Original Article

Increased level of Histamine in keloid Tissue

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Received: 17 July, 2020; Accepted: 08 November, 2020

Abstract

Background: Keloid and hypertrophic scars (HTS) caused by an imbalance between the production and destruction of collagen during wound healing with an unknown underlying pathophysiological mechanism. This study was designed to evaluate the histamine level in the Keloid and HTS and comparison of results with normal skin.

Materials and Methods: This pilot study included 36 participants, aged from 18 to 70 years with keloid (n=11), HTS (n=13) and normal (n=12) skin. The level of histamine in the skin samples was measured using enzyme-linked immunosorbent assay (ELISA).

Results: Histamine level in keloid samples was significantly higher than in the normal (p=0.0012) or HTS (p=0.0028) groups. However, there was no significant difference between the normal and HTS samples (p=0.92).

Conclusion: The increased histamine level in the keloid tissue may contribute to its pathogenesis and the application of anti-histamines could be of benefit for the prevention and treatment of keloids.

Keywords: Histamine; Hypertrophic scar, Keloid, ELISA, Antihistamine

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Please cite this article as: Niazi F, Hedayatyanfard K, Soroush M, Habibi B, Haddadi N-S, Rostami Kh, et al. Increased level of Histamine in keloid Tissue. Novel Biomed. 2021;9(1):1-4.

Introduction

Keloid and hypertrophic scars (HTS) are two types of scars with complex pathogenesis. These two kinds of scar differ pathologically and each needs different therapeutic approaches. The current treatments are not fully effective and cause irreversible side effects. The poorly defined underlying mechanism is an obstacle for the development of new treatments. Both keloid and HTS are the results of deregulation of normal wound healing ending with excessive extracellular matrix production and fibrin deposition. Mast cells and their mediators are involved in different phases of wound healing[1]. Some data have shown that mast cells are increased in the scar tissue[2]. Their number or activation has also been stated to be lower in tissues that heal with minimal scarring[1]. Administration of mast cell inhibitor, disodium cromoglycate, to mice

decreases the scar and inflammation. Histamine is a biogenic amine mainly released from mast cells and acts on four main histamine receptors (H1-H2) belonging to the G protein-coupled receptor superfamily.

Histamine enhances vasodilation and capillary permeability resulting in the influx of neutrophils. It supports the growth and differentiation of fibroblasts and collagen synthesis[1]. Several studies have suggested the use of anti-histamines for scar treatment. However, there is not any data regarding the concentration of histamine in any kind of scar. This study was designed to evaluate the histamine level in keloid and HTS.

Methods

The present study was a descriptive cross-sectional study, which was carried out on 36 patients (18-70 years old) with keloid (n=11), HTS (n=13), or normal skin (n=12) who were referred to Modarres and 15 Khordad Hospital, Tehran, Iran, from September 2016 to 2017. The ethical committee of the Shahid Beheshti University of Medical Sciences approved this study (IR.SBMU.RETECH.REC.1397.564) and all participants signed the informed consent form. The study was in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act.

The exclusion criteria were 1) history of any cancer or severe systemic disease; 2) current treatment with chemotherapy or immunosuppressive drugs; 3) pregnancy or breastfeeding; 4) any treatment for scar within the past two months. The samples of the scar tissue were isolated from the center of the lesion. The tissue samples were then cut into small pieces, and then an equal amount of all tissue samples were removed and mixed with a certain volume of PBS (pH 7.4, 100mM). Thereafter, all tissue specimens were homogenized and centrifuged at 4000 rpm for 10 min to obtain their supernatants. The level of histamine was measured in supernatants in duplicate using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Human histamine, ZellBio GmbH, Germany; Cat No: ZB-11552C-H9648). The ordinary one-way analyses of variances with Tukey test was used to compare the means (GraphPad Prism software version 8.0.2). A p value of $0<0.05$ was considered as significant level.

Results

Histamine level was significantly different among the groups ($F(2, 33)=9.297$, $p=0.0006$). The concentration of histamine in keloid (54.69±7.36, mean ± SD) was significantly higher than normal (43.4±7.33, $p=0.0012$) and HTS (44.44±6.08, $p=0.0028$) tissue specimens. There was no significant difference in the levels of

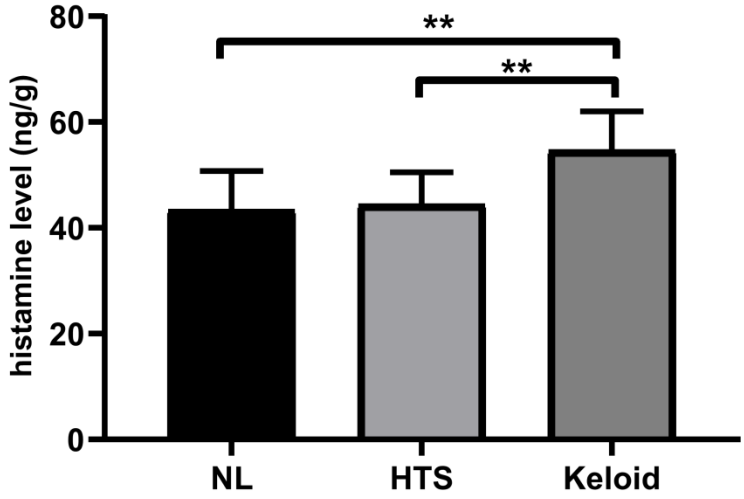

Figure 1. Histamine concentration (ng/ml) in normal, HTS, and keloid groups. All data are shown as mean ± SD; ** and P<0.05 was considered statistically significant.

Table 1: Demographic characteristics of patients.

	Keloid (n= 11)	HTS (n=13)	Normal skin (n=12)	p value
Gender, n (%)				
Male	6 (54.54%)	8 (61.53%)	5 (41.66%)	>0.05
Female	5 (45.46%)	5 (38.47%)	7 (58.34%)	
Age, year (mean ± SD)	35.9 ± 3.93	23 ± 1.76	27.16 ± 2.17	>0.05
Scar site (n, %)	Neck (2, 18.1%)	Face (1, 7.7%)	Neck (8, 66.7%)	
	Hand (2, 18.1%)	Neck (8, 61.5%)	Arm (1, 8.3%)	
	Arm (2, 18.1%)	Hand (1, 7.7%)	Elbow (2, 16.7%)	
	Sternum (4, 36.7%)	Arm (2, 15.4%)	Abdomen (1, 8.3%)	
	Leg (1, 9%)	Lumbar (1, 7.7%)		
Etiology (n, %)	Flame (5, 45.5%)	Flame (9, 69.23%)		
	Trauma (5, 45.5%)	Trauma (3, 23.07%)		
	Spontaneous (1, 9%)	Chemical (1, 7.7%)		

histamine between the normal and HTS groups (p=0.92) (Fig. 1). Demographic features of the patients are shown in Table 1.

Discussion

Histamine level was significantly increased in keloid tissue compared with HTS and normal skin samples. This increased level may be related to the increased number or activity of mast cells. The results are in line with a study conducted by Wilgus *et al.*,[2] in which they reported the increased number of mast cells in scar tissues. Their number or activation has also been found to be lower in tissues undergoing scar-less healing than those that heal with more fibrotic scars[1]. Cutaneous wound healing in the fetus at early stages of development, unlike the mature skin, is not accompanied by inflammation. The number of mast cells in fetal wounds in embryonic day 15 mice showed to be nearly half of those in embryonic day 18 mice. They also have smaller size with fewer granules. Additionally, injection of lysate obtained from cultured skin mast cells of embryonic day 18 mice to wounds of fetuses with embryonic day 15 resulted in the formation of the scar while administration of lysate from embryonic day 15 mice to embryonic day 18 mice led to scarless results[3].

Production of scar significantly is reduced in mast cell-deficient mice in comparison to wild type animals[3]. Mast cells have histamine-containing granules that are responsible for many of their functions[1]. Mast cell inhibitors effectively decrease scar formation in mice while the rate of wound repair is not affected. H2 receptor antagonists are found to block collagen production in cultured keloid fibroblasts[4]. Interestingly, histamine has a key role in endothelial cells proliferation and angiogenesis by activating H1 and H2

receptors, which may be contributing to the keloid formation. The number of vessels and level of vascular endothelial growth factor is significantly higher in keloids than in normal skin[5]. The histamine level is significantly higher in keloids compared to HTS or normal skins.

Conclusion

Our data suggest the deed for conducting an interventional study to examine the potential impact of the use of topical anti-histamines for the prevention and treatment of keloids. Further investigations are needed to unravel the type of anti-histamine receptors that contribute to the scar formation.

Acknowledgment

This study was supported by a grant from the Shahid Beheshti University of Medical Sciences, Tehran, Iran (12763).

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