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Review Article

Post-burn pruritus: A brief review

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Abstract Post burn pruritis is one of the most prevalent chronic conditions afflicting the burn survivors. It is frequently debilitating and significantly impacts the quality of life. A wide range of pathophysiological factors and mechanisms have been postulated in recent years. Several pharmacological and non-pharmacological treatment options have been introduced, but the optimal management option has not yet been agreed upon. This article briefly reviews the pathophysiology, differential diagnosis, quantification scales and current management options of postburn pruritis.

Key words
Post-burn pruritus, histamine, antihistamines, Quality of life, neuropathy.

Introduction

Pruritus (Latin for 'itch') is defined as an unpleasant sensation that elicits a desire or a reflex to scratch.[1] Post-burn pruritus (PBP) is a distressing and pervasive complication of the burn wound healing process.[2] This might start a few of days following the burn, and 93% of burn survivors have postburn itch after they are discharged; 44% are still experiencing it 30 years later. The risk factors for pruritis appear to be female gender, multiple surgical interventions, limb/ facial burns, burns affecting larger surface area or extending deep, though smaller burns are not immune to it.[3] Pruritis is frequently debilitating because it interferes with sleep, daily activities, quality of life (QOL), and can complicate wound healing if scratching damages the neo-epithelium and grafted skin.

A significant problem encountered during the rehabilitation of burn patients is the alleviation of PBP and in recent years, a wide range of potential treatments have been proposed though there is still no agreement on the single best treatment.[4] This article briefly reviews the various aspects related to this disorder in the light of peer reviewed literature.

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Method

The databases PubMed, MEDLINE, ResearchGate, and Google Scholar were used to conduct the literature search. Studies were considered for inclusion in the evaluation if they examined or discussed various aspects of pruritus in patients with burn wounds. Studies conducted in language other than English were excluded.

Description of the Problem

PBP is a syndrome of stressful symptoms that is pervasive and the epidemiological evidence has confirmed that about 93% of major burn survivors experience PBP at discharge. Extremities are particularly prone to pruritus (100% over legs and 70% over arms), whereas facial burns rarely cause itching. About 44% of burn survivors, continue to experience pruritis at 30 years postburn.[1-3]

Pathophysiology

PBP may have five broad origins as shown in **Figure 1**, cutaneous (originating in the skin), neuropathic (due to nerve damage), neurogenic (due to central neural damage), psychogenic (due to psychological disorders), or mixed.[5] Cutaneous origin is the most predominant, but recent studies point towards dysfunction in sensory nerves (neuropathic) as the factor leading to persistence of pruritis.[6]

Many factors have been postulated to regulate PBP; the one having received greatest attention is histamine.[7]

Mast cells and keratinocytes release histamine, which stimulates histamine receptors 1 (H1) and 2 (H2) on nerve endings. It is believed that the primary cause of pruritus is this stimulation, during all stages of burn recovery. After healing, mast cells continue to proliferate in large numbers in the skin and serve as histamine-secreting factories. The effects of histamine can be exacerbated and lead to a worsening of pruritis if inflammatory substances (such as kinins, substance P, platelet activating factor, and serotonin) are persistent in the burn wound. Antihistamines have hence, served as the mainstay of post-burn pruritus therapy.[8-9]

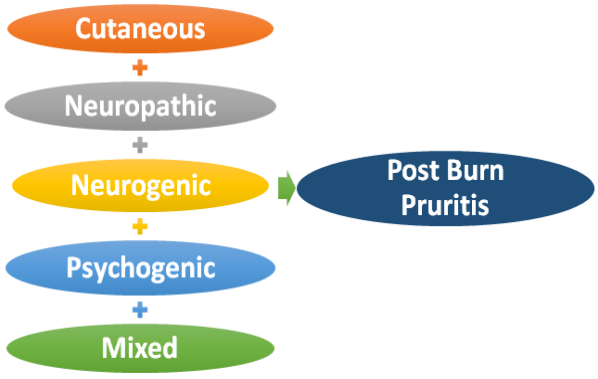

Figure 1 Origin of Post-burn pruritis.

Differential Diagnosis

PBP requires differentiation from the disorders that can be broadly classified into the three categories as following:

i) Treatment-related

Pruritis may be a side effect of a number of treatments, including those frequently provided at different phases of burn management, such as antibiotics, analgesics, moisturisers, and psychiatric medications. Patient depicted in **Figure 2A** had severe pruritis with rash due to application of silicone sheet that had been prescribed to minimise the hypertrophied scars. She got complete relief **(Figure 2B)** by discontinuation of silicone sheet, and two weeks course of second generation antihistaminic with topical steroids.

There are numerous cases concerning drug eruption following a burn injury at intervals ranging from 2 days to 22 years in the literature. Multiple fixed drug eruptions to medications (such minocycline) have been described by Dalla Costa *et al.*[10] and Mizukawa[11] in the sites of healed burns.

Figure 2 (A) Pruritis with rash over right forearm due to usage of silicone sheet. (B) After two weeks of usage of oral antihistaminic and topical steroids.

According to Du-Heon *et al*., mupirocin ointment caused a significant allergic reaction with pruritis around a chemical burn site.[12]

ii) Underlying Dermatologic Disorder

Many conditions mimic the presentation of burns and hence may be mistakenly diagnosed as burn injuries. They may even wrongly be labelled as abuse/ neglect of the children or elderly. These include atopic dermatitis, psoriasis, eczema and erythema multiforme.

Heider *et al*. has reported a case of mistaken diagnosis of child abuse wherein the real cause was eczema.[13] Similarly, Abtahi-Naeini *et al*. has reported a case of Ehlers-Danlos syndrome that had initially be misdiagnosed as child abuse because of scars.[14]

If there are erythematous patches or plaques over the burn or around it, the likelihood of contact dermatitis is considerable. In an intriguing example given by Sawyer and Williams, herpes zoster ophthalmicus was ultimately determined as the cause of rash in what was initially diagnosed as chemical burn diagnosis.[15]

iii) Sensory-Neural Disorders

Peripheral neuropathy is a well-known common long-term consequence of burns that affects 11% to 52% of survivors to varying degrees. Due to the insidious onset, the neuropathy can easily get misdiagnosed as PBP.[16]

Quantification of Itch

Although it is crucial to evaluate the effects of various therapies, quantifying PBP is challenging due to its variable subjective nature. In order to explain the magnitude of PBP, several verified scale systems have been published in the literature. Visual Analogue Scale (VAS)[17] and Itch Man Scale (IMS)[18] are examples of tools that are easy to use but do not provide information on the more specific aspects of the itching sensation. In contrast, the 5-D itch scale,[19] Leuven Itch Scale,[20] 12 item pruritus severity scale,[21] and ItchyQuant[22] are complicated and unusable.

An easy-to-use scale named, "The Pruritus Severity Scale" (PSS) was introduced by Beecher *et al*. in 2021[22] for precise quantification of the components of itching; it can be used to evaluate management outcomes, clinical trials, and patient care in general. Using bi-variate correlations, it was discovered that the PSS has a positive linear association with the previously validated scoring techniques (VAS, IMS).

Treatment

As illustrated in **Figure 3**, a number of pharmacological and non-pharmacological techniques are used in clinical care to address PBP, however none of the currently available treatments are completely successful.[24-25] The available modalities include:

Pharmacological

Antihistamines They are the first-line treatment for both adult and pediatric burn patients. Antihistamines suppress downstream signals by binding to histamine receptors, stabilizing them in the inactive state. Due to the skin's predominant expression of H1 and H2 receptors, the majority of postburn antipruritic medications tend to inhibit either of these receptors. There are two generations of H1 receptor blockers.

The first-generation H1 blockers (e.g., diphenhydramine, chlorpheniramine, hydroxyzine) are non-specific and also bind to

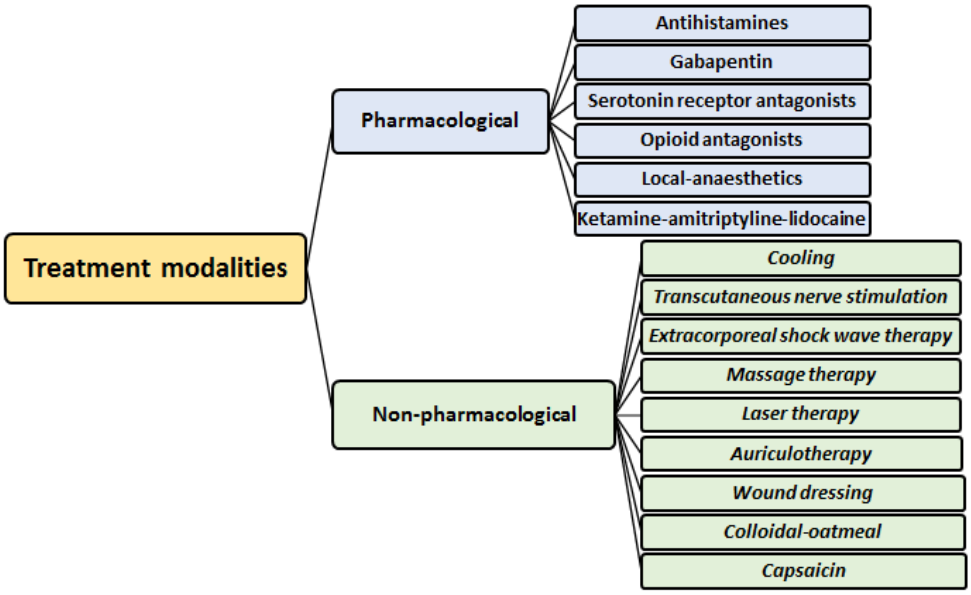

Figure 3 Treatment modalities of post-burn pruritis.

other receptors (e.g. muscarinic, adrenergic, serotonin). The 2nd -generation antihistamines (e.g. fexofenadine, cetirizine, loratadine) are more specific and have a more sustained duration of action with minimal non-specific effects.[26-27] H2 receptor antagonists, such as ranitidine and cimetidine, have also been found to have effect.[27] Demling and DeSanti[28] found that Doxepin dramatically reduces itching and erythema in the healed burn wound when administered topically as a cream, while avoiding toxicity that is otherwise associated with oral intake.

Gabapentin and pregabalin The primary site of action of gabapentin (and its prodrug pregabalin) is in spinal cord where it blocks the release of excitatory neurotransmitters thereby relieving neuropathic pain , but the precise mechanism of action in PBP is not fully clear though it is thought that gabapentin by increasing inhibitory neurotransmitter gamma-aminobutyric acid (GABA) inhibits those peptides that may have role in amplification of pruritus (such as calcitonin gene-related peptide). Pregabalin is comparable to gabapentin but is more potent in nature. Both these drugs have been proposed as antipruritic agents and to be administered either as monotherapy or in conjunction with antihistamines.[29]

Pregabalin for the treatment of PBP was studied by Ahuja and Gupta[30] and they concluded that moderate to severe pruritus (VAS 6-10) can be successfully managed with a systemic, centrally acting drug like pregabalin or gabapentin to either completely eradicate the condition or to reduce it to manageable levels. Even though other treatments like massage and antihistamines can manage PBP to a good extent, patients with lesser degrees of itch ranging in VAS scores between 4 and 5 may benefit from the addition of pregabalin due to its quicker, more reliable, and fuller reaction as well as anxiolysis.

Serotonin receptor antagonists Serotonin is thought to be released from platelet aggregates in burn wounds and since pruritus is conducted via nerve fibres whose stimulation can be enhanced by serotonin, inhibiting the serotonin receptor is a potential therapeutic approach. As such, serotonin receptor antagonist like

ondansetron,[31] and serotonin reuptake inhibitor like paroxetine,[32] have been assessed as antipruritic agents.

Opioid antagonists There are "pruritis specific" neurons in the spinal cord that typically remain in an inactive state as a result of spontaneous firing of two inhibitory neurons: nociception-specific and wide dynamic range neurons.[33-34] Opioid agonists, such as morphine sulfate, are believed to induce itch as an adverse effect by impairing the activity of these inhibitory neurons. These findings have led to proposals that opioids facilitate firing of "pruritis specific" neurons and that inhibition of opioid receptors may potentially suppress pruritis.[33] Accordingly, pharmacological blockade of mu-opioid receptors has been found to suppress pruritis in rodents effectively[35] and thence, opioid antagonists such as naltrexone have been proposed as postburn antipruritic agents.[36]

Local-anaesthetics Local anaesthetics like lidocaine impede the propagation of nerve impulses by blocking sodium channels. Kopecky *et al*.[37] in a pilot study applied eutectic mixture of local anaesthetics (EMLA) onto the newly healed, intact skin in five children and found it to be safe and effective.

Topical ketamine-amitriptyline-lidocaine (TKAL) Topical ketamine-amitriptyline-lidocaine (TKAL) combination is thought to lessen pruritis by blocking the N-methyl-D-aspartate receptor and sodium channels, which in turn lessens the reactivity of peripheral nerve fibers. Various studies have proven the efficacy and tolerability in pruritis due to various dermatological disorders though there are no specific studies on postburn pruritis.[38-39]

Non-pharmacological

Cooling of the wound Cooling the skin by 2°C to 4°C leads to activation of small myelinated A-delta afferent fibres that in turn activate ion channels, called transient receptor potential cation channel subfamily M member 8 (TRPM8), and inhibits unmyelinated C-fibres carrying pruritis signals.[40] By this mechanism, common cooling agents, such as camphor, menthol, icilin, and showering/bathing transiently diminishes pruritus.[41] Galeotti *et al*.[42] have shown that menthol has an additional mechanism of inducing cooling by selective activation of Q-opioid receptors. However, topical coolants need to be applied at low concentrations (1% to 5% for menthol) as higher concentrations can cause irritation.[43] Joo *et al*.[44] investigated cold pack therapy as a treatment modality for PBP by recruiting 23 patients with severe pruritus and refractory to antihistamine and gabapentin administration. For four weeks in a row, patients engaged in more than three 20-minute sessions every day, and their condition significantly improved as assessed with numerical rating scale (NRS), 5-D Itch Scale, Leuven Itch Scale.

Transcutaneous electrical nerve stimulation (TENS) TENS by stimulates large diameter afferent nerves and blocks A-delta and C-fibres. thereby relieves pruritis in various dermatological disorders such as atopic dermatitis, macular amyloidosis and lichen simplex.[45-46] This clinical observation has inspired attempts at evaluation of TENS as a potential non-invasive treatment approach for PBP.[47-48]

A patient specific modification of this approach is Pain Scrambler therapy. Joo *et al*.[49] recruited sixteen subjects of severe PBP, who had shown no improvement with various treatment modalities. Therapy was administered with the MC-5A Pain Scrambler Therapy technology device for 40 min. daily (Monday through Friday) for 10 consecutive days and the stimulus was gradually increased to the maximum

bearable intensity for individual patients. The numerical rating scale (NRS), 5-D Itch Scale, and Leuven Itch Scale were administered and evaluated immediately before and then after 5 and 10 therapy sessions. A significant improvement ($p<0.05$) was attained by the patients.

Extracorporeal shock wave therapy (ESWT: ESWT is a non-invasive treatment option, wherein a sequence of sound waves is generated by a vibration source and subsequently dispersed throughout the skin. Many recent series have found ESWT to significantly reduce post burn pruritus. Joo *et al*.[50] demonstrated a significant improvement in the numerical rating scale (NRS), 5D-Itch Scale, and Leuven Itch Scale after administration of 1000-2000 shock waves/ treatment session with 100 impulses/cm^2, each with low-energy flux density (0.05-0.20mJ/mm^2) and a 1-week interval between treatments for 3 weeks. Samhan and Abdelhalim[51] attained similar encouraging results with respect to PBP and the quality of life (QOL) with the use of low-energy extracorporeal shockwave therapy (low-energy ESWT).

Massage therapy Various clinical trials have evaluated the possibility of message therapy in post burn pruritis and a possibility has been raised that the application of pressure through massage may potentially trigger action potentials in faster conducting large myelinated fibres and outcompete pruritic signals to the central nervous system from less myelinated, slow conducting C-fibres. Besides, massage with emollients such as cocoa butter and petroleum jelly moisturize the neo-epithelium that is deficient in dermal appendages.[52] Roh *et al*.[53] prospectively studied the impact of skin rehabilitation massage therapy (SRMT) on itch, skin status, and depression in burn survivors and demonstrated that SRMT may lead to improvement in cosmesis and well as PBP.

Laser therapy Laser therapy is believed to induce patterned columns of microthermal wounds thereby eliciting wound repair programmes that allow healing in an organized fashion, thereby mitigating pathological scar symptoms and improving scar pigmentation, erythema, pliability, texture, height and pruritus.[54-55] Ebid *et al*.[56] studied the use of pulsed high-intensity laser therapy (HILT) in PBP and found that with HILT in combination with cetirizine therapy, VAS scores decreased significantly and the QOL showed improvement on long-term.

Auriculotherapy is a version of acupuncture applied with an idea that an ear is a micro system with representation of the entire body on the outer portion of the auricle. Chen *et al*.[57] investigated the effectiveness of auriculotherapy among burn victims from the Formosa Color Dust Explosion in Taiwan using Burn Man Itch Scale and found that stimulation of the auricular Shenmen and Subcortex acupoints may effectively pruritis.

Wound dressing are impregnated with biologically active compounds (such as silver bound to activated charcoal) that can relieve PBP.[58] Dunn and Edward-Jones[59] studied the role of silver-coated dressings and thought that sustained release of silver ions into the wound reduces prevent bacterial growth, thereby reducing inflammatory cytokines, such as tumor necrosis factor and interleukin-12 protein which results in relief of PBP.

Colloidal-oatmeal has been shown to reduce pruritus in certain series. In a study by Matheson *et al*;[60] significant relief was achieved when colloidal oatmeal was used as a shower or a bathing agent between the 5^{th} and 7^{th} day

postburn. The proposed mechanism of action is that colloidal oatmeal tends to form an occlusive coating over the skin and thus, maintains an optimal level of pH and hydration of the skin.[61]

Capsaicin Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is an alkaloid from chilli peppers and is believed to cause depletion of neuropeptides from peripheral nerves which in turn leads to selective, long-lasting depression of C-polymodal nociceptors, thereby resulting in inhibition of generation of pruritis signals.[62] Topically applied capsaicin is in use as a safe and effective treatment for pruritis of various origins and hence, there is a potential of its application in PBP.[63-64]

Role of psychological support

Studies have found the high incidence of persistent PBP in patients and the resulting negative interference with quality-of-life in patients with submissive personality traits and less support-seeking attitudes.[65] Hence involvement of psychologists and psychotherapists early in the care of the burns victim to offer psychological support is desirable to ameliorate the morbidity of burns-associated pruritus.[52]

Conclusion

Post-burn pruritus (PBP) is a frequent and significant complication of burn injury, which negatively impacts the quality of life of the survivor. The precise mechanism of PBP has not been understood as yet. Multiple pharmacological and non-pharmacological treatment modalities are available but there is no consensus of the best single treatment yet. Simple single therapies are generally introduced as be the first line therapy; however, early introduction of combination therapy is made if first line fails in order to avoid chronicity. There is an ample scope of research and improvement in this field.

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