	1
Dyspepsia	n/a	n/a	1
N/V	n/a	n/a	3

DISCUSSION:

The use of arginine as a daily oral protein supplement daily has proven effective in pressure ulcer healing rate and size. Although the exact dosage needed is unknown, most hospitals and nursing homes implement protein supplement usage with the assist of clinical dietitians. Arginine comes in both powder and liquid forms and is readily available in pharmacies, health stores such as GNC and supermarkets with no prescription required. Online price search shows the prices of arginine supplements ranged from $7 to $40 depending on the

size and strength of the supplement. For patients with Medicare part B, billing code B4155 can be used for billing, but does not guarantee claim reimbursement.[12] The coverage for Medicaid varies by state. Most hemodialysis and severe malnourished patients with documented albumin or pre-albumin status are eligible for coverage.

An unexpected finding was revealed in Leigh et al. The study has an even distribution of participants who were categorized as well-nourished and malnourished using the SGA tool. The author was able to assess the effect of baseline nutritional status at the beginning of the study and pressure ulcer healing rate. The study revealed that participants who are well-nourished from the start had less severe pressure ulcers at the end of the study regardless of the treatment group.[2]

Throughout the three studies, there were limitations that may have affected the results of each study. In Brewer et al, the small sample size of 18 participants could have hindered the chance of detecting the true benefits of arginine and reduce the statistical control. Furthermore, the use of historical data instead of double blind research method does not reveal important information such as nutritional status and the initial PUSH scores of the historical patient cohort. Therefore, comparisons within each pressure ulcer stages were impossible. One of the major limitations in Leigh et al was that the pressure ulcer healing rate was assessed over a 3-week period instead of time-to-heal method. The effect of arginine after 3 weeks cannot be determined, and thus the long-term effectiveness of arginine cannot be determined. However, the author pointed out that one previous research showed “clinically significant evidence in pressure ulcer healing in 3 weeks”, therefore, a 3-week time frame is practical and provides valid results.[2] Van Anholt et al. and Brewer et al. both discussed the inability to control the nursing schedules and

methods of dressing changes. Although wound care education was provided to the nursing staff, each patient is different and dressing change methods was individualized.[1,9]

Arginine is considered relatively safe oral supplement with minimal adverse reactions. Some studies have shown that 1% to 10% of participants given >10 g of arginine single doses can cause constipation, vomiting or diarrhea in ill patients.[10] Although rare, other uses of arginine include congestive heart failure, chest pain and wasting in HIV/AIDS patients.[11] Intravenous arginine has been used in pediatric patients for the treatment of pituitary dwarfism. The FDA reported recent incidence of pediatric overdosing of arginine hydrochloride injection due to packaging and mislabeled confusion.[11] The product's packaging and labeling has been modified since. There are no known contraindications for arginine oral supplement, but keep in mind to use with caution in patients with impaired kidney function, and taking potassium supplements as arginine may cause high potassium level in the blood. As of 2013, only one fatal cardiac arrhythmia incidence has been reported.[11]

CONCLUSION:

All three studies analyzed have shown that arginine oral supplement is effective in pressure ulcer healing time and size in adult patients with stage II, III and IV pressure ulcers. Accelerated wound healing not only improves the quality of life, but also plays an important role in reducing the cost of healthcare and the length of stay. Which in turn, complications such as sepsis, amputation and death can be prevented. Although it is vital to treat pressure ulcers, prevention should be included as the treatment plan as well. Future studies should use larger sample size and focus on the dosage needed for prevention.

References

1. Brewer S, Desnerves K, Pearce L, et al. Effect of an arginine-containing nutritional supplement on pressure ulcer healing in community spinal patients. J Wound Care. 2010;19(7):311-316.
2. Leigh B, Desneves K, Rafferty J, et al. The effect of different doses of an arginine-containing supplement on the healing of pressure ulcers. J Wound Care. 2012;21(3):150-156.
3. Lyder CH. Chapter 144. Pressure Ulcers. In: Lawry GV, Matloff J, Dressler DD, Brotman DJ, Ginsberg JS, eds. Principles and Practice of Hospital Medicine. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56204670. Accessed September 29, 2013.
4. Pressure Ulcers Among Nursing Home Residents: United States, 2004. Centers for Disease Control and Prevention web site. http://www.cdc.gov/nchs/data/databriefs/db14.htm. Published February, 2009. Accessed September 29, 2013.
5. Barbul A, Efron DT. Chapter 9. Wound Healing. In: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE, eds. Schwartz's Principles of Surgery. 9th ed. New York: McGraw-Hill; 2010. http://www.accessmedicine.com/content.aspx?aID=5013857. Accessed September 29, 2013.
6. Bicket DP, Mathews C, Patel M, Saaraswat T. Chapter 40. Common Geriatric Problems. In: South-Paul JE, Matheny SC, Lewis EL, eds. CURRENT Diagnosis & Treatment in Family Medicine. 3rd ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=8155773. Accessed September 29, 2013.
7. Powers JG, Odo L, Phillips TJ. Chapter 100. Decubitus (Pressure) Ulcers. In: Wolff K, ed. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56053262. Accessed September 29, 2013.
8. Pham B, Teague L, Mahoney J, Goodman L, Paulden M, Poss J, Li J, Ieraci L, Carcone S, Krahn M.
9. Van Anholt R, Sobotka L, Meijer EP, et al. Specific nutritional support accelerates pressure ulcer healing and reduces wound care intensity in non-malnourished patients. Nutrition. 2010;26(9):867-872.
10. Grimble GK. Adverse gastrointestinal effects of arginine and related amino acids. J Nutr. 2007;137(6 Suppl 2):1693S-1701S.
11. L-Arginine. WebMD website. http://www.webmd.com/vitamins-supplements/ingredientmono-875-L-ARGININE.aspx?activeIngredientId=875&activeIngredientName=L-ARGININE. Updated 2009. Accessed November 30, 2013.
12. Medicare Part B Nestle Healthcare Nutrition Products. Nestle Health Science Website. http://www.nestle-nutrition.com/nirf/cm2/upload/D4A2590C-6FDA-402C-88CF-F35167AA416F/Reimbursement_Information_Sheets.pdf. Updated August 2011. Accessed December 8, 2013.