CLINICAL AND PATHOHISTOLOGICAL EXAMINATIONS OF KELOID AND HYPERTROPHIC SCAR MANAGEMENT AND THE POSSIBILITIES OF PREVENTION

Ph.D. thesis

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1. INTRODUCTION

Modern research of pathologic scarring has been intertemporal for three centuries from the beginning of the 19th century to present day. Its significance and topicality is determined by a combination of several factors. The aetiology of keloids remained unknown in spite of the genetic, experimental and clinical examinations. Despite the different and well-known predisposing and risk factors hypertrophic scarring did not lose its clinical significance due to the growing number of operations in manual professions and the frequency of burn injuries. The schematic incision line, while keeping the practicality of optimal exploration in view does not take the direction of the lines of force into account, and often the non-adequate and traumatizing operation techniques result in a great number of patients consulting doctors with linear hypertrophic scars. ***J. Alibert*** French surgeon named the abnormal proliferating scars keloid after the Greek word “chele” (meaning pincer/claw) as the unlimitedly growing amorphous mass of scar reminded him of pincers. This terminus technicus, a milestone of surgery, first appeared in his 1806 Paris publication. This was followed by several hundreds of thousand publications dealing with pathologic scars in the past two centuries. In the second half of the last century, in the modern phase of clinical and experimental researches new and newer scar treatment methods were applied in a routine-like manner. First, from the 1960s, the pressure garment treatment became widespread. It was followed by administering intralesional steroid injections in the perioperative phase. By combining the long standing methods, supplemented by radiotherapy, the combined/complex therapy became compulsory and vital to keloid treatment as it was proven long before that the recidivation rate was close to a 100% in cases of exclusively operative treatment. Later this basis combination was complemented with newer methods. In the 1980s the positive impact of sheetings containing silicone-polymer on scar maturation was recognized. The silicone gel sheeting treatment makes a positive effect by increasing hydration. In the last decades of the 20th century the newest techniques for the treatment of pathologic scarring were adapted. There were promising results with different lasers. Cryotherapy was also introduced, and then new, locally administrable medicines were implemented. These adjunct treatments can be complemented by other alternative methods in the postoperative phase. For measuring the efficiency of the various therapeutic methods and for the comparability of results there was a need

for an objective and quantitative scar assessment system. The leading burn and plastic surgery centres of the world introduced an assessment system with international consensus, the so-called Vancouver-scar scale, which satisfied the aforementioned needs and today is an applied, standard scar-scaling method. The exact quantitative measuring of scars is also important, as well as determining the subjective complaints of the patients. With the introduction of newer, wide-spread and widely accepted methods carrying out randomized, prospective clinical experiments, evaluation and comparative analysis of scar treatment methods became possible. Despite experimental researches and the better results of clinical treatment the significance of pathologic scarring and the related fields of its investigations are not lessened. Clinical experiences demonstrate the assumption that the emerging of the symptoms consist of many factors affecting simultaneously. The multi-factorial origin is underpinned by experimental results as well. In the future, research based on cellular, extracellular and molecular level may prove the roles of many factors unknown today. Before defining and detailing aims it would be reasonable to evaluate the experimental research models and a review of molecular biology of wound healing.

2. THE MOLECULAR BACKGROUND OF WOUND HEALING

During the past decade examining scar healing and its research on molecular level was one of the most productive areas in terms of knowledge. This continuous development resulted in a new perspective in clinical practice, in established or still researched, however promising methods. To understand and examine the process of pathologic scarring it is necessary and vital to discuss the newest results of wound healing in molecular biology. It is crucial to differentiate between the acute and chronic wound by precisely defining them. Today’s approach is that successful wound healing depends on the appropriate angiogenesis, more precisely on the formation of new capillaries and granulation tissue. The almost outworn classification of the stages of wound healing process are the strongly connected inflammatory, proliferative and remodellization phases. Earlier these phases corresponded to the regeneration and reparation phases as well. This unified, clear-cut stage division reflecting more knowledge was further broadened, mainly with the detailed definition

of the angiogenesis. These new classifications and labelling represent the growth of knowledge. According to this the early and late phases of angiogenesis, the vascular proliferation and stabilization, and finally the suppression of angiogenesis can be differentiated. The reformation of capillaries is regulated by the complex and strongly connected molecules out of which the angiogenic growth factors play determinative role. In the structure of the extracellular matrix the so-called matrix proteins are the most important, the type I and III collagen, the fibronectin and tenactin. Matrix cytokines were known long before but the multiple bioactive role of extracellular matrix in scar healing was only proven recently. The regulation processes of on cell and tissue level materialize through receptor transmitted signalling, reexpression of special proteins, cytokine production, mechanic and chemical signalling, and through the interaction and topography of cells. Stages of normal wound healing occur along the delicate balance of stimulating and supremative factors. For clinicians dealing with disorders of scar healing so far the conventional treatment consisted of “passive” interventions such as transmitting antimicrobic agents, using antiseptic dressing and relieving tools. A change of perspective in the everyday clinical practice can only be reached by getting to know the molecular processes and regulation of wound healing, understanding the experimental methods for intensifying wound healing and the active participation in the promising pharmacologic treatments.

3. AIMS

In a decade, between 01 November 1995 and 31 October 2004 we have treated more than 500 patients with different types of pathological scars with a wide range of sizes, with diverse appearances and various localizations. We were searching for the solutions of those problems occurring at the treatment of pathologic scars, which we were facing during unsuccessful treatments by applying therapeutic and prophylactic methods and histopathological, immunohistochemical and electron microscopic examinations.

1. Is the formation of mature dermis-originated collagen fibre and its structuring to orderly form justifiable by the two generally recognised methods: silicone gel sheeting and intralesionals steroid therapy?

2. Using transmission electron microscopic examinations, we were trying to find what intracellular (molecule level) changes are induced by silicon gel patch and intralesional steroid treatment in the process of pathological scarring?
3. Furthermore, we compared the macroscopic – clinical morphological – and light microscopic cell level changes in the differently treated cases of keloids and hypertrophic scarring.
4. We were inquiring whether the compared examination results mentioned above approve the place of the generally recognised and widely used scar treatment methods in clinical practice, or they should be reconsidered and with further researches their role should be determined in the first-, or second line protocol?
5. Finally, we were aiming to work out those preventive and follow up treatment protocols, which are elementary to the basic treatment yet missing today.
6.What kind of cellular and connective tissue phenomena can be detected during the macroscopic morphology of scar changing? What may be the conclusion for the clinical practice?
7. Which is first-, and second line therapeutic method to choose from in the case of hypertrophic scarring and keloids?

4. THE CLINICS OF PATHOLOGIC SCARRINGS

4.1 The Vancouver-scar scale and score
4.2 The quantitative methods
4.3 The aetiology of pathologic scars
4.3.1 The causes and risk factors of hypertrophic scar formation
4.3.2 The possible causes of keloid formation
4.4 Preventing pathologic scar formation
4.5 The principles of plastic surgery and the rules of operative techniques
4.6 Methods of prevention

5. THE SILICONE GEL SHEETING TREATMENT

5.1 The chemical structure and effect of silicone gel sheeting
5.2 The clinical use of silicone gel sheeting: continuous or interrupted treatment

5.3 Silicone gel sheeting treatment protocol

The patients used an exclusively predetermined type of sheeting (Epiderm®, Biodermis Corp., and USA), daily, continuously for 12 hours. The sheeting of appropriate size and shape exceeded the edges of scars 2-2 cm in each direction. The patients were thought how to use the sheeting and informed about the treatment and its documentation. The follow-up examinations happen in every 2 weeks. Besides digital photo documentation and Vancouver scoring the changes of subjective complaints were also recorded.

5.4 Clinical case study

6. THE INTRALESIONAL STEROID TREATMENT

6.1 The chemical structure and effect of the corticosteroid applied

6.2 The rules of clinical use

6.3 The intralesional steroid treatment protocol

In our department we use triamcinolonum acetonidum (***Inj. Kenalog***) 2% solution diluted with Lidocain to 10%. One ampoule Kenalog contains 40mg of active agent, after dilution it contains 4mg/ml. From the solution we inject 1-1 ml per square centimetres with linear technique choosing the needle between 12G and 18G. The size of the needle depends on the status of the scar. Usually, treatments are carried out every two weeks according to therapy.

6.4 Clinical case study

7. CLINICAL EXAMINATION OF SILICONE GEL SHEETING AND INTRALESIONAL STEROID TREATMENTS

7.1 Patient group and method

In our department, the Department of Surgery of the University of Pécs, during the 4-year period between 01 April 2001 and 31 March 2004 more than 250 patients were treated with complaints cased by pathologic scars. For our experiment well cooperating patients were selected from the abovementioned patient group, out of whom 2 groups of patients suffering from keloid- and 2 groups suffering from hypertrophic scar were formed. In each patient group 12-12 patients were

treated (altogether 48 people) according to the known protocol. Control examinations were carried out in every 2 weeks for four months. In the patient groups the distribution of sexes was the following: male:female =1:2. The average age of the patients was 43 years. The youngest patient was 17, the oldest 67 years old. More than half of the patients belonged to the age group between 30 and 50 years. The important risk and/or predisposing factors including accompanying illnesses, as well as the distribution of scars according to localization were summed up separately. Diabetic patient and those suffering from autoimmune illnesses were excluded, just like the patients receiving systemic or local steroid/non-steroid treatment for their accompanying illnesses. Due to the extremely god cooperation the treatment of patients was a 100% completed in all groups.

7.2 Clinical examinations

First the therapeutic results of both standard methods were analysed separately according to scar types. The dual (cross) comparative evaluation helped to determine the place of the methods in different protocols.

7.3 The results of silicon gel sheeting and intralesional steroid treatment of hypertrophic scars

The therapeutic response to intralesional steroid treatment is quicker and more expressed than in case of silicone gel patch, however, therapeutic response is significant in both cases. Considerable remission is verified by photos its most distinctive clinical symptom is the easy corrugation of epithelium on the surface of the scar. Silicone gel patch therapy becomes ineffective between the 12^{th} -14^{th} weeks. After the 8^{th} week there was no further administration of intralesional steroids into the well reacting scars (to avoid unwanted local intergrowth), nevertheless the therapeutic effect of the drug was measurable even later on in the significant decrease ($p>0.05$) of the activity symptoms of scars.

7.4 The results of silicon gel sheeting and intralesional steroid treatment of keloids

Comparing the results of the treatments it can be said that there is a quicker therapeutic response to intralesional steroid treatment than in case of silicone gel patch. As opposed to the silicone gel treatment, results of steroid treatment of keloids

are significant. Macroscopic morphology of scar changing on the photo documentation of patients supported the results, convincingly illustrating the changes of the MPHV-score parameters.

7.5 The comparison of silicon gel sheeting treatment of hypertrophic scars and keloids

Keloids hardly reacted to silicon gel patch treatment; the therapeutic response was not significant. Analysing the silicon gel patch treatment of the two scar types it is observable that in case of hypertrophic scars the effectiveness of the method marked and compared to keloids the difference between therapeutic response is significant (keloid: $p>0.05$, hypertrophic scar: $p<0.05$).

7.6 The comparison of intralesional steroid treatment of hypertrophic scars and keloids

The intralesional steroid treatment had significant results in treating both types of scar, however, in case of hypertrophic scars the effect of the treatment is more and more marked after the 10^{th} week as compared to keloids, the Vancouver-score drops steeply. In the hypertrophic scar patient group the subjective complaints entirely disappeared in the 9^{th}-10^{th} week of the treatment. However, regarding the outcome there is no significant difference between the accomplished therapeutic responses of the two groups ($p < 0.05$).

7.7 The change of the patients' subjective complaints

The change in the patients' subjective complaints is determined by the ***Likert-scale***.

7.8 Results

From analysing our results it can be concluded that in the treatment of hypertrophic scars the silicon gel sheeting treatment is effective, therefore it is the primary method to choose. Further results of patient groups also supported its place in therapeutic protocol. While treating keloids the intralesional steroid treatment first-line weapon, as the silicone gel sheeting had only moderate effect. With its use there was no significant difference in the results, therefore it only plays an adjunct role in the therapeutic protocol of keloids. In case of the silicone gel sheeting treatment-resistant hypertrophic scars, intralesional steroid treatment is the primary choice as this type of

scar had quick and expressed therapeutic response in case of all patients. Based on our clinical results we put down ***recommendations for therapeutic, prophylactic and follow-up protocols according to scar types***. We differentiate so-called first and second-line methods. The differentiation of therapeutic methods to be displayed cannot be taken as a final, “gold standard” state as with the introduction of newer results and possible treatments the protocols are subject to change.

8. MORPHOLOGICAL EXAMINATION OF HYPERTROPHIC AND KELOID SCARRING TREATED WITH SILICONE GEL SHEETING AND INTRALESIONAL STEROID: PATHOHISTOLOGICAL, IMMUNO-HISTOCHEMICAL AND TRANSMISSION ELECTRON MICROSCOPIC RESULTS

8.1 Patient groups and methods

To be able to evaluate and compare results more completely we examined *not only* hypertrophic scars and keloid chosen from patient groups which were treated occurring to intralesional steroid and silicon gel patch protocol and were operated and removed *but also* untreated hypertrophic and mature scars.

8.2 The results of pathohistological examinations

We examined haematoxylin-eosin stained segments with different magnification (between 100x and 500x). The state of cell like elements and the connective tissue are even more visible with trichrome staining.

8.3 The results of immunohistochemical examinations

We examined the actin activity which was displayed the metabolic activity of different cellular elements. The endothel cells of atrophic scar showed metabolic activity moderately, while the numerous fibroblasts of hypertrophic scars and keloids indicated it to a marked degree.

8.4 Transmission electron microscopic examinations

***Examinations were carried out at the University of Pécs in the Central* Electron Microscopic Laboratory with a JEOL 1200EX-II type transmission electron microscope. Examinations were carried out according to a precisely determined protocol. Electron microscopic examinations were carried out with magnification ranging between 5000x and 50000x.**

8.5 Results

We compared results of mature scars, untreated scars and hypertrophic scars treated by standard therapeutic methods used as control group with the results of keloids. In the electron microscopic morphology of mature and different pathologic scars individual cellular and extracellular properties can be found. These characteristics did not change or disappeared as a result of standard therapeutic methods, only decreased to different extent. Fibroblasts examined in hypertrophic scars have the same characteristics as intact, dermis-originated fibroblasts; the difference was only observable in morphologic characteristics indicating metabolic activity. On the contrary, the electron microscopic structure of fibroblasts examined in keloids fundamentally differs from cells in the dermis of intact skin. Only in the cytoplasm of these fibroblasts of keloid-origin is this electrodense material observable – that is greatly overproduced and stored, and fills almost the entire periblast – and which, with pathohistological and immunohistopathological examinations proved to be glycoproteins (earlier labelled as mucopolysacharids). Besides, the intra- and extracellular position of irregularly structured pro-collagens and collagen fibrillums was observable. The structure of the extracellular matrix is complex; it is built up regularly of molecular and cellular mechanisms. In these processes glycoprotein molecules have an essential role because they comprise the upholder system of the matrix thus they are responsible for the flexibility and the stability of the scars. The reason for keloid formation is unknown but keloids bear the most important and the highest relevancy of clinical characteristics (progressive, unrespectful growing over histic boundaries) which is caused by the individual structure of the extracellular matrix: it is specific of uncontrolled, unregulated matrix elements generating in a very high number. According to our present knowledge for this pathological process fibroblasts identified only in keloids are responsible. **We named keloid originated fibroblasts as “keloidocytes” because they have pathognomonic value**.

Researching the formation of keloidocytes may lead us closer to the final recognition of the aetiology of keloids. Examining DNA replication may give further knowledge as keloids behave as semi-malignant tumours, therefore these examinations may help the understanding of the biological behaviour of keloids.

9. Novel findings

1. It was proven by our examinations that silicon gel patch should be chosen as the first line treatment in cases of hypertrophic scars, while treating keloids it has only adjuvant role, thus in these cases the first line treatment should be the intralesional therapeutic method.
2. The morphological examinations we carried out supported our clinical results that the silicon gel patch treatment is only effective in cases of hypertrophic scars.
3. During the examinations of keloids by transmission electron microscope we detected fibroblasts at first, which can only be found and are characteristic to these kinds of scars. Because they have pathognomonic value, we named these increased quantity of keloid originated pathological fibroblasts containing glucose-amino-glycans as keloidocytes.
4. We revealed the fact that after administering intralesional steroids it is crucial to the fast therapeutic response that the medicine is immissioned into the “core” of the scar in order to greatly reduce activity of cell like elements in keloids.
5. According to our clinical and histological examinations we determined therapeutic, prophylactic and follow up protocols of the different scar types, which may also serve as recommendations for plastic surgery centres.

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