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Role of Verapamil in Keloids Management: Review Article

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ABSTRACT

Background: A keloid arises due to excessive production of collagen and fibroblasts in the dermis as an abnormal healing response to skin injury. Unlike hypertrophic scars, it grows beyond the original margins of the scar. The exact pathogenesis is still unclear. It is due to either excessive production or decreased degradation of collagen fibers. Some molecular abnormalities are incorporated such as the excess production of growth factors and inactivation of pro-apoptotic genes. Keloids are difficult to treat and the ideal treatment modality isn't yet identified. A wide range of treatment modalities have been used as intralesional injections, radiotherapy, cryotherapy, surgical excision, occlusive dressing, and compression therapy. Intralesional verapamil has been successfully used in the management of keloid and hypertrophic scars. It acts through inhibition of the synthesis of extracellular matrix, reduction of fibrous tissue production, inhibition of IL-6, VEGF, TGF-β1 and induction of fibroblast procollagenase synthesis and apoptosis.

Methods: PubMed, Google scholar and Science direct were searched using the following keywords: Verapamil and keloids management. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included.

Objective: Evaluate of the potential role of verapamil in keloids management.

Conclusion: Intralesional verapamil has a lower risk of side effects than standard corticosteroid injections for treating keloid and hypertrophic scars.

Keywords: Verapamil, Keloids management.

INTRODUCTION

Prevalent keloid is a dermal fibroproliferative condition due to improper wound healing and excessive collagen deposition. It looks like a raised scar, which might be mistaken for hypertrophic scars, a more frequent type of scar [(1)]. Distressing issues, such as keloids, can develop to cosmetic disfigurements that have a significant psychological impact. In addition, keloids can cause sensations like as itching, burning, and soreness, which have a negative impact on a person's ability to perform daily tasks and activities. Earlobes and cheekbones as well as anterior chest and shoulders are the most vulnerable places for keloid development [(2)].

In contrast to hypertrophic scars, keloids spread outward from the initial wound, resulting in a scar that is more noticeable than the surrounding skin. Pain, hyperaesthesia, and pruritus are frequently linked with keloids, and this can have a significant impact on the patient's quality of life [(3)]. Keloids are more common among people of African, Asian, and Hispanic heritage who are between the ages of 10 and 30. Due to more aesthetic operations like ear piercing. Females are more prone to have keloids than males [(4)].

The aim of the review was to evaluate the potential role of verapamil in keloids management.

Methods:

A search strategy has been performed to determine the related literature. Initially, the objective of review was identified: Evaluation of the potential role of verapamil in keloids management. Relevant keywords included: Verapamil and keloids management. These databases were searched for articles published in English in 3 data bases: PubMed, Google scholar and science direct. Also, Boolean operators (AND, OR, NOT) had been used such as verapamil and keloids management and in peer-reviewed articles between 1996 and 2021. Documents in a language apart from English have been excluded as sources for interpretation. Papers apart from main scientific studies had been excluded (documents unavailable as total written text, conversation, conference abstract papers and dissertations).

Clinical picture:

Depending on the severity of the damage, keloids may begin to form between a few months to a year. Lesions have been recorded that were not caused by a disease. However, it is more possible that the injury was forgotten or that the keloid formation was delayed for months or even years because of its insignificance. Keloids can form in any part of the body, although the deltoid, pre-sternal chest, upper back, and ear are the most prevalent places. Palms and soles, eyes and genitalia are all unusual places to find these parasites. Keloids are nodules that protrude from the skin's surface and are composed of a firm, rubbery material [(5)].

Keloids are difficult to treat and the ideal treatment modality isn't yet identified. A wide range of treatment modalities have been used as intralesional injections, radiotherapy, cryotherapy, surgical excision, occlusive dressing, and compression therapy. Clinical trials to compare the safety and efficacy of these variable modalities are always needed to establish the best treatment protocol [(6)].

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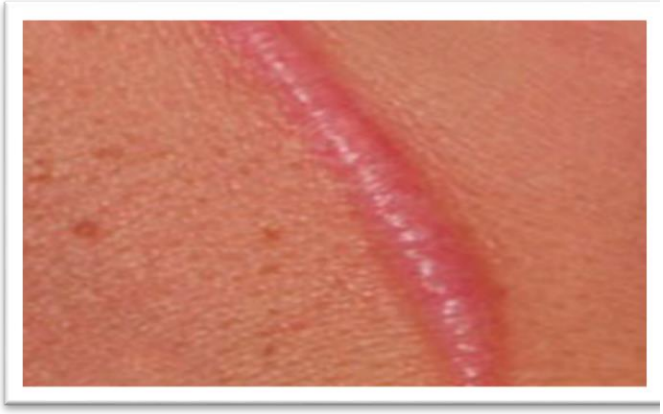

Figure (1): Ear lobe keloid scar from piercing [7].

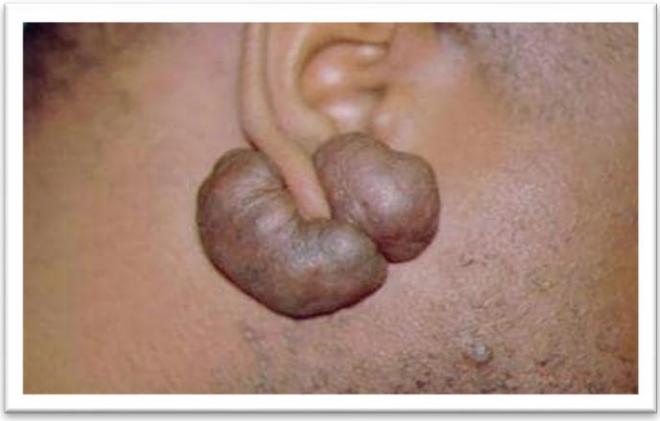

Figure (2): Hypertrophic scar [8].

Intralesional Verapamil:

Calcium channel blocker verapamil is used to treat hypertension, angina pectoris and cardiac arrhythmias because of its ability to inhibit calcium channels. Migraine headaches can also be prevented with this medicine. Cryopreservation has also employed verapamil as a vasodilator. It is a class-IV antiarrhythmic drug [9].

Mechanism of action and medical uses:

The primary coronary and systemic arteries are dilated, and myocardial contractility is decreased as a result of the decrease in extracellular calcium ion trans membrane influx that verapamil causes [10]. Calcium channel blockers dilate blood arteries by relaxing the smooth muscle lining them. As a result, they are now commonly used to treat conditions including hypertension and angina pectoris. Because of a lack of oxygen delivery to the heart, angina results in a sharp, stabbing pain. Verapamil, a calcium channel blocker, causes blood vessels to dilate, increasing the heart's supply of oxygen and blood flow. This relieves pain in the chest, but only when taken on a regular basis. Once the agony starts, it won't go away. Once the pain begins, a more potent vasodilator such as nitroglycerin may be necessary [11].

Mania and hypomania can be effectively treated with verapamil, both in the short and long term. The antimanic effect of verapamil can be increased by adding magnesium oxide to the therapy regimen. It has been used to help pregnant individuals with manic symptoms, especially in the first three months of their pregnancies. It doesn't appear to be teratogenic in a substantial way [12].

Pharmacokinetics:

Oral administration of verapamil results in absorption of more than 90% of the drug, although bioavailability is only 10%–35% due to the drug's rapid first-pass metabolism. It has a volume of distribution of 3–5 /kg and is 90% bound to plasma proteins. After oral dosing, plasma concentrations peak 1 to 2 hours later. At least 12 inactive metabolites are formed in the liver during its metabolism (though one metabolite, norverapamil, retains 20 percent of the vasodilating activity of the parent drug). Only 3–4 percent is excreted unaltered; 70% is eliminated through the urine and 16% through the faeces. In this case, the relationship between plasma concentration and dosage is non-linear. 1–2 hours after oral administration, the drug begins to take effect. Its half-life is between five and 12 hours (with chronic dosages). Hemodialysis does not remove it, and it is expelled in human milk as a waste product. Nursing should be stopped while verapamil is being used because of the risk of an adverse reaction in nursing infants [13].

Contraindications:

People with significant left ventricular failure, hypotension (systolic blood pressure less than 90 mm Hg), cardiogenic shock, and hypersensitivity to verapamil should avoid using verapamil [14].

Intralesional verapamil in the treatment of keloids:

Scars caused by keloids and hypertrophy can be effectively treated with intralesional verapamil. Extracellular matrix synthesis is blocked, fibrous tissue development is reduced, IL6, VEGF are inhibited, fibroblast procollagenase synthesis is induced, and apoptosis is incited. Intralesional verapamil has a lower risk of side effects than standard corticosteroid injections for treating keloid and hypertrophic scars [15].

Verapamil has been found to reduce the development of keloids and hypertrophic scars following plastic surgery when used in abdominoplasty and mammoplasty scar treatment. Several patients with keloid reported good results with this treatment. Scar tissue breakdown is accelerated as a result of increased release of the enzyme procollagenase [16]. Additionally, Verapamil suppresses the formation of extracellular matrix components such as collagen, fibronectin, and glycosaminoglycans by inducing procollagenase expression and increasing collagenase levels in the body. Fibroblasts in keloids have been discovered to have higher amounts of IL-6 and VEGF. Increased apoptosis and decreased cell proliferation are the result of verapamil's effects on IL-6 production, as well as on TGF-β1 apoptosis.

Verapamil depolymerizes the actin filaments of fibroblast cells, which changes their morphology [17]. Calcium antagonists have been shown to alter the shape of cells from bipolar to spherical. Exactly how this is done remains a mystery to this day. Calcium channel blocker may act like a calmodulin inhibitor, causing cells to gather in a ball. The actin cytoskeleton would be altered or rearranged in a calcium-independent mechanism. Calcium antagonists may also disrupt stress fibres, causing a change in cell shape and triggering protease synthesis [18].

Side effects:

Constipation is the most prevalent side effect of verapamil (7.3%). Dizziness (3.3%), nausea (2.7%), low blood pressure (2.5%), and headache (2.2%) round out the list of potential adverse effects. Other possible adverse effects include edoema, congestive heart failure, pulmonary edoema, lethargy, increased liver enzymes, shortness of breath, low heart rate, atrioventricular block, rash and flushing in fewer than 2% of the population [14].

Furthermore, studies have shown that IL verapamil is both effective and safe for the treatment of keloids. Keloids were removed, then pressure dressings and IL verapamil were used to reduce their height by 55% at a 28-month follow-up interval [19]. Another study found that IL verapamil was as effective as IL triamcinolone acetonide at treating keloids when used in combination with IL verapamil. It was determined that both were efficient and produced comparable outcomes (ie, reductions of scar vascularity, pliability, height, and width). In comparison to IL verapamil, IL triamcinolone had a faster effect, but it also had more side effects [20].

CONCLUSION

Intralesional verapamil has a lower risk of side effects than standard corticosteroid injections for treating keloid and hypertrophic scars.

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