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Research Paper

Vitamin C: A Boon to Wound Healing

Dr. Hani Yousuf Naik [1] , Rashi Bansal [2] , Dr. Sinchan Nayek [3] ,
Dr. Dungar Singh [4] , Kaustav Pramanik [5]

1. *Oral and Maxillofacial Surgeon – MDS (I.T.S Dental College and Research Centre , Greater Noida)*
2. *Intern – BDS (Pacific Dental College and Research Centre , Udaipur , Rajasthan)*
3. *Dental Surgeon - BDS (Pacific Dental College and Research Centre , Udaipur , Rajasthan)*
4. *Intern – BDS (Pacific Dental College and Research Centre , Udaipur , Rajasthan)*
5. *Intern – BDS (Pacific Dental College and Research Centre , Udaipur , Rajasthan)*

ABSTRACT
Vitamin C is also known as Ascorbic Acid (AA). It is in involved in all phrases of wound healing. Vitamin C is required for neutrophil apoptosis and clearance in the inflammatory phase. During the multiplication phase, Ascorbic Acid contributes towards synthesis ,maturation,secretion and degeneration of collagen. Vitamin C affects the maturation phase by altering collagen synthesis and formation of scar. The body tries to maintain homeostasis of Ascorbic Acid, thereby ensuring accessibility for collagen production. Plasma and tissue levels of vitamin C decreases after wounding as a result, supplements may be helpful for healing, although levels more than saturation are excreted. Both nutritional status of patients with either acute and chronic wounds and possibility of deficiency of Ascorbic Acid may hinder the healing to which the clinicians must be aware of.
KEYWORDS: *Vitamin C, Ascorbic acid ,Wound healing ,Deficiency Supplements*

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To heal a wound variety of macronutrient and micronutrient and it depends on the stage of healing(Lansdown et al, 1999; Patel, 2005).During the multiplication phase, collagen fibers are produced by fibroblasts process which is dependent on the proper availability of dietary nutrients such as copper, iron and vitamin C(Flanagan, 1997). Wounds such as pressure ulcers or acute burn injuries can lead to increase in metabolic and catabolic state hence increases nutritional needs, explained by Demling (2009). Amongst the micronutrients which are involved to heal wound, Anderson(2005) advocates vitamin C which is commonly known as Ascorbic acid(AA),is the most important due to its influence on collagen production and formation of new blood vessels. Ascorbic acid cannot be synthesized by humans and must therefore be ingested in adequate amount from their diet(Pauling, 1970). Individual having deficiency in vitamin C suffer from prolonged healing and they tend to have weaker scar integrity and abnormal capillary formation, confirming a consensus opinion that Ascorbic Acid is the only true vitamin deficiency to impair wound healing(Burns et al, 2003).This review will consider the structure and function of Vitamin C together with its role in collagen production and as an antioxidant in relation to wound healing.

PHYSIOLOGY OF ASCORBIC ACID -

Ascorbic Acid's chemical name is 2,3-didehydro-L-threo-hexano- 1,4-lactone. It is an acidic, water soluble antioxidant and cofactor of several enzymes. It cannot be synthesized due to deficiency of gulonolactone oxidase(GLO)(Linster and van Schaftingen, 2006). It is oxidised to semi-dehydroascorbate and then dehydroascorbic acid (DA) when Ascorbic Acid acts as a donor of ions to cell reactive free radicals(Kalay and Cevher, 2012).The reconversion of DA via enzymes to Ascorbic Acid was discussed et al(2011) despite Kasahara et al (2009) maintain that DA is unstable and irreversibly decomposes to di-keto-L-gulonic acid, suggesting monodehydroascorbic acid (MDA) has a more important role to play in AA recycling.

Ascorbic acid is present throughout the body in varying amount in serum plasma the cellular component and bone cells (Jacob 1996).Plasma levels are associated to the amount of diet consumption and tissue levels reflects the bioavailability of Ascorbic acid. The concentration of AA within immunocompetent

cells is between 10 and 100 times that of plasma levels (Ströhle et al, 2011). In the experimental study of plasma and urinary pharmacokinectics of vitamin C ,with its increasing amount, it was found that the intracellular concentration reached peak point of Ascorbic acid and that doses of ascorbic acid replete individuals via their diet beyond 100mg per day were excreted in the urine (Graumlich et al 1997).

Recently in the laboratory study it was seen that homeostasis of Ascorbic acid levels in rats, despite they being unable to synthesise ascorbic acid, was rapidly maintained by a process of reductive regeneration from MDA (Kasahara et al (2009). This was attained by administering varying doses an ascorbate oxidase derivative (an enzyme), and checking the subsequent levels of AA in vitro and in vivo. It becomes necessary to maintain the Ascorbic acid levels within cells and organs because the speed of Ascorbic acid decomposition and recomposition from its oxidised metabolites is high. Interestingly, it was also observed that the plasma levels of AA were continuosly lower in hyperglycaemic rats, giving an outcome for wound healing in diabetic patients, due to the increased production of reactive oxygen species and consequent oxidative stress.

It was identified by Villacorta et al(2007) that it occurs when there are more free radicals than that eliminated which leads to tissue injury and inflammation.

According to Ames et al(1993) use of male laboratory bred rats are not considered for study as rats have a basic metabolic rate approximately seven times higher than that of humans, which likely affects the metabolised rate of Ascorbic acid. Addition to it, healing of wound in male rats are obstructed by androgens (Gilliver et al, 2007) and laboratory breeding may introduce genetic abnormalities, potentially affecting the dependency and validity of the study.

There is ongoing research regarding the biological mechanisms of Ascorbic Acid. For example, the precise transport route of AA into the tissues was investigated by Corpe et al (2005). Probable membrane transporter similar compound to AA in vitro(6-bromo-6-deoxy-L-ascorbic acid) which is a transporter substrate which is completely specific to the Na+-dependent vitamin C transporters SVCT1 and SVCT2.Previously, Rumsey and Levine (1998) had proposed that substrate affinity and substrate availability can affect transport, which in turn can be adversely affected by glucose in the plasma. This evidence shows that there is a possible link between AA transport, effect of glucose and the role of neutrophils.

Padayatty and Levine (2001) identified the process whereby neutrophils recycle and concentrate extracellular AA internally via transportation when exposed to bacteria, a depletion of which Jacob (1996) suggests causes a type of intracellular scurvy.

In the late inflammation phase of wound healing neutrophils primarily phagocytose bacteria and release proteinases to disintegrate surrounding components in order to prepare for tissue deposition (Hart, 2002). Therefore, a disruption of this process in relation to a serum deficiency in AA may result in a reduced somatic ability

ROLE OF ASCORBIC ACID -

Ascorbic acid has many roles. It is involved in many somatic processes and indirectly in a numerous enzymatic activities, which include the degradation of tyrosine, synthesis of epinephrine from tyrosine, bile acid formation, absorption of iron and neurotransmitter synthesis (Jacob, 1999; Murray et al, 2000; Villacorta et al, 2007). AA also acts as a direct and indirect antioxidant by influencing the activity of the immune system via phagocytes, leucocytes and lymphocytes (Ströhle et al, 2011). During the respiratory burst high levels of vitamnin C present inneutrophils provide protection of tissue against reactive oxidants and free radicals(Jacob 1999). This respiratory burst from neutrophils and monocytes is a necessary product of immune system phagocytosis to degrade internalised pathogens (Bürzle et al, 2013). A study using murine AA depleted mice investigating the effect of vitamin C defieciency in neutrophils .on in vitro testing of these neutrophils it was determined that it did not undergo timely apoptosis and did not appear to be phagocytosed by macrophages. The authors suggested that, in vivo, these neutrophils may not be cleared from the wound and indeed may degrade to spill the toxic contents into the wound bed, thereby degrading tissues and prolonging the inflammatory phase of wound healing.

Villacorta et al (2007) identified collagen as the principal protein of structures such as skin, bones, cartilage, tendons and blood vessels. An in vitro study was conducted to examine osteoblast activity in presence of ascorbic acid(Urban et al (2012). Collagen type I of osteoblast-like cells increased in line with AA concentration, peaking at 200 μg/ml. While these results may not precisely reflect human osteoblast activity, it does suggest that AA positively influences collagen biosynthesis by acting as a cofactor in pro- collagen production (Baum and Arpey, 2005).the mechanism by which collagen synthesis is affected by lack of AA: collagen triple-helix α-chains are bonded by hydrogen and stability is provided in part by hydroxyproline residues.

AA is responsible for the activation of the enzyme prolyl hydroxylase which catalyses proline hydroxylation, the absence of which causes immediate degradation of the triple helix and resultant defective collagen synthesis. Blood vessels, tendons and skin are consequently affected by becoming friable (Lodish et al,

2004). A deficiency therefore results in a defect in the structure of collagen, thereby impeding the proliferative phase of wound healing (Sanders and Emery, 2003).

DEFICIENCY AND SUFFICIENCY –

James Lind became aware of a disease that afflicted sailors mainly in 175. He did one of the first clinical experiments to examine potential causes of scurvy (Patel, 2005).The effects of a variety of diets on sailors and determined that 'oranges and lemons were the most effectual remedies for this distemper at sea' was examined by him (Lind, 1983).Ascorbic Acid deficiency is known as Scurvy. The major symptoms include easy bruising, pin point haemorrhages, bleeding gums and poor wound healing (Coffee, 1998).

However, Dickerson (1993) argues that AA deficiency is difficult to establish clinically, given the time taken for the diverse symptoms to manifest. The optimum amount of AA for health is currently unknown (Padayatty and Levine, 2001). Previously Ames et al (1993) identified that, in the United States, the recommended intake of 60 mg per day of AA is only effective in preventing observable deficiencies—although this was increased to 75 mg for women and 90 mg for men more recently (Padayatty and Levine, 2001). The body pool is thought to be around 1500 mg when 75 mg of AA are consumed daily, and maximum metabolic turnover is approximately 40 mg per day in healthy individuals (Graumlich et al, 1997). Currently, deficiency is defined as a leucocyte AA level below 0.01 mg per 108 cells (Food Standards Agency (FSA), 2003). Subsequently, the FSA (2006) recommended a dietary intake of 40–50 mg of AA of AA for a healthy adult.

AA IN WOUND HEALING -

Dietary deficiencies affect wound healing adversely and hence metabolism profile of macro and micronutrients changes (Collins et al, 2005). According to Brown and Phillips (2010), there are no specific guidelines for AA in wound healing, although Demling (2009) recommends between 500 mg and 2 g for support of energy production when increase in metabolic state, which constitutes more than 10 times the recommended daily intake as suggested by FSA (2006).

In order to provide insight into the nutritional status of patients with wounds, Pitt et al (2007) investigated the diet of those admitted for diabetic foot complications. AA was not deemed to be deficient, but it is difficult to determine how well the methods of data collection and analysis accurately reflected the true levels. This is because AA levels were not determined by chemical methods; rather, the amount consumed was reduced from a short- term retrospective recall and the method of data analysis id not allow for the increased nutritional needs required for wound healing.

A study to understand the wound healing antioxidant profile in immunocompromised rats(Gupta et al 2002). Tissue samples were collected from wounds on specific days and investigated for antioxidant enzymatic activity in vitro. It was observed by the author that there was significant increased rates of superoxide dismutase (SOD) and reduced rates of the neutralising and detoxifying enzymes against levels in the immunocompetent rats ($p<0.05$).

It was noted that there is decrease levels of Ascorbic Acid in the skin, as well as antioxidants. This suggests that beneficial AA-influenced antioxidant activity is hampered by the altered chemical profile of immune deficiency, thereby delaying wound healing, particularly in the inflammatory phase.

USE OF SUPPLEMENTS IN WOUND HEALING -

There was no improvement in pressure healing ulcer using vitamin C supplements (Ter Riet et al 1995). The intervention group received 1000 mg of AA per day compared to 20 mg in the control group. Hence even after 12 weeks there was no significant differences noted in healing outcomes between the groups. In another study by Long et al (2003), increasing levels of AA supplements were administered to trauma patients. Plasma levels remained deficient with lower levels of AA supplements at 300 mg and 1000 mg per day. On administrating 3000 mg per day, normal plasma levels of Ascorbic acid was detected. Baseline levels of AA on admission were on average 0.11 mg/dl, which according to the authors was considered lower than the normal range of 0.45–1.2 mg/dl which indicated that radical depletion of AA is a physiological response to injury. Therefore to ensure adequate antioxidant levels, immediate high supplements doses of ascorbic acid is important thereby protecting cells and tissues from oxidative damage in the inflammatory phase of wound healing (Padayatty and Levine, 2001).

A randomised control trial by Blass et al (2012) to measure oral supplementation of antioxidants including AA in trauma patients with wound healing disorders failed to establish the exact mechanism by which the appreciable difference in wound healing occurred in the treatment group. However, the level of AA supplements used in the control group conformed to the recommended daily dose of 40 mg by the FSA (2006). Rather than using supplements, Lima et al (2009) conducted a study on wound healing in rats using a topical AA cream containing 10% AA. The results indicated a consistent acceleration in wound response in the treatment group at specified days post-wounding. The number of macrophages were reduced, which may have

reflected the anti-inflammatory property of the cream. Statistically significant increases in the density of collagen fibres were noted throughout the healing period in the treatment group, with wound closure on day 8 as opposed to day 12 with the control group ($p<0.05$). However, the results may not be clinically significant as both wound groups ultimately healed, and without infection.

CLINICAL IMPLICATIONS

Edmonds (2007) explains how wound healing is impaired in nutrition deficiency and that attempts at wound healing without addressing nutritional needs will result in a delayed wound response, which in turn may demoralise the patient.

As there are no functional tests for Ascorbic Acid deficiency on which we can depend , so the levels needs to be determined by leucocytesor more preferably plasma measurements because the results are more easily elucidated (Jacob 1999).

Easier methods to determine nutritional status and Ascorbic acid deficiency should be used as ready access to the form of chemical analysis is unlikely.

Apparent symptoms of AA deficiency includes inflamed hair follicles, coiled hairs on the arms and back and bleeding, swollen gums (Lansdown, 2004) and may be a sign for nutritional investigation. By using a recognised tool such as the Malnutrition Universal Screening Tool (MUST)

(Malnutrition Advisory Group, 2011), The Department of Health (DH) (2010) suggested that screening for nutritional status should take place at the patient's first clinical appointment (Malnutrition Advisory Group, 2011). Despite available evidence, De Tullio (2012) claims much of the relevance of AA metabolism is ignored, resulting in little translation to clinical practice.

CONCLUSION

A review of the literature suggests that Ascorbic Acid plays a comprehensive role in all phases of wound healing with regard to cellular apoptosis, antioxidant processes, collagen synthesis and bone formation (Anderson, 2005).

Ascorbic Acid is required for timely neutrophil apoptosis and clearance in the inflammatory phase (Vissers and Wilkie, 2007). During the multiplication phase, AA differentially interacts in the integral processes of synthesis, maturation, secretion and degradation of collagen (Ronchetti et al,1996).

The integrity of collagen production in the maturation phase is disturbed by the deficiency of Ascorbic Acid which results in scar formation. (Burns et al, 2003). The body strives to maintain essential circulating levels of AA by rapid regeneration of the metabolites that are oxidised after scavenging free radicals. Subsequently, levels of the necessary catalyst for collagen synthesis are constantly available (Kasahara et al, 2009). The use of initial high-dose AA supplements appears to be useful in healing as plasma and tissue levels are rapidly depleted in response to wounding, particularly if the individuals are already scorbutic (Long et al, 2003). Collins et al (2002) suggest considering AA supplements in those at risk of pressure ulcers or established wounds. However, supplements beyond cellular—and therefore beyond plasma —saturation point are simply excreted (Long et al, 2003). It is incumbent upon clinicians to be aware of the nutritional status of patients with wounds, and to refer for a nutritional assessment where appropriate. As exact levels of AA can only be determined by laboratory testing, an element of pragmatism must be adopted and clinicians must be vigilant for any visual clues of deficiency in patients with either acute or chronic wounds.

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