Chapter

Hypertrophic Scarring

Jesus Escriva-Machado, Eduardo Camacho-Quintero, Alejandro Maciel-Miranda, Samuel Almeida-Navarro and Julia De la Luz-Hernandez

Abstract

Hypertrophic scars represent important problems because of the presence of pain, pruritus, contractures, as well as unsatisfactory aesthetic results. Currently, the evidence shows that a multidisciplinary management through prevention, adequate choice of suture, atraumatic surgical technique, and early noninvasive measures can favor the handling of these problems and continue with invasive measures that employ intralesional drugs. Clearly, the combination of surgical, technical, and pharmacological interventions will maximize therapeutic results.

Keywords: hypertrophic scar, scar, pathological scar, surgical scar

1. Introduction

Hypertrophic scars (HS) are defined as a pathological scars that have abnormal thickness and are raised from the previous wound [1]. Such scars are the most common complication of burn injury and abnormal wound healing response after traumatic injury, surgery, or inflammation [2, 3]. These lesions are characterized by their red to purple color, raised appearance, decreased pliability, and tenderness with concomitant symptoms including pruritus and pain [4–9]. Patients with HS may suffer from stiffness, cosmetic disfigurement, joint contractures, as well as impediment in physical function and daily activities, and even psychological issues such as depression or anxiety [1, 10–12].

2. Epidemiology

The best clinical predictor for the development of hypertrophic burn scars is a prolonged inflammatory wound healing phase. This result usually corresponds with a wound that has not epithelialized and continues to exudate for more than 3 weeks [13]. Hypertrophic scars generally develop at about 2 months after a burn and will continue to proliferate for a year or longer. HS maturation may not occur until 18 or even 24 months after a burn. The exact time point of regression or maturation of HS remains unknown [8–10, 14, 15].

According to the literature, about 32–72% of surgical skin wounds result in HS after 1 year [16, 17]. In Asian, the prevalence rate of HS after burn injury is as high as 70%, much higher than in Caucasian populations. Contractures after burns have a prevalence of 38–54% of patients, with up to 46% patients undergoing at least one reconstructive procedure after their acute hospital stays [18, 19] (**Figure 1**).

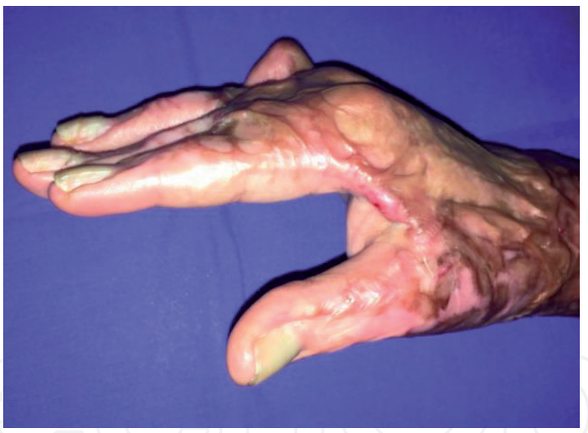

Figure 1.
Patient with a history of flame burn. Hypertrophic scars that affect the first interdigital space.

In order to prevent and treat pathologic wounds, one must first understand the basics of normal wound healing.

3. Wound healing

The desirable result of normal wound healing is replacement of the initial hemostatic clot with skin that approximates the aesthetic, mechanical, and functional properties of the preinjury tissue.

Historically, wound healing has been arbitrarily divided into three phases, with some authors adding hemostasis as the inciting phase. Although wound healing occurs on a time continuum, division of the process into phases allows for ease of description and evaluation. Changes in the steps of normal wound healing may result in either a "hypoplastic" or chronic nonhealing wound or a hypertrophic "over-healed" wound [20].

The clotting cascade is activated immediately after trauma, a consequence of the disruption of the vascular endothelium and exposure of the basal lamina that results in extravasation of blood constituents and concurrent platelet activation. Subsequently, the release of growth factors causes the deposition of extracellular matrix (transforming growth factor β), chemotaxis (platelet-derived growth factor), epithelialization (fibroblast growth factor and epidermal growth factor), and angiogenesis (vascular endothelial growth factor) [21, 22].

4. Inflammatory

An inflammatory phase develops and persists for 4–6 days. This phase is characterized by hemostasis and leukocytic infiltration led by polymorphonuclear leukocytes. Neutrophils, as well as monocytes, fibroblasts, and endothelial cells deposit on a fibrin scaffold formed by platelet activation. The presence of neutrophils is followed closely by monocytes that are quickly activated into tissue macrophages. These cells cause further tissue debridement and secrete additional cytokines as well as growth factors that promote fibroblast proliferation, angiogenesis, and keratinocyte migration [23].

5. Proliferative

The proliferative phase of wound healing begins at 4 days and persists up to 14 days; this phase is heralded by the transformation of monocytes to macrophages.

Keratinocytes initiate epithelialization and are present on the wound edge as well as from dermal appendages such as hair follicles, sweat, and sebaceous glands. Epidermal growth factor, fibroblast growth factor, transforming growth factor β, and multiple cytokines originate cell detachment and mitotic division; then, fibroblasts appear in the wound after 24 hours of this stimulation and produce collagen. This process requires adequate oxygen supply. In fact, without oxygen to assist in the hydroxylation of proline and lysine residues, chemical bonds will not form appropriately to create a mature form of collagen. These bonds are very critical because their absence can prolong the stage and result in a chronic wound. They serve as the basis for the final stage of maturation and remodeling [24].

6. Maturation

Appropriate wound maturation and remodeling result in a quickly healed and minimally visible scar; whereas, prolongation or deviations from this phase can cause hypertrophic, keloid scars or chronic nonhealing wounds. This initial collagen is thinner than uninjured. Type III collagen initially comprises 30% of the granulation tissue matrix, compared with 10–20% in uninjured skin. Over time, the ratio of type III collagen decreases, and type I collagen increases. An overall increase in collagen formation is seen for 4–5 weeks; after this time wound strength increases and parallels the increase in type I collagen [25, 26].

7. Cellular basis, signals and pathways of hypertrophic scars

Fibroblasts and myofibroblasts are pivotal effectors cells in HS [27]. The activation of fibroblasts and differentiation into myofibroblasts (that are a phenotypically intermediate cell type between fibroblasts and smooth muscle cells) are the central processes in the pathophysiology of hypertrophic scars. The larger the area of the wound, the greater migration of myofibroblasts. This situation results in more prominent scarring [28, 29]. Many origins of fibroblasts or myofibroblasts have been characterized: local dermis and subcutaneous tissues around the wound

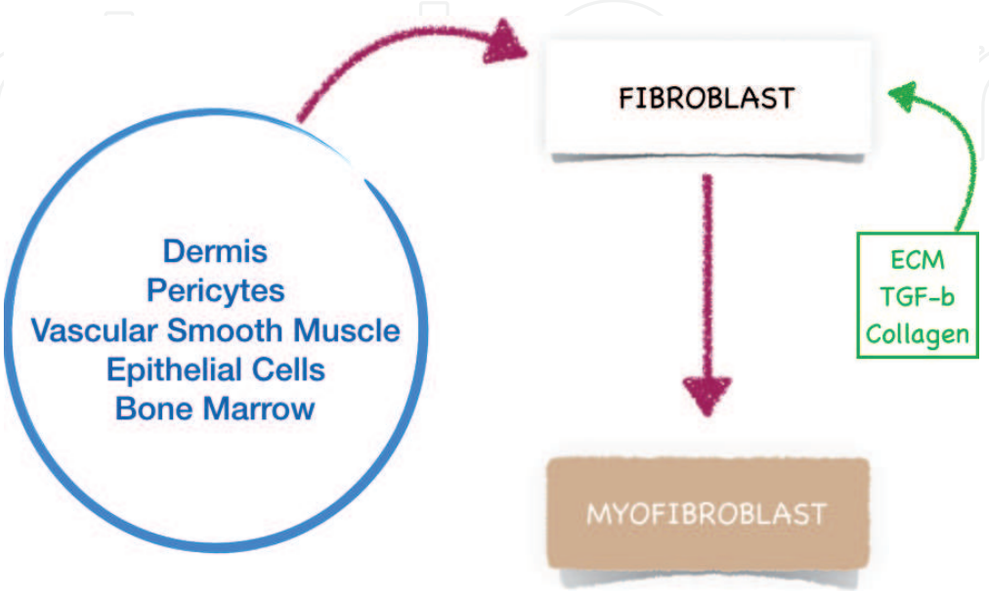

Figure 2.
Activation of fibroblasts and differentiation into myofibroblasts are the central processes in the pathophysiology of hypertrophic scars.

site, pericytes and vascular smooth muscle cells, tubular epithelial cells through epithelial-mesenchymal transition (EMT), tissue specific stem cells, and bone marrow-derived peripheral blood fibrocytes (**Figure 2**) [30].

The proliferative fibroblasts produce massive collagen and make extracellular matrix (ECM) that accumulates below the dermis. One sign thought to be of particular importance is that transforming growth factor-beta (TGF-b), acting through a signaling pathway in fibroblasts, appears to cause an increase in production of ECM and leads to cellular proliferation [31, 32]. Over time, some cells can develop autocrine TGF-b positive feedback loops that can lead to a self-propagating cycle of excessive extracellular matrix production and cell proliferation. Moreover, fibroblasts infiltrate and degrade the fibrin clot by producing matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs). This action results in an imbalance between the formation and degradation of matrix [33].

8. Risk factors

Risk factors for the development of pathologic scarring in the setting of burns have been reported to include darker skin color [1, 34], female sex [35], young age [17, 35, 36], allergy [16, 37], bacterial colonization [38], stretch and burns to the neck or upper limb [35], multiple surgical procedures [35], meshed skin graft [35], increased time to healing [1, 35, 38, 39], and burn depth [35].

Factors that reduce the risk of presenting HS are: chemotherapy [40], smoking [17], statins [41], and genetic background that does not have association [42] (**Table 1**).

Increase HS	
Darker skin color	Stretch
Female sex	Neck and upper limb
Young age	Multiple surgical procedures
Allergy	Meshed skin graft
Bacterial colonization	Increased time healing
Burn depth	
Decrease HS	
Chemotherapy	
Smoking	
Statins	

Table 1.
Overview of factors associated with the development and reduce risk of HS described by other authors to date.

9. Genetic

No convincing evidence exists for a familial pattern in patients who suffer from HS. In a systematic review, the authors did not find any pedigree studies on HS [42, 43].

10. Dark skin

In the literature, dark skin has a higher incidence of HS compared with lighter skin of Caucasians. Dark skin contains more and larger fibroblasts that deposit more collagen, related to what was previously written [1, 34, 36].

11. Female sex

Gangemi and colleagues observed in a multivariate regression model that female sex, young age, burn sites on the neck and/or upper limbs, multiple surgical procedures, and meshed skin grafts were risk factors for postburn pathologic scarring [35].

12. Age

Evidence supports the negative association of age with HS. Excessive scars develop mostly in younger patients between 11 and 30 years old. The inflammatory response decreases with age: epidermal turnover is slower in elderly individuals, and the epidermis contains fewer cells [17, 35, 36, 44].

13. Allergy

Hypothesize that increased degranulation of mast cells observed in allergic individuals supports HS formation. This relationship of allergy with HS formation is supported by level III evidence [16, 37].

14. Bacterial colonization

Bacterial toxins stimulate and prolong the inflammatory phase of wound healing and, thereby stimulate HS [38, 45].

15. Evaluation of hypertrophic scar

Currently no standardized system method exists to assess postsurgical scars. In the literature, scar assessment has mainly been focused on burn scars, but an increasing interest in postsurgical scars is seen, both to evaluate postoperatively as well as to have a closer and objective monitoring when therapeutic measures are applied so as to conclude whether the management is effective or, on the contrary worsening the situation of the scar [4, 9].

Comprehensive scar assessment must include three different dimensions: (a) physical characteristics; (b) cosmetic appearance; and (c) patient's symptoms (**Table 2**).

To date, only four scales have been psychometrically studied: the Vancouver Scar Scale (VSS), the Patient and Observer Scar Assessment Scale (POSAS), the Manchester Scar Scale (MSS), and the Stony Brook Scar Evaluation Scale (SBSES) (**Table 3**).

Scar assessment
Physical characteristics
Cosmetic appearance
Symptoms

Table 2.
Points to scar assessment.

Scar scales
Vancouver scar scale
Patient and observer scar assessment scale
Manchester scar scale
Stony Brook scar evaluation scale

Table 3.
Scales psychometrically studied for the evaluation of scars.

16. Vancouver scar scale (VSS)

The VSS was created in 1990 and is the most widely used rating scale for scars. Four physical characteristics are scored: height, pliability, vascularity, and pigmentation. Each variable is ranked to obtain a total score ranging from 0 to 13, with 0 representing normal skin [46, 47] (**Table 4**).

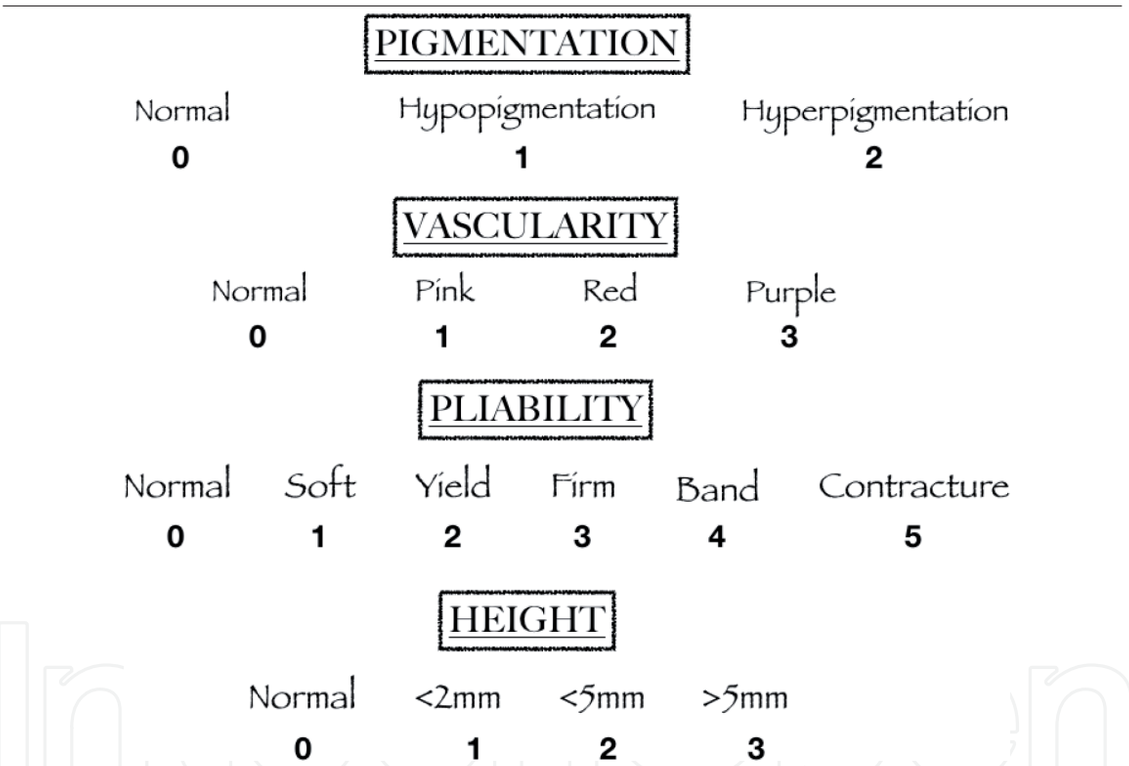

Table 4.
Vancouver scar scale.

17. Manchester scar scale

The MSS includes six items: contour, texture, color, distortion, shiny surface, and overall patient's opinion [47].

18. Patient and observer scar assessment scale

The POSAS is a recent and promising scar assessment tool that incorporates both observer and patient scar ratings [47, 48].

19. Stony Brook scar evaluation scale

Scars are assigned 0–1 point for the presence or absence of the following: width greater than 2 mm at any point of the scar, raised (or depressed) scar, and darker coloration than surrounding skin. The total score is then derived from the scale and ranges from 0 (worst) to 5 (best) [47, 49].

20. Treatment of hypertrophic scar

Different methods have been described for the treatment of hypertrophic scars. Among those have been found prevention, re-excision with primary closure, massages, compression clothes, silicone sheets, intralesional injections, laser therapy and topical treatments (**Table 5**).

Treatment of hypertrophic scar
No invasive
Prevention
Pressure garment therapy
Scar massage
Laser therapy
Silicone gel sheeting
Invasive
Triamcinolone acetonide
5-Fluorouracil

Table 5.
Treatment of hypertrophic scars.

21. Prevention

The prevention is the conjunction of measures that reduce inflammation and provide rapid wound closure such as early debridement of dead space, reducing the risk of infection through rinsing and disinfection, as well as optimal dressings that provide moist wound healing and/or early surgical wound coverage. During the operation, the surgeon should also use adequate sutures and avoid excessive tension. Surgical closure must be meticulous with an atraumatic technique to generate a successful and minimal linear scar. In the training of plastic surgery, the use of fine and atraumatic instruments is taught for the handling of the tissues for example hooks for retraction. Without a doubt, the tension found in the closure of a wound plays a very important role in widened and hypertrophic scars; these tension forces separate the edges of the wound and generate a wider scar with time. This result can be decreased with the liberation and advancement of the edges, in addition to the placement of correct subdermal sutures [50].

Once the wound has been prepared and is ready for closure, the proper suture and suture technique must be selected. Wounds may be closed with simple interrupted, horizontal mattress, vertical mattress, figure-of-eight, or running sutures. The choice of the suture is of great importance, and most of the time despised, attention should be paid to the estimated time to resorption since the suture may or may not provide adequate support during the healing process. With a Level II

of Therapeutic Evidence, polydioxanone (PDS) has been found to result in less scar widening and less scar hypertrophy at 6 months compared with polyglycolic acid (PGA). In the first 3 weeks of wound healing, the strength of a wound is only a small fraction of its eventual strength. Sutures removed or degraded before this time have little effect in preventing wound spreading. Polyglactic acid suture loses strength after 3 weeks, at which time the wound is still relatively weak. These results are similar to removing a nylon suture from the wound in 1 week [51, 52].

Leaving a permanent intradermal suture in place for several months has been shown to decrease spreading, and a synthetic suture possibly retains strength for 6–8 weeks and may have the same effect. This result is caused by the difference in the absorption time and what comes from the loss of tensile strength. On an average PGA scars were wider than PDS scars by 33% (means 9.6, 7.2), the difference that was statistically highly significant (Wilcoxon test $p < 0.001$) [51, 52].

In another study that used the Vancouver Scar Scale (VSS), the scar's width and quality of polydioxanone (PDS) was compared with that of polyglactin 910. The scars were evaluated at 1, 3 and 4 months postoperatively. On follow-up, the mean scar width in Polyglactin 910 was significantly more than that of PDS. The VSS score was significantly lower in the PDS group at the third and fourth month follow up and signified better scar quality [53].

22. Noninvasive measures

22.1 Pressure garment therapy (PGT)

The theory behind the use of PGT may be quite simple and relies on two main concepts; first, the restriction of blood flow to the scar area inhibits the growth of hypertrophic scar tissue and second constant compression does too [54]. Some evidence indicates that PGT may have an effect on the remodeling of hypertrophic burn scar elements such as fibrillin and elastin [55]. In an experimental model with swine that received pressure treatment with a device mounting and delivery at 30 mm Hg of constant pressure for 2 weeks, the total collagen quantification using hydroxyproline assay showed a 51.9% decrease after pressure initiation. Pressure treated scars also had lower levels of collagen I and III after pressure treatment ($P < 0.05$) compared with sham and untreated scars [56]. Using a newly developed pressure therapy system, the Smart Pressure Monitored Suits. Pre and post treatment comparison demonstrated significant improvement in scar pigmentation, thickness, VSS scores, as well as scores of pain and itch ($p < 0.01$) for the early intervention group prescribed within 60 days after injuries compared with the late intervention group prescribed after 61 days. The early group demonstrated superior effect in improving scar lightness, yellowness ($p < 0.01$), thickness ($p < 0.01$), pigmentation score ($p < 0.05$) and pain score ($p < 0.01$) than the late group in comparison between the two groups at similar postburn timing [57].

However, a meta-analysis of clinical results suggests that PGT does not appear to alter global scar scores, but does appear to improve scar height, although this difference is small and of questionable clinical importance. The beneficial effects of PGT remain unproven while the potential morbidity and cost are not insignificant [58].

22.2 Scar massage

Scar massage is used in burn units globally to improve functional and cosmetic outcomes of hypertrophic scarring following a burn; however, the evidence to support this therapy is unknown [59].

22.3 Laser therapy

The three main groups of lasers that can be used to improve scars include pulsed dye lasers (PDLs), Nd:YAG lasers, as well as ablative and nonablative fractional lasers.

A systematic review of the effectiveness of the ablative 10,600 nm CO_2 laser, shows objective improvement in scar color, thickness, and sensation, but not in scar elasticity. All studies reported improvements in the mean total VSS score and/or VSS component scores (pliability, height, vascularity, pigmentation), without statistically significant differences between raters. Statistically significant improvements in both the patient and the observer sections of the POSAS were reported after CO_2 laser treatment. Despite these positive findings, all studies were of low or unclear quality. As a result, insufficient scientific evidence exists to determine the effectiveness of laser therapy for hypertrophic burn scars from this systematic review [60].

22.4 Silicone gel sheeting (SGS)

In 2006, a Cochrane review found weak evidence to support the use of SGS [61]. SGC was effective to reduce thickness, pain, itchiness, and pliability of hypertrophic scars in Chinese the population after 6 month's intervention [62]. Silicone products, either in gel or sheet, are superior to onion extracts including heparin and allantoin in the treatment of the hypertrophic scar [63].

23. Invasive treatment

23.1 Intralesional corticosteroids

In patients with ongoing hypertrophy, more invasive measures are indicated. Intralesional corticosteroids is the only invasive option that has enough supporting evidence [64, 65]. The most commonly used is triamcinolone acetonide (TAC), the dose and treatment interval is variable ranging from 10 to 40 mg/ml given between 2 and 4 weeks interval. The success rate is 50–100% in different studies with 9–50% experiencing recurrence [66, 67]. The TAC injection should be limited to the scar and avoid the periscar tissues. The adverse outcomes of skin atrophy, pigmentation, and telangiectasias are unacceptable by some patients [68–71].

The injection of TAC is not contraindicated in children, but that dose adaption to the child's weight is advised to avoid systemic exposure [72, 73].

Additional injectable treatment options that may help to treat hypertrophic scars (and keloids) include 5-fluorouracil and verapamil.

23.2 5-Fluorouracil (5FU)

The use of antineoplastic agents as treatment options is logical because these abnormal tissues are in hypermetabolic states. 5-FU has been known to affect the fibroblast proliferation in tissue cultures because of its antimetabolite activity and has been shown to be an effective treatment for inflamed hypertrophic scars [28].

23.3 Triamcinolone acetonide and 5FU

This combination is associated with significantly greater reductions in scar size and erythema compared with triamcinolone acetonide alone in a 12-week

double-blind study of 40 patients [74]. In a randomized control trial that include 120, patients the mean reduction in scar height was significant in 5FU + TAC group versus TAC alone. Recurrence was seen in 39.2% of patients of the TAC group while in 17.5% of 5FU + TAC group (P = 0.012) [75].

Verapamil is a calcium channel antagonist that both decreases collagen synthesis and increases collagen breakdown. In a randomized, single-blind study of 54 patients with hypertrophic scars or keloids, scar vascularity, pliability, height, and width were reduced with intralesional verapamil, although the rate of reduction in these parameters was slower than with intralesional triamcinolone [76]. A randomized controlled of 50 patients the VSS scores were achieved with no therapeutic event or significant improvement was seen in verapamil group versus TAC group [77].

Pruritus is a chronic problem associated with many hypertrophic scars. Besides the emollient creams mentioned above, the use of local or systemic antihistamines may be useful and depends on the total body surface area involved in the areas of

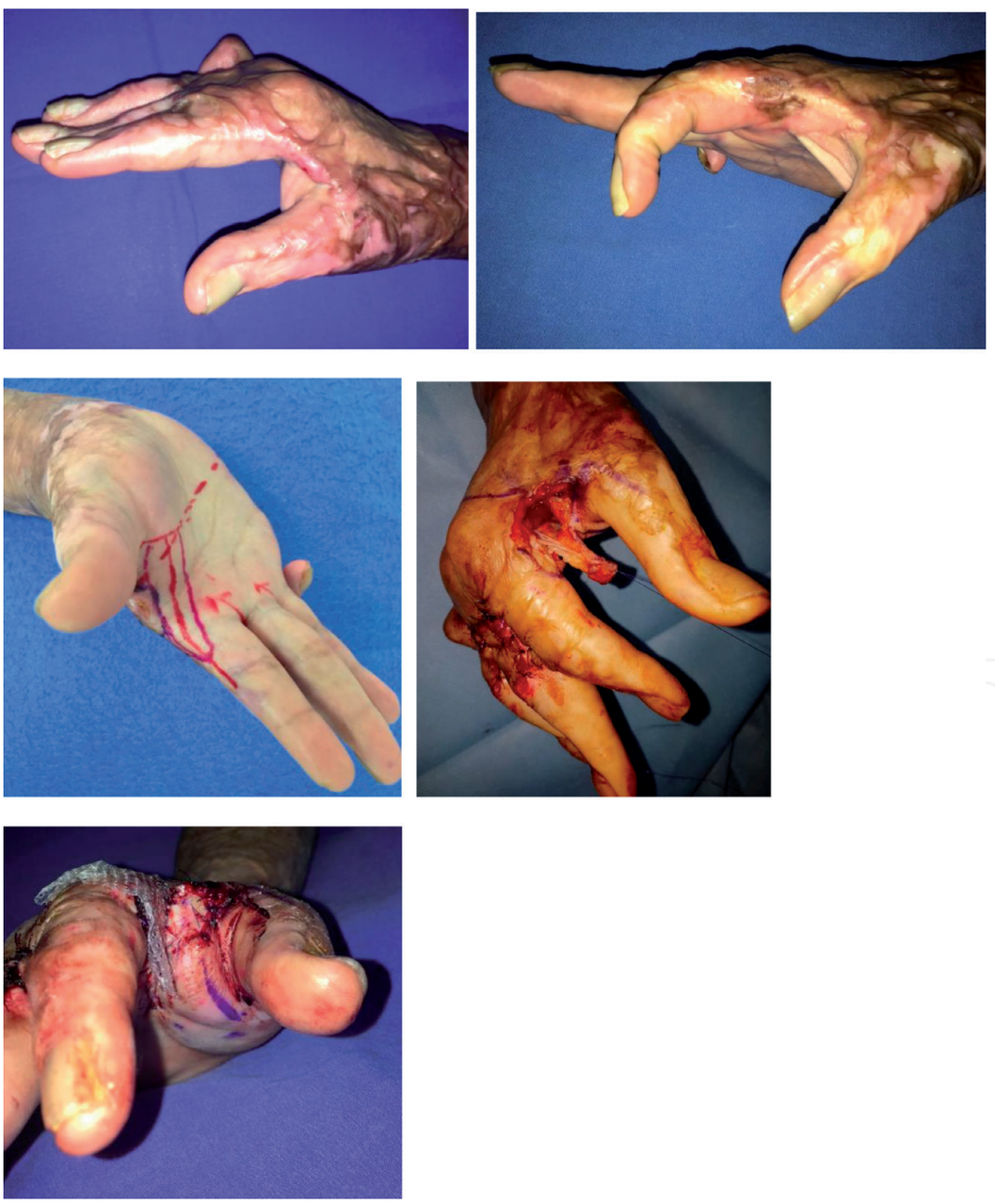

Figure 3.
Release of first interdigital space with flap based on perforating of digital artery of index finger.

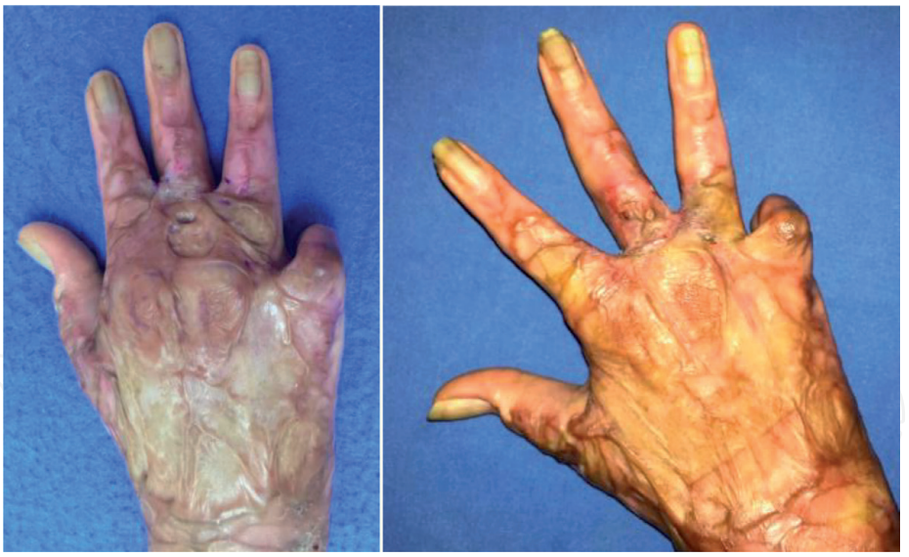

Figure 4.
Multiple syndactyly release in a single time with seagull wings flap.

itchiness. Some early evidence suggests that naltrexone may be a useful treatment for burn-related itching [78].

23.4 Surgical treatment

Surgical interventions for burn scars are usually postponed until the scar is considered "mature" or what may be 6–12 months after maturity, primarily because of the concern of recurrence of the scar. This may also have been influenced by burn scar reconstructive release surgeries performed by grafting and flaps. Most believe that the best option is the treatment with flaps [79] (**Figures 3** and **4**).

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