

Effect of Enalapril on Hypertrophic Scars and Keloids

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Abstract: Scarring is a major concern to patient and surgeon following any kind of trauma. Excessive scarring can dramatically affect a patient's quality of life, both physically and psychologically. Incidence rates of hypertrophic scarring vary from 40% to 70% following surgery to up to 91% following burn injury, depending on the depth of the wound. Most current treatment give unsatisfactory results. Recent studies have explored the role of tissue Angiotensin receptors in tissue healing. With potential benefit of Angiotensin converting enzyme inhibitors in preventing cardiac and pulmonary fibrosis, its role in cutaneous scarring needs to be explored. There is need for randomized control trials to study the role of Enalapril in cutaneous scarring. Angiotensin converting enzyme inhibitors and angiotensin receptor antagonist could be potential candidates for management of hypertrophic scars.

Key words: Hypertrophic scars, Keloids, Angiotensin converting enzyme inhibitors, Enalapril.

1. EFFECT OF ENALAPRIL ON HYPERTROPHIC SCARS AND KELOIDS

A total of 100 million patients develop scars in the developed world each year as a result of 55 million elective operations and 25 million operations after trauma [1]. Excessive scars is a result of aberrations of physiologic wound healing and may develop following any insult to the deep dermis, including burn injury, lacerations, surgery, piercings and vaccinations. By causing pruritus, pain and contractures, excessive scarring can largely affect a patient's quality of life, both physically and psychologically. Incidence of hypertrophic scarring vary from 40-70% following surgery to up to 91% following burn injury, depending on the depth of the wound [2-3]. Keloid formation is seen in individuals of all races, except albinos, dark-skinned individuals have been found to be prone to keloid formation, with an incidence of 6% to 16% in African populations [4].

Recurrence rates of keloids after excision range between 45% and 100% [5]. Excision may result in a longer scar than the original keloid, and recurrence in this new area of trauma may lead to an even larger keloid [6].

Since the mid-1960s intralesional steroid injections have been used as one of the most common approaches to reduce hypertrophic scar and keloid formation. Most of the known effects of corticosteroids are thought to result from its suppressive effects on the inflammatory process in the wound [7], and secondarily due to diminished collagen and glycosaminoglycan synthesis, inhibition of fibroblast growth and enhanced

collagen and fibroblast degeneration [8]. Response rates have been highly variable ranging from 50% to 100%, and a recurrence rate of 9% to 50%. Side effects include dermal atrophy, telangiectasia, hypopigmentation and pain at the site of injection [9].

2. PATHOGENESIS OF HYPERERTROPHIC SCARS/ KELOIDS

Histologically, both hypertrophic scars and keloids contain an excess of dermal collagen. Hypertrophic scars contain mainly type III collagen oriented parallel to the epidermal surface with abundant nodules containing myofibroblasts, large collagen filaments and plentiful acidic mucopolysaccharides. Both lesions represent aberrations in the normal process of wound healing, in which there is an obvious imbalance between the anabolic and catabolic phases. Evidence to date strongly suggests a more prolonged inflammatory period, with immune cell infiltrate present in the scar tissue of keloids, the consequence of which may contribute to increased fibroblast activity with greater and more sustained ECM deposition [10].

Inflammation is not the only important step in the development of the fibrotic response. One reason to support this hypothesis is the failure of current antiinflammatory therapies, even in combination with potent immunosuppressive agents, to improve outcomes in fibroproliferative diseases such as pulmonary fibrosis [11]. Current research focuses on direct inhibition of specific fibrogenic events like cytokine elaboration, fibroblast proliferation and ECM deposition. Central to the formation of hypertrophic scar and keloid scar tissue is an alteration of the fibroblast phenotype [12]. When compared with normal fibroblasts, keloid fibroblasts show increased numbers of growth-factor recep-

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tors and respond more to growth factors like PDGF and TGF- β , which may upregulate these abnormal cells from the beginning of wound healing [13].

3. ANGIOTENSIN AND ITS ROLE IN WOUND HEALING

For many years the renin-angiotensin system (RAS) has been investigated only with regard to its cardiovascular and renal homeostatic actions [14]. In recent years the conventional role of Angiotensin II (AngII) has been challenged with evidence to suggest that this active octapeptide hormone of the RAS, is not only produced locally within tissues but also plays a key role in tissue repair, regulation of the ECM and production of fibrous tissue [15].

Tissue RASs have been shown to be capable of the local generation of Ang II, which makes them independent of plasma-borne AngII and facilitates locally restricted effects [16]. This tissue RAS, which acts independently of the circulating renin angiotensin system, has been demonstrated in models of cardiac, hepatic and renal fibrosis [17].

Angiotensin II stimulation has been shown to regulate proliferation of skin fibroblasts and production of extracellular matrix; two key processes in wound healing. AngII has been proposed to be involved in the stages of cutaneous wound healing including increasing vascular permeability, recruiting inflammatory cells, cell proliferation and migration, neovascularisation and fibrosis [16]. Evidence has also shown that AngII has fibrotic properties. It stimulates fibroblasts to synthesize the extracellular matrix components collagen I, fibronectin, laminin and elastin [18]. AngII has also been demonstrated to have a role in the regulation of endothelial cell proliferation and differentiation and new vessel formation during Neovascularisation [19].

Two distinct AngII receptor subtypes are present AT1 and AT2 [20]. Pharmacological studies using specific antagonists have determined that most of the physiological actions of Ang-II are mediated by the AT1 receptor (such as vasoconstriction, cellular growth, production of the extracellular matrix) [21]. This receptor is also involved in the recruitment of inflammatory cells, angiogenesis, cell proliferation and extracellular matrix synthesis [20].

McKirdy *et al.* [22] identified the presence of AT1 receptors using immunohistochemistry in Dupuytren's disease. They found that these receptors were co-localised with areas of myofibroblast expression, which

has implications for the potential of pharmacological regulation using ACE-inhibitors to modulate contracture disease processes. Also, in AngII type 1-receptor (ATR1 knock-out-mice) wound healing was markedly delayed [23].

AT2 receptor-mediated actions counteract those of AT1 receptor-coupled actions. These opposing actions of AngII receptors predispose the RAS to take part in regulatory mechanisms. This phenomenon can be seen in the regulation of cell proliferation by AngII and also collagen synthesis, which are both stimulation via the AT1 receptor and inhibited via the AT2 receptor [16]. In tissue repair and remodelling, changes in angiotensin receptor distribution have been described observed in a variety of organs [24,25].

During wound healing, migration of keratinocytes and dermal myofibroblasts are stimulated by Ang II, mediated by the AT1 receptor. The AT2 receptor appears to have a counteracting effect on cell migration [26]. Studies have shown that skin wound healing is regulated by the balance of opposing signals between AT1 and AT2. Ang II-induced stimulation of collagen production was mediated via the AT1 receptor, while the AT2 receptor had an inhibitory effect on basal collagen synthesis in skin fibroblasts from AT1a receptor knockout mice [27]. It is thought that over-induction of AT1 signalling may contribute towards pathological fibrotic responses such as scarring. Interestingly, the AT2 receptor, which is sparsely expressed in the vast majority of human tissues, is markedly upregulated during wound healing [16].

4. ACE INHIBITORS AND FIBROSIS

Angiotensin Converting Enzyme (ACE) is present in tissues composed largely of fibrillar collagen such as coronary arteries, adventitia of great vessels and intramyocardial coronary arteries as well as the scars [28]. Several reports have described the effects of ACE-inhibitors on myocardial infarction. Treatment with ACE inhibitors is known to cause reduction of left ventricular collagen content and to attenuate remodelling post myocardial infarct (consequently improving left ventricular function) [29]. ACE inhibitors like Enalapril have also been shown to reduce radiation induced lung fibrosis [30]. Diabetic nephropathy [31], Dupuytren's disease, hepatic fibrosis [32] and pancreatic fibrosis [33].

There are reports of association of hypertension with keloid and hypertrophic scar indicating a common etiology of elevated ACE expression [34-36]. In a study

by Arima *et al.* [37] it was observed that there was increased incidence of hypertension in patients who had more than 3 in number keloids and larger than 10cm² keloids [37]. Iannello *et al.* [38] presented 2 case reports using low-dose enalapril to treat postoperative keloids. One of the patients started therapy with enalapril (10 mg, once a day) and after 4 months reported rapid improvement and eventual recovery of the keloid scar. The second case involved a postsurgical abdominal keloid scar of 2 years duration. After 6 months of low-dose enalapril therapy, there was marked improvement in the cosmetic appearance of the keloid. Ogawa *et al.* [39] demonstrated significant improvement in of extensive keloid in a hypertensive patient on starting on enalapril treatment. In a recent study it was seen that early administration of enalapril reduced incidence of hypertrophic scarring and also reduced the collagen content of already formed scars [40].

It is thus seen that ACE inhibitors and Angiotensin receptor antagonist have a role in reducing scarring following injury. Further randomized trials are required to demonstrate potential use as a novel therapeutic agent for the treatment of scars.

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