Impact of Iron Supplementation on Wound Healing with and without Ascorbic Acid Supplementation

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BACKGROUND

Cost Impact of Wound Healing

As the population continues to age and the life-expectancy for people with limited mobility increases, clinicians are forced to look for improvements in quality standards of care for patients with pressure ulcers in an effort to reduce length of stay and medical costs[1]. Pressure ulcer damage is two-fold: economic damage as well as damage to patient health. It is estimated that prevalence of pressure ulcers is 3-11% in hospitalized patients and 18% in bedridden patients[1], contributing to more than 3 billion dollars in healthcare costs per year[2, 3]. This amount does not account for lost work time, decreased productivity, disability payments, or cost of rehabilitation. Pressure ulcer acquisition also increases risk for complications related to infection. Patients can experience a decrease in their functional status due to walking difficulty, chronic pain, and psychosocial damage[2]. Improving standards of wound care is essential for decreasing length of stay and accelerating the rehabilitation process in patients with pressure ulcers.

Previous Research

1. Phases of Wound Healing

Pressure ulcer development has been studied extensively. It is now known wounds go through a set progression during the healing process that consists of four distinct, overlapping phases that are necessary for the wound to completely heal. During the hemostasis phase vascular constriction, platelet aggregation, degranulation, and fibrin formation takes place[3].

The second phase is the inflammation phase. Neutrophil infiltration, monocyte infiltration, and differentiation to macrophage occur during this phase. Macrophages clear out apoptotic cells, which then stimulate keratinocytes, fibroblasts, and angiogenesis and begin the process of tissue regeneration. In this manner, macrophage action sets the stage for the proliferation phase of wound healing[3].

Proliferation begins the process of re-epithelialization, angiogenesis, collagen synthesis, and extracellular formation. It is characterized by the re-epithelialization of the provisional matrix previously constructed in the inflammatory phase. Fibroblasts and endothelial cells are the most common cell type in this newly constructed tissue. These cells play active roles in capillary growth, collagen formation, and formation of granulation tissue[3]. This phase is particularly sensitive to nutritional deficiencies[4]. Synthesis of the extracellular matrix brings the wound out of the proliferative phase and into the last phase of wound healing[3].

The maturation phase can last for an extended amount of time. It consists of collagen remodeling and vascular maturation and regression. During this phase, vascular density of the wound returns to normal and the wounded integument is restored to the original integrity[3].

2. Factors Influencing Wound Healing

Many factors influence wound healing status, but most factors can generally be categorized as either local or systemic factors. Local factors directly influence characteristics of the wound itself. Systemic factors refer to the overall health or disease state of the individual that affects the ability to heal[3]. This study will evaluate the effects of nutrition, a systemic factor, on oxygenation, a local factor, within the lager anticipated outcome of

increased wound healing in patients with pressure wounds.

Oxygenation is the local factor of interest. Oxygen is important for cell metabolism with production of ATP, and plays a critical role for most wound healing processes. Oxygenation helps prevent infection, induces angiogenesis, increases keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast proliferation and collagen synthesis, and promotes wound contraction. In addition, production of superoxide by polymorphonuclear leukocytes is critically dependent on oxygen levels. Vascular disruption and high oxygen consumption of metabolically active cells cause the microenvironment of the early wound to be hypoxic and even more so in chronic wounds. In wounds where oxygenation is not restored, healing is impaired. Increased level of ROS production due to hypoxia exceeds the beneficial effect and causes further tissue damage. Oxygen is needed to sustain the healing process[3].

Nutrition is the systemic factor that will be tested during this study, specifically iron and vitamin C. Overall proper nutrition is also important for proper cellular metabolism. Malnutrition prolongs the inflammatory phase, which decreases fibroblast proliferation, angiogeneseis and collagen synthesis. It can also weaken wound healing and increase risk of infection. Collagen synthesis requires hydroxylation of lysine and proline, and co-factors such as ferrous iron and vitamin C. Impaired wound healing results from deficiencies in any of these co-factors[3].

3. Previous Research on Effects of Nutrition on Wound Healing

Pressure sores have historically been more prevalent in malnourished patients. In general observation, increased calories and protein increases wound healing speed[4]. More specifically, for oral nutrition support, amino acid supplementation has been the focus of many previous studies. Arginine supplementation is thought to increase the amount of hydroxyproline and wound collagen deposition. It was also seen to stimulate the host's T-cell response, increase fibroplasia and generation of nitric oxide[5], while promoting a positive nitrogen balance[6]. Glutamine has been shown to synthesize amino acids and nucleotides in the cell.

Concerning nutrition support, Anholt et al. and Cereda *et al.* found that formulas enriched in arginine, zinc, antioxidants, protein, and vitamin C accelerated the wound healing process[7, 8]. Bauer *et al.* concluded that standardized oral nutrition supplements are more effective than specialized supplements in clinical setting[9]. Theilla *et al.* found that feeding formula enriched with fish oil was associated with decreased pressure ulcer progression and decrease in serum levels of C-reactive protein[10]. Further research is needed on the effects of single nutrients on the wound healing process.

Current Nutrition Recommendations

Nutrition interventions directly enhance the healing process of pressure ulcers[11]. Current recommendations for optimal nutrition in healing pressure ulcers from the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition state that the goals of nutrition are to facilitate the wound healing process, decrease risk of infection, and maintain or replenish nutrient stores[12].

1. Energy Intake

In general, 30-35 kcals per kilogram should be provided for patients with pressure ulcers. Aggressive nutrition intervention is recommended for patients with inadequate intake. Patients should have the most liberalized diet possible to encourage oral intake. The goal of energy intake is to regain weight loss or maintain current weight[12]. Individual macronutrient requirements may be adjusted based on age, gender, nutrition status, basal metabolic rate, BMI, activity level, stress of illness, comorbid conditions, severity and number of wounds, size of wound, and stage in wound healing process. Continual re-assessment of nutrition status of

patients with pressure wounds should be conducted to ensure the individual's needs are being met[13].

Protein plays a vital role in the synthesis of enzymes involved in wound healing, cell and collagen proliferation, and connective tissue formation. Prescription of protein should be calculated in relation to wound status and how much protein is lost[13]. Protein intake should be enough to provide positive nitrogen and spare energy. Patients with pressure ulcers are recommended to have at least 1-2g protein per kg, although the higher prescription can be a risk for dehydration in elderly patients[12]. Amino acid supplementation of Glutamine and Arginine have been studied extensively, but the evidence for each remains inconclusive for the matter of wound healing and is deficient to demand that they be supplemented to increase quality of care[13].

There is an increased need for essential fatty acids with any kind of injury. Prostaglandins, which play a major role in cellular metabolism and inflammation, are synthesized with linoleic and arachidonic acid. Deficiencies in these lipids can cause impaired wound healing. In burn patients, omega 3 fatty acids have been seen to improve immune function, reduce infection rates, and improve survival when the diets were supplemented with omega 3 fatty acids[13].

2. Vitamin, Mineral, and Fluid Intake

A standard multivitamin with minerals are recommended if vitamin or mineral deficiencies are present[12]. Vitamins A and C are directly involved in the formation of collagen. 10,000 to 50,000 IU per day of vitamin A and 100 to 200 mg per day of vitamin C is recommended for enhanced wound healing in patients who are deficient in these vitamins[13].

Micronutrients are critical for proper cellular metabolism during wound healing. A dose of 5 to 10 times the recommended daily allowance is suggested for patients with protein energy malnutrition. Forty mg of zinc supplementation for 10 days has been warranted for increased wound healing, although excessive zinc intake can interfere with copper and iron absorption, so this dose is not recommended for an extended amount of time[13].

Adequate fluid intake ensures proper perfusion and oxygenation of tissues. Proper hydration also prevents and treats skin breakdown. Current fluid recommendations from ASPEN are 30mL/kg or 1 to 1.5 mL/kcal consumed. Fluid recommendations may be titrated to match fluid loss through wound[13].

Iron Functions

Iron plays a role in blood and respiratory transport of oxygen and carbon dioxide, and is an active component of the enzymes involved in cellular respiration and generation of ATP. Heme and non-heme containing enzymes play a functional role in the mitochondrial respiratory chain when transferring electrons and when storing energy. Ribonucleotide reductase is an iron containing enzyme that is the rate limiting enzyme in the production of DNA. Iron is also involved in immune function and cognitive performance. Iron deficiency affects humoral and cellular immunity. T-lymphocyte circulation and natural killer cell activity decreases in individuals with iron deficiency[14].

Non-heme iron is transported via transferrin from the site of absorption to other tissues that are deficient. Transferrin saturation can also signal to the body's iron absorption cells. Normal transferrin saturation in healthy adults is 30-35%. A low percentage of the total iron-binding capacity of transferrin would cause absorbing cells to transport iron to the blood[14].

Ferritin is an intracellular store of iron that carries bound iron from the brush border to the basolateral membrane of the absorbing cell. The body stores 200-1500mg of iron as ferritin and hemosiderin with 30% stored in the liver, 30% stored in bone marrow, and the remaining amount stored in spleen and muscles. The amount of circulating ferritin in the blood closely reflects the amount of total body iron stores,

making it a valuable measurement for evaluating iron status. DMT1 binds and transports ferrous iron to the brush border[14].

Hemoglobin holds four iron molecules, providing four sites to bind oxygen. Oxygen binds to iron in the lungs, releases oxygen in response to low pH environment, and hemoglobin then binds carbon dioxide and releases it in the lungs. Myoglobin serves as an oxygen reservoir in muscles[14].

Iron absorption is regulated by hepcidin, a hormone produced in the liver. It acts on the mucosa cell in the gut to enhance or inhibit iron absorption. Liver iron levels, inflammation, hypoxia, and anemia elicit a regulatory response of hepcidin[14]. Treatment with Omeprazole can also have an effect on iron absorption. In patients taking Omeprazole, poor iron absorption has been noted[15].

Role of Iron and Vitamin C in Wound Healing

During the proliferative phase of wound healing, collagen synthesis requires hydroxylation of lysine and proline. Ferrous iron and vitamin C are needed in this reaction as cofactors. Collagen is the most important component of the extra-cellular matrix[16]. Severe iron deficiency can result in impaired collagen production[3]. Iron supplementation has been concluded to increases VO2max and hemoglobin levels in patients with heart failure and anemia[17, 18].

Ascorbic acid is the most potent enhancer for iron absorption. It allows iron to remain soluble in the alkaline pH of the lower small intestine. Vitamin C contributes to iron absorption and metabolism of several amino acids. Vitamin C deficiency is also related directly to decreased collagen synthesis and fibroblast proliferation, resulting in impaired healing, capillary fragility, and poor immune response[16].

HYPOTHESIS

Increased wound healing rates are suspected from patients receiving iron and vitamin C supplementation together as to increase iron absorption, tissue oxygenation via hemoglobin, and production of collagen and fibroblasts. As a result patients will have decreased length of stay and risk for infection. The goal of this project is to optimize wound healing strategies in order to decrease risk for infection and consequently decrease hospitalization related costs.

METHODS

Research Design

This project will be classified as a retrospective, cross sectional review consisting of four cohorts: wound healing rate of patients with flap surgery and no supplements, wound healing rate of patients with flap surgery and vitamin C supplement, wound healing rate of patients with flap surgery and iron supplement, and wound healing rate of patients with flap surgery supplemented with vitamin C and iron together.

Inclusion/Exclusion Criteria

Patients included in this study are male Veterans in the spinal cord injury unit who received flap surgery for pressure ulcer treatment. Patients may start multivitamin as is frequently determined necessary by doctor. Multivitamin prescription will not disqualify patients from being in study, but will be documented and discussed with results of study. Patients will be excluded from study if they were diagnosed with protein energy malnutrition identified as consuming less than 80% of nutrition needs, active smoking, hemoglobin A1C greater than eight percent, NPO status, those refusing iron supplements, and those with insufficient data recorded in the medical chart.

Food intake

Veterans will receive standard medical nutrition therapy for pressure ulcer treatment consisting of 25-40 kilocalories per kilogram based on individual requirements, and 30 mL of fluid per kilogram or 1 to 1.5 mL for every kilocalorie consumed. Patients

documented as having inadequate oral intake or protein energy malnutrition will be excluded from the study.

Criteria for Supplementation

Labs will be drawn to assess levels of iron, ferritin, transferrin, transferrin saturation, and vitamin C. Iron will be supplemented when serum iron is below 40 mg/dL. Vitamin C will be supplemented when levels are below 0.2 mg/dL. Vitamin C will be supplemented 500 mg twice a day as Ascorbic Acid. Iron will be supplemented 325 mg as Ferrous Sulfate.

Data Collection and Analysis

Data collection will come from several sources. Wound healing will be measured by Wound Ostomy and Continence Nurse (WOCN). The Computerized Patient Record System (CPRS) will be used to review labs and healing rates of previous patients with flap surgery. The Medical Information Officer (MIO) will be consulted to gather names of patients with flap surgery. This project will evaluate patients with flap surgery from 2012 to present. Tracking supplementation, lab values, and wound healing rate will be recorded in a de-identified Excel spreadsheet. Average time to heal based on supplementation will be compared within treatment groups.

DATA SECURITY AND PRIVACY

Paper

Paper documentation will be kept in a locked file cabinet in the investigator's office, room 2A118, in the 6 section of the Memphis VAMC and access will be restricted to the primary investigator and approved organizations/personnel only. Key personnel that are no longer approved for the study will have their access privileges terminated.

Electronic

Electronic data will be stored in a secure research folder on the VAMC p: drive under the file path \Documents\151\Investigator Folders\Mrs. Thompson Kimberly\6-digit IRBNet #. The data will only be accessible to the research administrative staff and approved organizations/personnel. Key personnel that are no longer approved for the study will have their access privileges terminated.

Research Records

The investigator research records will be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1).
Data Loss

If it is discovered that study data has been lost, the investigator, or one of the approved study personnel, will immediately notify the Information Security Officer (ISO) and/or the Privacy Officer (PO). If the lost data contains individually identifiable health information (IIHI), the person who discovers the loss will ensure that the PO and ISO are notified within one hour of the discovery.

Release of PHI:

The individually identifiable health information (IIHI) collected for this study will not be reused or released to others unless required by law. The Memphis VAMC Research Administration, IRB and R&DC, the Research Compliance Officer (RCO), the Office for Human Research Protections (OHRP), the Office of Research Oversight (ORO), the Office of Research & Development (ORD) and the VA Office of the Inspector General (OIG) may be allowed access to the study research records for regulatory purposes. NOTE: *Others such as the Department of Health and Human Services (DHHS), the Food & Drug Administration (FDA), sponsor, etc. may need to be added to the previous list to include any others that may be listed in a written consent and HIPAA authorization if required by the study.*

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