Scar Symptoms: Pruritus and Pain

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10.1 Pain: Definition and Subtypes

Pain is defined as a distressing sensory experience associated with potential or actual tissue damage with cognitive, emotional, and social components [1]. Pain can be classified into acute and chronic, based on the duration of symptoms as well as nociceptive and non-nociceptive subtypes with regards to the neurophysiological processes involved.

Acute pain is the predicted physiological response to an adverse mechanical, thermal, or chemical stimulus and most frequently occurs after traumatic injury/surgery as part of the inflammatory response. Chronic pain is defined as pain lasting for three or more months showing no resolution to treatment [1].

Nociceptive pain can be defined as pain arising from the sensitization/activation of peripheral nociceptors and will only continue if the inciting stimulus is maintained [2]. Non-nociceptive pain can be classified into neuropathic and psychogenic pain. Neuropathic pain denotes a primary anatomical or biochemical abnormality arising within the CNS, resulting in persistent and chronic sensory disturbance following the initial injury [3]. It occurs as a result of damage to neural tissue in peripheral and central nervous system and relates to aberrant somatosensory processing. While a detailed account of psychogenic pain is outside the remit for this review, we will elaborate extensively on neuropathic phenomena since they are frequently observed in scar practice.

10.2 Pain Pathway

10.2.1 Peripheral Receptor Activation

Specialized sensory nociceptor fibers in peripheral tissues are activated by a broad spectrum of stimuli including mechanical, thermal as well as chemical with the most frequent being acetylcholine, bradykinin, adenosine triphosphate, and prostaglandins [4].

10.2.2 Ascending Pathway

First-order neuron pathways are responsible for carrying impulses to the dorsal column initially and then other parts of the CNS as part of the ascending pathway and comprise the following different subtypes [5].

A-beta fibers: These are low stimulation threshold, myelinated fibers, activated by vibration and touch; under normal conditions, they convey nonpainful stimuli; nevertheless, they play a crucial role in carrying painful sensations in chronic neuropathic pain.

A-delta fibers: These thinly myelinated fibers have a high threshold potential and are involved in the initia-

tion of the reflex response associated with painful stimuli; they transmit pain faster than unmyelinated C fibers and contain the neurotransmitter L-glutamate.

C-fibers: These fibers are unmyelinated, have a high threshold for activation, and their stimulation causes delayed perception of pain that is often described as diffuse stabbing or burning. As well as glutamate, they contain other neurotransmitters like substance P (SP) and calcitonin gene-related peptide (CGRP).

Second-order neurons start from the dorsal horn and cross over to the contralateral side of the ascending spinothalamic tract to reach the thalamus and pons. The components of the dorsal horn involved in nociception express several receptors including α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), voltage-gated calcium channels, N-methyl-D-aspartate (NMDA), as well as gamma-aminobutyric acid- α (GABA-A) receptors [4].

Third-order neurons start at the thalamus and end at a number of different cerebral loci.

Processing regarding the magnitude and spatial characteristics of painful stimuli is provided by the somatosensory cortex and the ventral posterior thalamic nuclei. At the same time affective and motivational aspects of pain are processed by the ventromedial posterior thalamic nucleus and its cortical connections [6].

Furthermore, positron emission tomography studies have proposed that pain-related activation of anterior cingulate cortex (ACC) has a direct relationship with an individual's emotional and behavioural reactions to pain [7]. Midbrain periaqueductal gray matter, the region responsible for fight or flight response has also been shown to have interconnections with the ACC [8].

10.2.3 Descending Pathway

The dorsal horn of the spinal cord receives input from higher centers, which can modulate the peripheral nociceptor input barrage by the descending pathway.

The descending pathway starts at the limbic system of the brain area, namely the periaqueductal gray/parabrachial area, rostral ventromedial medulla, and nucleus raphae magnus, whose stimulation, in turn, inhibit nociceptors in the laminae of the spinal cord. Key transmitters involved include noradrenaline, serotonin, as well as endogenous endorphins and enkephalins [9].

Aside from descending signals, nociceptive impulses can also be modulated by segmental input from A-beta fibers under the gate control theory of pain. In other words, non-nociceptive fiber signals carried by the large diameter A fibers can interrupt the transmission of pain indirectly by inhibiting the effect of pain fibers ("closing the gate") [10].

Fig. 10.1 Schematic diagram of several mechanisms of peripheral and central nervous system neuropathies. Peripheral sensitization include injured afferent hypothesis when a neuroma formed by injury to peripheral afferent fibres causes increased sensitivity to different stimuli resulting in abnormal excitability [11]; intact nociceptor hypothesis in which spontaneous activity may develop in the nociceptors that survived peripherally after injury innervating the region of the transected nerve secreting agents altering the activity of uninjured afferents [12]. Central sensitization include increased activity in of the dorsal horn projection neurons in the dorsal root ganglion after a peripheral nerve injury causing the release of excit-

atory neurotransmitter glutamate [13]; loss of A β -myelinated fibers input causing loss of afferent inhibition resulting in more noxious stimuli reaching the CNS (Deafferentation theory) [14]; degeneration of inhibitory CNS neurons (GABA interneurons) in the dorsal horn resulting in decreased inhibition of nociceptive pathways causing chronic pain [15]; loss of anti-nociceptive descending pathways resulting in increased excitability to the CNS resulting in increased pain [16]; abnormal cortical input as a result of misdirected axonal growths at the site of injury causing reorganization of the somatosensory cortex with distorted skin mapping of the area innervated by the injured afferent [17].

Neuropathic pain refers to a type of non-nociceptive pain, which has many neurophysiological phenomena central to its genesis and symptom maintenance. These can involve the central nervous system primarily or secondarily due to changes to the peripheral nervous system components (sensitization). **Figure 10.1** provides a pictorial representation of key processes involving the peripheral and central nervous system in neuropathic states.

10.2.4 Peripheral Sensitization

Different mechanisms have been proposed for the occurrence of abnormal signals in the peripheral nervous system capable of ultimately sensitizing the central system, including:

- **Injured afferent hypothesis:** According to this theory, a neuroma formed by injury to the peripheral afferent fibers causes growth of unmyelinated C fibers from damaged axons and results in abnormal excitability. This spontaneous activity occurs due to increased sensitivity to mechanical, chemical, and thermal stimuli [11, 12].
- **Intact nociceptor hypothesis:** This concept proposes that intact nociceptors (i.e., those surviving the original injury in the periphery and innervating the region affected by the transected nerve fibers) develop spontaneous activity [11]. Changes in ion channels, expression of receptors, and secretion of agents like prostaglandin, bradykinin, and tumor necrosis factor- α have the potential to sensitize nociceptors, thereby altering the properties of uninjured afferents [12].

10.2.5 Central Sensitization

The following mechanisms have been proposed to underlie central sensitization:

- Increased activity of dorsal horn projection neurons: There is an upregulation of $\alpha_2\delta$ subunit of calcium channels in the dorsal root ganglion and spinal cord after a peripheral nerve injury; this results in increased release of excitatory neurotransmitter glutamate [13].
- Deafferentation theory (loss of afferent inhibition): Tissue injury causes loss of A β -myelinated fibers input, which is the primary mechanism promoting hypoactivity of interneurons. These interneurons primarily inhibit nociceptive afferents resulting in more noxious stimuli reaching the CNS centers [14].
- Loss of CNS inhibitory neurons: γ -Aminobutyric acid (GABA) interneurons in the dorsal horn nerve fibers undergo degeneration, causing decreased inhibition of the nociceptive pathway contributing to chronic pain and hypersensitivity [15].
- Loss of descending inhibition: Inhibition of the anti-nociceptive descending pathways can result in increased excitability of the CNS, and this is thought to cause loss of sensory input following peripheral nerve injury [16].
- Synaptic reorganization: Acute deafferentation in the nervous system is thought to stem from peripheral nerve transection resulting in a misdirected axonal growth at the site of injury and cause abnormal cortical input. This mediates somatosensory cortex reorganization with distorted skin mapping originally innervated by the injured afferent [17].

The sensitization phenomena described above appear to play a key role in the generation and maintenance of chronic sensory phenomena in burn scars (see the following section) as well as keloid scars. It is interesting to note that the clinical profile of symptoms in keloids is such that pain in keloid is felt at the center while itch is mostly felt at the periphery raising the suspicion of a small fiber neuropathic state. Its severity has been suggested to correlate with pruritic intensity with a disproportionate number of regenerating unmyelinated C fibers at the periphery causing itch. Keloids with itch have also demonstrated an overall lower epidermal innervation density pointing toward mechanisms of peripheral nervous sensitization [18, 19]. Another study reporting a large number of thinner nerve fibers in deeper layers of keloidal skin has hypothesized the presence of the intensive fibrous compression (entrapment neuropathy) accounting for painful symptoms [20].

10.2.6 Pruritus: Definition and Subtypes

Pruritus is derived from the Latin word *prurio*, which means “to itch” and can be defined as the unpleasant sensation, which leads to the desire to scratch [21]. It can be divided into acute and chronic as well as into different subtypes based on the pathophysiological processes involved. In terms of chronicity, the acute itch has been proposed to last up to 6 months post-injury/insult to the skin in burns patients, corresponding to the early remodeling phase of wound healing [22]. Pruritic sensations in the healing wound could potentially be explained on the basis of histamine release as part of the inflammatory response and partly by virtue of abundant mast cell present in hypertrophic scars [23]. Nevertheless, the persistence of these symptoms beyond the wound healing and into scarring phase could not be solely explained on a histaminergic basis (see below).

Twycross et al. [24] has classified pruritus into the following four main subtypes:

- Pruritogenic: Arising in the skin because of injury/inflammation
- Neuropathic: Stemming from within the afferent neurologic pathway
- Neurogenic: Having a central nervous system origin in the absence of neurologic pathology
- Psychogenic: Associated with psychiatric conditions

While a number of non-skin pruritic disorders may appear to consistently fit in one discreet category, the scar-related itch is thought to have a number of non-pruritogenic origins.

10.2.7 Pruritic Pathway

10.2.7.1 Peripheral Receptor Activation

A wide variety of substances have been implicated in the generation and propagation of antegrade pruritic stimuli including:

Histamine

A number of histamine receptors have been described in the literature. The surface of sensory nerve endings have H1 and H2 receptors that are activated by histamine stored in the keratinocytes and mast cells [25]; H3 and H4 receptors are also found on peripheral and central neurons regulating neurotransmitter release and mast cells [26, 27]. As a by-product of collagen production, histamine synthesis is increased in the healing wound, and this can account for the generation of pruritic stimuli in the healing wound/freshly formed scar [28].

Acetylcholine

Human keratinocytes have been shown to synthesize, store, and release acetylcholine, which, through the activation of M3 muscarinic receptors in the skin, can produce an itch-associated response [29, 30].

Bradykinin

Histamine release can be caused by bradykinin secretion through mast cell degranulation [31]. It also stimulates the release of calcitonin gene-related peptide, substance P, and prostaglandin E2 at the site of tissue injury resulting in inflammation [32].

Proteinases

Dermal mast cells synthesize proteinases, including tryptase and chymase, which interact with proteinase-activated-receptor-2 located on C fibers neurons, contributing to impulse generation [33].

10.2.8 Peripheral Nerve Fibers (PNF)

A specific group of “unmyelinated C fibers” appears to be responsible for the transmission of itch; they start at the dermo-epidermal junction and reach the spinal cord via the dorsal root ganglion. These fibers have a characteristic slow conduction velocity (0.5 m/sec) with a prolonged histamine response and extensive terminal branching. The main transmitters released include substance P and calcitonin gene-related peptide [34].

10.2.9 Spinal Cord/Itch Specific Neurons

Andrew and Craig, in their experiments on cats, showed “itch-specific” neurons to be located in the superficial part of the dorsal lamina I of spinothalamic tract [35]. They are characterized by their lack of ongoing discharge and low conduction velocities and terminate at the thalamus before crossing over to the contralateral side in the spinal cord.

10.2.10 Thalamocortical Level

The exact parts of the brain activated by the pruritic pathway are still not fully characterized; lamina I of the spinothalamic tract was originally postulated to terminate in the medial dorsal and ventral medial nucleus of the thalamus in primates [36]. However, positron emission tomography studies have failed to show any subcortical activation in healthy individuals and instead show significant activation in contralateral somatosensory cortex and in both ipsilateral and contralateral motor areas (premotor cortex, primary motor cortex, and

supplementary motor area). The cingulate gyrus and prefrontal cortex have also been implicated in neuronal transmission and this may potentially be the reason for the associated emotional component seen in scratching behaviour of patients suffering from pruritus [37].

The generation and maintenance of pruritic symptoms into a chronic state has been postulated to relate to a state of central nervous system sensitization, based on a combination of clinical, neurophysiological, as well as pharmacological data [38]. The salient observations supporting a neuropathic state in chronic pruritus in burns patients are summarized below.

- (a) Emerging pharmacological evidence behind the effectiveness of antihistamines at different time-points during rehabilitation indicates that in the later phases of healing, wounds and scars become unresponsive to antihistamine therapy [39, 40, 41]. This may point toward the involvement of the central nervous system in the maintenance of these symptoms and is further supported by the superiority of centrally acting agents including gabapentin and pregabalin [34, 35, 42, 43] and transcutaneous electrical nerve stimulation modalities in symptom management [41, 44].
- (b) Neurophysiological studies in burn scars show that phenomena similar to those occurring in chronic neuropathic pain exist in terms of the presence of increased sensitivity to stimuli (hyperalgesia/hyperkinesia) on the background of otherwise overall decreased sensibility. This finding provides some evidence of possible deafferentation as a mechanism for CNS sensitization [44, 45].
- (c) Clinical presentation highlights a pattern of symptom exacerbation at night time, which is found typically in neuropathic states [46, 47].
- (d) The neurological pathways of both symptoms share common features including the role of substance P and CGRP as well as similar areas of the central nervous system activated in the generation of symptoms as in neuropathic pain [48, 49].
- (e) Neuropeptide expression data. Hypertrophic scar biopsies in patients with pain and itch demonstrated a higher density of neuropeptides (SP and CGRP) compared to controls, whereas these were absent in non-hypertrophic scars providing a link between neuropeptide expression and impulse transmission. Interestingly, SP immunoreactivity was present in the densely packed areas of scar hypertrophy [50].

Another study in grafted burn skin showed the coexistence of overall decrease in axonal population and a preferential increase in SP fibers correlating with pruritic symptoms; this provides a link between a state of SP hyperinnervation in a milieu of deafferentation possibly leading to a neuropathic state [32]. Furthermore, neuropeptides like SP are thought

to play a key role in perpetuating fibroproliferative pathology establishing a cycle of nociception and scar hypertrophy [50, 51].

Other authors have proposed the role of opioids in the generation of pruritic impulses in hypertrophic burn scars [52].

10.2.10.1 Incidence/Prevalence of Pain and Itch in Scars

Pain is a major sensory disturbance and has been described as contributing to the “hidden cost” of cutaneous scars. According to a study based on semi-structured interviews in a UK scar specialist service, it has been identified that 26% and 44% of patients reported pain and itch in association with their scars, affecting their physical comfort and functioning [53].

In a corroborative study, pain and itch have been found to correlate with physical impairment ($P \leq 0.001$) in a study of 100 patients with keloid and hypertrophic scarring attending a German dermatology department using the Questionnaire on Experience with Skin Complaints. Similar work utilizing the Dermatology Life Quality Index (DLQI) tool confirmed that keloids have a statistically significant effect on the quality of life compared to physiologic scars ($p < 0.001$); additionally, they are associated with a statistically significant increase in pain and itch disturbances ($P < 0.01$ and 0.001 respectively) [54].

A cross-sectional health-related quality of life (HRQL) assessment study focused on indicators of the burden for 106 keloid patients using one disease-specific (Skindex-29) and two generic (SF-36 and EQ-5D-5L) HRQL measures; results indicated that pain and itch were the strongest predictors of impairment and related to low mental and emotional status [55].

A study evaluating chronic pain due to central sensitization in burn scars showed a 35% prevalence of pain in scarred tissue one or more years after injury [56, 57]. Additionally, work evaluating 98 burn survivors, reported 25% of patients having painful scars and 20% experiencing shooting pain more than 30 years post-injury [21]. A retrospective review involving 72 patients suggested that the first complaint of neuropathic pain presents on average at 4.3 months after injury and that there is a qualitative progression pattern; symptoms are initially reported as “pins and needles,” then being predominantly stabbing or burning pain followed by “shooting” sensory qualities [58].

A multicenter cohort involving 510 patients was used to evaluate the incidence and prevalence of burns itch. In this long-term prospective study, 64% of individuals reported itch to be a significant problem over a 2-year period. At three months, 87% of individuals reported severe itching; this fell to 70% at 12 and 64% at 24 months

respectively. Predictors of itch at three months post-burn included total burned surface area (TBSA), female gender, number of surgical procedures (deep dermal injury), and post-traumatic stress disorder (PTSD) symptoms at two weeks post-injury. Interestingly, at 24 months the only predictors for itch complaints were the latter two (PTSD at two weeks post-injury and the presence of deep dermal injury). The authors proposed that acute itch (up to 6 months) corresponding to the early remodeling phase of wound healing effects, both partial and full-thickness burn injuries. Chronic itch, on the other hand, affects patients with certain predisposing factors, providing a link between the chronicity of symptoms and markers of injury severity as well as psychological stress [59].

Another multicenter, large cohort study of adult burn survivors, reported high prevalence and severity of post-burn pruritus. Two cohorts of individual with burns were studied; the first included 637 patients followed prospectively over a 2-year period and identified that pruritus initially affected more than 90% of individuals and persisted in more than 40% of burn survivors in the long term. The second cohort comprised 336 patients who sustained burn injury 4–10 years before assessment using the 5-D itch scale. Pruritus was reported as severe in 76% patients within this group, moderate in 29%, and mild in 52% [60].

Schneider et al. [61] conducted a retrospective review of 430 pediatric burn survivors with a mean TBSA of 40.8%. Findings included that pruritus is present in most children (93%) and is of moderate intensity at discharge. The frequency and intensity of symptoms decreased over time; nevertheless continued to affect 63% of children at two years post-injury; furthermore, regression analysis showed significant correlations between pain and itch intensity at each time point. Most interestingly, no association was identified between pruritic intensity and burn etiology, age, gender, or burn size.

10.2.10.2 Management of Symptoms

Sensory symptoms in scars can be managed using a variety of approaches; undoubtedly, the most important initial step toward successful management relies on reliable and consistent monitoring of symptoms. A plethora of clinical measurement scales have been described in the literature; some of the most commonly utilized mono-dimensional scales include verbal, visual, as well as numerical analogue scales [62]. Other evaluation methods like the “itch man scale” incorporate a pictorial element, which makes them more suitable for pediatric patients or those unable to complete analogue scales [63]. Multidimensional tools including the 5-D Pruritus Scale have the advantage of incorporating components of the sensory experience other than intensity, including duration and disability, hence offering the opportunity

to capture the degree of disturbance in a more comprehensive manner [64].

A variety of pharmacological and non-pharmacological adjuncts are available and frequently using a combination of modalities provides an optimal therapeutic approach.

10.2.11 Non-pharmacological Adjuncts

10.2.11.1 Psychological Support

A multidisciplinary approach toward treating sensory disturbances in scars is vital, and psychological support has been suggested as an integral part of the management plan [65]. This is particularly pertinent given the association between psychological stress and perseverance of sensory symptoms into a chronic state [38].

10.2.11.2 Cooling

The application of cooling agents as part of wound care and scar management can help temporarily relieve pruritic sensations. The beneficial effect of cooling can be explained by the temperature-sensitive activation of certain excitatory ion channels, including vanilloid receptor 1 as well as ascending pathway C fibers [34, 66].

10.2.11.3 Hydration/Moisturization

Two recent literature reviews have found that there is limited and low-level evidence behind the optimal choice of a moisturizing and hydrating product for burn scars [67], with a small number of studies investigating the value of different products available. The rationale for moisturization of a scar relates to addressing the increased rate of transepidermal water loss (TEWL) seen in scars and potentially inhibits the fibrogenic action of fibroblasts by virtue of the hydrating effect [68].

The ideal moisturizer should have both occlusive as well as humectant ingredients. Occlusive substances (e.g., oils) function to impede water loss, whereas humectants (e.g., glycerin, propylene glycol, etc.) attract water from the dermis into the stratum corneum. The presence of a defective barrier against transepidermal water loss in scarred skin implies that a humectant-only-based preparation would enhance fluid loss, hence should be avoided [69].

A small randomized study has indicated that mugwort lotion is a promising topical agent for the relief of an itch in burns hypertrophic scarring [70]; additionally, a non-prescription moisturizer containing a blend of protease enzymes (Provas) applied every 8 hours for four weeks has been shown to reduce itch severity parameters as well as the affective burden significantly [71].

A similar randomized controlled study among 52 patients with postburn itch found that a preparation of beeswax and herbal oil had a statistically significant better effect on itch compared to aqueous cream

($P = 0.001$); additionally, symptoms recurred later comparatively ($P \leq 0.001$), and the use of antipruritic medications was lower ($P = 0.023$) [72].

A different literature report compared the effects of hydrocolloid dressing versus moisturizer in 20 patients with keloid and hypertrophic scars over a 2-month period in a randomized controlled prospective manner. Results indicate that both products achieved a similar reduction in itch ($P < 0.03$) and pain ($P < 0.08$) presumably by virtue of scar hydration [73].

One of the most interesting reports in the literature focused on the comparison between a hydrating gel-cream and three fluid silicones in a group of healthy volunteers. The moisturizer Alhydran (BAP Medical, Belgium) has been found to have an equivalent effect on hydration and occlusion suggesting that these may be the most important in topical scar care preparations as opposed to active substances like silicone, which have become extremely popular in recent decades [74].

10.2.11.4 Massage

Massage has been shown to be effective for the management of pain, itch, and anxiety associated with scars in a number of studies [75–77]. The first randomized study included 20 patients in the remodeling phase of scar formation; these were divided into either a 30-minute massage with cocoa butter to a moderate-sized scar tissue area twice a week for five weeks or standard therapy (cocoa butter application to scars applied by physical therapists without massage motions). The massage therapy group showed reduced pain, itch (both measured using visual analogue scales), as well as anxiety scores consistently throughout the study period [75]. Similar results were obtained in a study with a comparable design with regards to pain, itch, and anxiety in adolescent burn victims [78].

A Korean group investigated the effects of skin rehabilitation massage for three months in a group of 18 burn survivors; this involved the combination of light stroking movements followed by acupressure using oil as a medium applied for 30 minutes once a week for three months. Results indicated a statistically significant improvement of pruritus in the massage group ($t = -2.942$, $p = 0.006$) as well as depression ($t = -2.920$, $p = 0.007$) [76]. The underlying mechanisms of action of massage include the principles of the “gate theory” of pain modulation as well as the increased vagal activity, reducing stress hormone levels in the recipient [10, 79, 80].

10.2.11.5 Silicone Gels/Sheets

Silicone is widely used for the treatment of symptomatic hypertrophic scars. The proposed beneficial mechanisms involved include increased skin hydration (by virtue of occlusion) and a decrease in fibroblastic activity [81, 82].

The literature contains a number of high-quality studies regarding the role of silicone for the prevention of hypertrophy including a randomized placebo-controlled, double-blind prospective trial on sternotomy wounds showing a statistically significant effect on pain and itch symptoms [83].

Topical application of silicone gel versus placebo gel has been investigated in a randomized within-subject comparative clinical trial. Results suggested that silicone gel promoted maturation of early burn scars (mean age of scars in the study 4 months) and a decrease in itch symptoms in a statistically significant manner [84]. Similar beneficial effects were reproduced in a different study employing silicone gel application to burns hypertrophic scarring showing a significant difference in terms of scar vascularity starting at the first month of application [85].

Another study utilized silicone gel sheets in the conservative management of six keloid patients for 24 weeks. Symptoms of pain and itch showed a decrease after four weeks of the gel sheeting application and disappeared after 12 weeks. After 24 weeks, a histological decrease in the number of mast cells was observed, which may explain the therapeutic benefit seen by virtue of a decreased concentration of mast cells derived mediators [86].

A number of comparative studies exist in the literature, which aimed to elucidate the role of silicone products in the scar care arena.

A randomized clinical trial of 45 post-traumatic hypertrophic scars found that silicone gel sheeting applied 24 hours/day for six months was superior to 15-minute-long daily massage in reducing scar thickness in a statistically significant manner ($p < 0.001$); of particular note is that pain and itch reduction did not reach statistical significance in this study [87].

A separate prospective single-blinded study compared the efficacy of 585 nm flashlamp-pumped pulsed dye laser and silicone gel sheeting and control in the management of 20 patients with hypertrophic scars; results showed an overall reduction of blood flow, volume, and pruritus for all the study subgroups but failed to show any statistically significant difference between treatment and control groups [88].

A prospective split sternotomy scar study [89] involving 14 patients randomized to treat one-half of the scar with triamcinolone acetonide (TAC) and the other with silicone gel sheeting worn for 12 hours for 12 weeks. The primary outcome of patient preference was analyzed, and recruitment was terminated after 11 patients had completed the study, 10 of whom favoured silicone gel treatment. The average time for the symptomatic improvement of silicone-treated patients was 3.9 days as compared to triamcinolone acetonide, which was 6.8 days ($p < 0.05$). The authors proposed

that the enhanced compliance to silicone-based treatments relates to the painless and noninvasive nature of silicone-based adjuncts.

10.2.12 Transcutaneous Electrical Nerve Stimulation (TENS)

TENS involves the application of low-voltage electrical impulses to the nervous system by means of electrodes placed on the skin [90]. The underlying mechanism of action involves the stimulation of rapidly conducting A-fibers, which inhibit the transmission of noxious stimuli carried by the slower C fibers according to the “gate theory of pain” [10].

A pilot study involving 20 patients with healed burns complaining of severe itch following burns demonstrated a statistically significant change in the reported visual analogue scale compared with placebo over a 3-week period [90].

10.2.13 Pharmacological Adjuncts

10.2.13.1 Capsaicin

This is a naturally occurring alkaloid compound, which interacts with the transient receptor potential V1 receptor resulting in the depletion of neuropeptides from peripheral nerves. Despite the fact that capsaicin forms one of the mainstay topical agents in many chronic pain services, a double-blind placebo-controlled randomized trial using 0.025% capsaicin cream on 30 patients with pruritic wounds revealed no significant effects on pruritic symptom relief [91, 92, 93]. Further work is warranted involving preparations with different concentrations of this agent in order to elucidate its exact role in the management of symptomatic scars.

10.2.13.2 Antihistamines

Antihistamines have traditionally been used as first-line agents for the management of pruritus. First-generation compounds (diphenhydramine, hydroxyzine, cyproheptadine, and chlorphenamine) act on histaminic, serotonergic, muscarinic, and alpha-adrenergic receptors. Second-generation compounds, like cetirizine, have minimal activity on non-histaminic receptors and hence have a more favourable side effect profile as well as a longer duration of action [94, 95]. The pharmacological action of antihistamine relates primarily to a reverse agonist action at histaminic receptors as well a central nervous system sedative effect (the latter action refers to first-generation compounds).

One of the initial studies involving 35 burns patient complaining of severe itching after discharge assessed the efficacy of three first-generation antihistamines,

namely chlorpheniramine, hydroxyzine, and diphenhydramine. The results of the study pointed toward no significant difference in therapeutic efficacy between the three compounds and only a 20% complete relief of symptoms in the cohort [96].

10.2.13.3 Gabapentin/Pregabalin

Gabapentin is a useful agent for the management of neuropathic pain associated with a variety of conditions, including post-herpetic neuralgia [97].

The mechanism of action of gabapentin involves a number of mechanisms, including:

1. Blockade of the $\alpha_2\delta$ subunits of voltage-gated Ca channels resulting in a reduced release of excitatory neurotransmitters [98].
2. Increased synthesis and release of γ -aminobutyric acid in the CNS [99].

A comparative study appraised two different therapeutic protocols for the management of burns pruritus in patients with healing and healed burns in a UK burn center incorporating a mixture of antihistamines and gabapentin; the authors concluded that gabapentin as monotherapy as well as in combination with another two antihistamines was more efficacious compared to chlorpheniramine alone and in combination with another two antihistamines ($t = 3.70$, $df = 89$, $P < 0.001$ for monotherapy and $\chi^2 = 12.2$, $df = 1$, $P = 0.001$ for polytherapy). Additionally, patients with higher initial pruritus scores needed a combination of pharmacological agents for effective symptomatic relief. This study raised the value of centrally acting agents in itch management and proposed the combination of peripherally and centrally acting agents in the treatment for burns pruritus [41].

Another landmark study comprised a four-arm, double-blind, randomized and placebo-controlled study of pregabalin in the management of postburn pruritus. Pregabalin is a newer analogue of gabapentin with comparatively better anxiolytic and pharmacokinetic properties. The study compared the following four groups: pregabalin; cetirizine and pheniramine maleate; the combination of pregabalin, cetirizine, and pheniramine maleate; and placebo. Results indicated that for moderate to severe pruritus (VAS 6–10) a centrally acting agent like pregabalin is indicated to significantly decrease itch; patients with milder itch (VAS 4–5) are best served with the addition of pregabalin even if massage and antihistamines can provide some control because of quicker, predictable response with the added benefit of anxiolysis [77].

10.2.13.4 Steroids

Steroid delivery to hypertrophic and keloidal scars is a well-established modality for the alleviation of scar-related symptoms, including pain and itch, and their

beneficial effects were first recorded in literature in the 1950s [100]. The international advisory panel in 2002 recommended triamcinolone acetonide (TAC) as the first-line treatment modality for keloid and second-line treatment for linear hypertrophic scar in reducing subjective symptoms associated with keloid and hypertrophic scar like pain and pruritus [101].

In 2014, a protocol re-evaluation was undertaken, which reinforced the prominent position of steroids in scar management albeit supported a combined approach incorporating the use of other agents including 5-fluorouracil, cryotherapy, laser, and silicone products [102].

Darvi evaluated the use of intralesional triamcinolone acetonide in treating hypertrophic and keloid scars in 65 patients with a 10-year follow-up. The dosage of TAC for 1–2 cm² of scar surface area was determined to be 20–40 mg, 40–80 mg for 2–3 cm², and 60–120 mg for scar surface area of 4–6 cm². In this study four injections of TAC were given for the total dose delivered to the scar at 1–2-week intervals with an ensuing symptomatic relief seen in 71% of patients; furthermore, a dramatic improvement of symptoms with full flattening of hypertrophic scars was seen in 50% and 71% in patients with keloid scars [103].

Manuskiatti [104] and colleagues performed a randomized controlled trial comparing the effects of intralesional triamcinolone acetonide with 5-fluorouracil or alone with 585 nm pulse dye laser. TAC-treated scars had better improvements in clinical symptoms (pain, itching) and scar induration, although the results were not statistically significant. Intralesional triamcinolone acetonide treatment, however, did produce side effects, including skin atrophy, telangiectasia, and hypopigmentation in 50% of the TAC-treated group. Boutli-Kasapidou and colleagues [105] evaluated a polytherapy protocol, including three triamcinolone acetonide intralesional injections every month combined with 12 monthly cycles of cryotherapy and 12-hour silicone dressing for 12 months. Patient satisfaction scale was used to grade the appearance cosmetically and subjective symptoms (pain, burning, and tension post 12 months). Similarly, an investigator satisfaction scale was used as well. The results showed that compared to monotherapy, polytherapy group had a major improvement in control of symptoms and appearance, reported by the patient and observed by the physician ($P < 0.01$). They concluded the beneficial effects of each treatment acting synergistically: Steroids downregulating the excessive collagen expression in keloids and making it softer, ischemic destruction and subsequent necrosis of keloids with cryotherapy, and silicon downregulating mastocytes.

Tan and colleagues [106] conducted a patient-controlled prospective study for 12 weeks with patients receiving intralesional triamcinolone acetonide (40 mg/mL), silicone gel sheeting, or no treatment (control).

The dose of triamcinolone acetonide varied between 0.1 ml to 0.5 ml of 40 mg/mL of TAC depending upon the size of the lesion. In this trial, 12% of silicone-treated keloids showed a significant reduction (>50%) in size compared with 94% of triamcinolone acetonide group (RR: 33.00, 95% CI: 2.14–509.33). There was also a significant improvement in erythema (RR: 21.00, 95% CI: 1.33–332.06). The improvement in itch and pain was not statistically significant when compared to control.

Martin et al. studied the combination of carbon dioxide fractional laser (10,600 nm), a pulsed dye laser (585 nm), and triamcinolone acetonide (40 mg/ml) injections monthly for seven sessions in a cohort of keloid scars; they reported favourable results in regards to pruritic relief [107].

Steroids can also be delivered to scars in the form of tape application. Advantages of this modality include the noninvasive nature and the ability to maintain a continuous level of steroid concentration to the symptomatic scar, which can ameliorate the inflammatory milieu responsible for the bulk as well as sensory symptoms [108].

10.2.13.5 Botulinum Toxin

Botulinum toxin is a protein neurotoxin produced by the spore-forming bacteria *Clostridium Botulinum*; it works by preventing the release of acetylcholine at the neuromuscular junction and causing chemoinmobilization as well as affecting a variety of cell types including fibroblasts [109]. It is an established adjunct in a variety of medical and aesthetic interventions and over the last number of years has been trialed in the scar management arena. The rationale for its use rests on the ability to decrease muscular tension underlying a scar as well as the ability to alter a host of fibroblast related pathways, including their proliferation and cell cycle [110].

A randomized, double-blind comparative trial [111] involving 24 females with idiopathic or post-traumatic keloids employed the use of either intralesional triamcinolone (10 mg/cc), given every four weeks for six sessions or 5 IU/cm³ intralesional botulinum toxin every eight weeks for three sessions; in both groups, therapy was continued until complete improvement of keloid was noted. The authors concluded that the effects of intralesional botulinum toxin A comparable to that of intralesional steroids with a significant reduction in volume height and redness of scar in both groups ($p < 0.01$). In the 7-month follow up both treated groups had a statistically significant reduction in subjective symptoms of pain and itching with a statistically significant difference in favour of the botulinum toxin A treated group with the added advantage of no side effects which were typically seen in steroid-treated patients.

Another blind study compared the effect of triamcinolone acetonide (maximum of 40 mg dose) plus pla-

cebo versus triamcinolone acetonide and botulinum toxin (20IU) for keloid scars injected every four weeks for a total of 12 weeks. Although the difference in height, vascularization, and the pliability were not significant between the two groups, there was a significant difference in favour of the botulinum group in terms of pain and pruritus control ($p < 0.001$) at the end of the study [112].

Similar results in terms of the superior alleviating effect of botulinum toxin have been reached in another randomized, single-blind study in 32 keloid patients [113].

The use of botulinum toxin has been reported in the burns literature as part of a pilot study involving nine patients, eight of which had skin grafts for deep partial-thickness to full-thickness burns, with an average TBSA of 24%. At the beginning of the study, 87.5% of patients rated their burns itch as being severe (>7/10), which fell to 0 at four weeks following the administration of toxin [114].

Further studies are warranted to delineate the exact role of botulinum toxin in scar symptom management.

10.2.14 Emerging Modalities

10.2.14.1 Autologous Fat Grafting

Autologous fat grafting has been widely used for the treatment of contour deformities and increasingly employed to remodel and regenerate tissue by virtue of mesenchymal stem cells present in adipose tissue [115, 116].

The proposed mechanism supporting the alleviation of scar symptoms is suggested to relate to the mechanical release of adhesions, neovascularization, and remodeling of scar tissue architecture [117]. Other mechanisms proposed for controlling neuropathic pain symptoms include blockade of nociceptive impulses and an overall reduction of the signal input to the central nervous system [118].

Fredman et al. [119] in a retrospective case review evaluated the effectiveness of fat grafting in neuropathic burn scars using the patient-reported outcome measurement information system (PROMIS) to assess pain following two fat-grafting sessions eight weeks apart. Results showed a statistically significant improvement in subjective outcomes at 1-year follow-up.

Huang et al. [120] evaluated autologous fat grafting in 13 patients with neuropathic scar pain. Pain evaluations were undertaken using the Visual Analogue Scale (VAS) and Neuropathic Pain Symptom Inventory (NPSI) preoperatively and at 1, 4, and 24 weeks postoperatively. Both VAS and NPSI scores showed a significant decrease starting at one week, alleviating neuropathic scar pain in the short term, which were statistically significant ($P = 0.009$ and $P = 0.007$).

respectively). The NPSI score continued to decrease at four weeks ($P = 0.0009$) till 24 weeks ($P = 0.0008$) with the most significant improvement in paresthesia, dysesthesia and evoked pain ($P < 0.001$). They concluded the autologous fat provides insulation and acts as a cushion to block abnormal sensations and prevent stimulation.

Two systematic reviews of the literature pertaining to the use of fat grafting and adipose-derived stem cells in scarring have shown improvements in scar characteristics including texture and size, improved pain profiles, increased angiogenesis, and an earlier return to function [121, 122]. It is clear that the use of fat-derived cells will play an important role in the future of scar treatments in the field of regenerative medicine.

10.2.14.2 Lasers

Laser stands for “Light Amplification by Stimulated Emission of Radiation” and exerts its effect on the tissue through photochemical/thermal/mechanical mechanisms [123].

The photothermal effect or photothermolysis is the most relevant mechanism in scar treatment with the main target being either blood vessels (pulsed dye laser) or water (CO_2 and Er:YAG laser). Lasers can be further subdivided into ablative and non-ablative based on whether the epidermis is affected or not and fractional and non-fractional: based on whether intact columns of skin are left behind or not after the treatment [124].

Pulsed Dye Laser is a vascular specific laser with haemoglobin being the target chromophore. Selective photothermolysis [125] with a short pulse duration leads to selective absorption of heat by haemoglobin, leading to thrombosis and vasculitis [126].

Ebid et al. [127] in a double-blind, randomized, placebo-controlled trial, compared the effects of pulsed high-intensity laser in the treatment of post-burn pruritus. They showed that a combination of a long period of high-intensity pulsed laser, antihistamine, and massage could effectively control moderate to severe burn pruritus, raising the value of incorporating laser modalities in antipruritic protocols.

Vasheghani and colleagues [128] showed that low-level laser therapy in second-degree cutaneous burns decreases the total number of mast cells in the remodeling phase while increasing the number of mast cells in the proliferative and inflammatory phases. Increased level of growth factors and anti-inflammatory cytokines and decreased level of pro-inflammatory cytokines like interleukin alpha and beta have been shown after treatment with laser therapy [129] elucidating potential mechanisms for the action of laser on pruritic pathways. Other proposed mechanisms include the direct action on reactive oxygen species, inhibition of cyclooxygenase

(COX) and prostaglandin E2 [130], as well as the fast axonal flow and microtubule disruption of A δ and C fibers transmission [131].

Alster and Williams [132], in an investigator-blinded split scar study of patients with keloid scarring, performed two sessions of flash pump 585 nm pulse-dyed laser treatment to half of the scar at 6–8-week intervals. They reported a significant improvement in the texture of the skin surface, scar height, erythema, pruritus with coarse, loose collagen, and increase number of mast cells seen histologically in the laser-treated side.

A prospective randomized controlled trial investigated the outcomes following ablative fractional CO_2 laser on 19 patients with burn scars (minimum age of scars for inclusion six months). Results demonstrated that three treatments of ablative fractional CO_2 laser (Deep FX setting on UltraPulse®, Lumenis; treatment parameters: single pass of 300 Hz, 5% density, and 50 mJ energy) significantly improved scar pain, itch based on Patient and Observer Scar Assessment Scale (POSAS) scores ($p = 0.047$ and <0.01 respectively). Additional findings included an improved dermal architecture at six weeks post-treatment [133].

10.3 Conclusion

Pain and itch represent the most common sensory symptoms accompanying scars and can have a significant impact on patients' quality of life. Over the last number of decades, our understanding of the pertinent pathophysiological mechanisms has improved considerably, especially with regards to the contribution of the central nervous system in the generation and maintenance of nociceptive and pruritic stimuli. Consistent and reliable monitoring of symptoms combined with a multimodal approach to treatment should be integral parts of holistic scar management.

Take-Home Messages

- Itch and pain can have a significant impact on individuals with scars.
- The contribution of the central nervous system in the generation and maintenance of symptoms is paramount.
- Accurate assessment and monitoring of symptoms are central to successful scar management.
- Multimodal approaches which target both peripheral and central nervous system components and incorporate non-pharmacological adjuncts are recommended.

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