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Review

Topical treatments of skin pain: a general review with a focus on hidradenitis suppurativa with topical agents

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Abstract

Hidradenitis Supprurativa (HS) is a painful chronic follicular disease. Few papers have addressed pain control for this debilitating condition. Possible topical agents include tricyclic antidepressants, opioids, anticonvulsants, NSAIDs, NMDA receptor antagonists, local anesthetics and other agents. The first line agents for the topical treatment of the cutaneous pain of HS are diclonefac gel 1% and liposomal xylocaine 4% and 5% cream or 5% ointment. The chief advantage of topical xylocaine is that is quick acting i.e. immediate however with a limited duration of effect 1-2 hours. The use of topical ketamine, which blocks n-methyl-D-aspartate receptors in a non-competitive fashion, might be a useful tool for the treatment of HS pain. Topical doxepin, which available in a 5% commercially preparation (Zonalon®) , makes patients drowsy and is not useful for controlling the pain of HS . Doxepin is available in a 3% or 3.3% concentration (which causes less drowsiness) from compounding pharmacies and can be used in compounded analgesic preparations with positive effect. Topical doxepin is preferred over use of topical amitriptyline because topical doxepin is more effective. Nevertheless, topical amitriptyline increase of the tactile and mechanical nociceptive thresholds and can be used for topical pain control in compound mixture of analgesics . Gabapentin and pregablin can also be used compounded with other agents in topical analgesic preparations with positive topical anesthetic effect. Capsaicin is not useful for topical treatment of the pain of HS. Sometimes compounded of anesthetics medications such as ketamine 10%, bupivacaine 1%, diclofenac 3%, doxepin 3% or 3.3%, and gabapentin 6% can extend the duration of effect so that medication only needs to be used 2 or 3 times a day. Still in my experience the easiest to get and most patient requested agent is topical diclonefac 1% gel.

Introduction

Hidradenitis Suppurativa (HS) is a painful chronic follicular disease that is likely related to aberrant innate cellular immunity to coagulase negative staphyloccous, abnormal keratinization of the follicle, and hyperkeratosis of the follicle. Loss-of-function mutations in the γ-secretase genes: NCSTN, PSENEN, and PSEN1 have recently been reported to underlie a subset of familial hidradenitis suppurativa (HS) in Chinese, Japanese, and European kindreds: however most cases of HS are sporadic and of unknown etiology [1].

In a previous paper, I dealt with the oral pain treatment of HS with NSAIDS, acetaminophen, COX2s, the anticonvulsants, gabpentin and pregablin, and the SSRI/SSNI, duloxetine and venlafaxine [2]. The issues of pain control has been discussed tangentially [3] in other papers but a practical discussion is what is needed to help HS patients on a day-to-day basis. This paper will deal with the treatment of the pain of HS with topical agents.

Topical anesthetics have been used to treat complex regional pain syndrome, post herpetic neuralgia, painful oral ulcers, digital ulcers in systemic sclerosis, pain after tonsillectomy, diabetic neuropathy, anal fissures, and high-grade oral mucositis. A number of papers and chapters have dealt with the topical treatment of pain [4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20]. In addition, topical agents are routinely used prophylactically for patients in preparation for cosmetic procedures and cataract surgery. Because

pain medications are usually put on intact skin and the skin of HS is often not intact, this poses a further complication in data extrapolation from previous papers related to other conditions to topical pain control for HS.

Mechanism underlying the sensation of pain.

In a healthy individual, pain may be defined as a complex sensory experience associated with actual or potential tissue damage [4]. Injury in the periphery tissue and nerves induces keratinocytes and blood vessels in the dermis to release excitatory factors, such as prostaglandins, substance P, and calcitonin gene-related peptide, which bind to receptors on nociceptive fibers and cause depolarization. These unspecialized, peripheral nerve fibers—C and Aδ polymodal nociceptors (myelinated Aδ fibers and unmyelinated C fibers) —can be stimulated by noxious thermal, chemical, and mechanical inputs. Generally, the intensity, localization, and timing of the initiating stimuli are reflected in the level of the neuronal signal. The nerves can merely be hypersensitive, as is seen in diseases like osteoarthritis. In contrast, with inflamed tissue, an external stimulus is not required to generate signal transduction and transmission to the dorsal horn. Such hypersensitive nerves can be inhibited by a number of different pharmacologic agents, such as opioids and cannabinoids [5]. It must not be forgotten that chronic pain also involves the central nervous system which is out of the reach of topical agents unless the topical preparations are systemically absorbed.

Topical preparations

Compounded creams, gels and ointments of topical analgesics use mixtures of water, glycerin, propylene glycol, methylparaben, and conventional emulsifiers as carriers of active substances. Some preparations use pluronic lecithin organogel (lecithin, isopropylpalmitate, pluronic F127 solution) as a carrier [8]. Topical preparations have a variety of benefits, limitations, and variations. Most topical medications are compounded in a topical preparation called lipoderm (pcca) [10], which helps to maximize the topical medication concentration that actually reaches the skin. Collaboration between the physician and the compounding pharmacist optimizes the use of compounded medications. The compounding pharmacist can: (1) aid the physician in selecting the best compounds in the appropriate concentrations to match the pain patient's needs; (2) demonstrate to the patients how to apply the topical compounded medication and supply printable simple instructions; (3) assist with patients' follow-up (i.e., inform the physician about patients' medical condition and compliance); (4) address topical adverse events (e.g., skin sensitivities, rashes, and other allergic reactions); and find appropriate topical substitutions or other pharmaceutical solutions. Compounding pharmacists have important knowledge that can aid HS patients [7]. Table 1 outlines the benefits and limitations of analgesia by cutaneous delivery

Table 1. Benefits and Limitations of Analgesia by Cutaneous Delivery

Benefits	Limitations	Variations on preparation
First pass metabolism and other variables associated with the gastrointestinal tract (such as pH and gastric emptying time) are avoided. Reduced side effects, and the minimization of drug concentration peaks and troughs in the blood. Ease of dose termination in the event of untoward side effects. Provides a viable solution for treatment when oral dosing is not feasible (i.e., in unconscious or nauseated patients.) Delivery can be sustained and controlled over a prolonged period. Direct access to the target site. Convenient and painless administration. Improved patient acceptance and adherence to therapy. Ease of use may reduce overall health	• Diffusion across the stratum corneum only occurs for molecules <500 Da. Topical agents must have both aqueous and lipid solubility. Both intra- and inter-individual variability in the permeability of skin, as well as differences between healthy and diseased skin, causes variable efficacy. Skin enzymes can cause metabolism before cutaneous absorption, reducing the potency of the drug.	Dermal patches Iontophoresis Creams Ointments Transdermal patches

Benefits	Limitations	Variations on preparation
treatment costs.		

Adapted from Stanos SP. Topical agents for the management of musculoskeletal pain. J Pain Symptom Manage. 2007 Mar;33(3):342-55.[30]

Use of topical medications

A clear distinction should be made between incidental absorption from topically applied drugs and that of transdermally absorbed drugs, whose action depends on systemic absorption (e.g. fentanyl, nicotine patches). For a topical drug formulation, however, the site of activity is the tissue directly underlying the application site, including the soft tissue and peripheral nerves. The goal of topical agents is to achieve similar efficacy to oral formulations with potentially lower systemic side effects. Only small molecules with a molecular weight <500 daltons can penetrate the viable epidermis, although in HS the dermis might be less viable and larger molecules might be able to penetrate. It is important to recognize that pharmacokinetic absorption from topical formulations can vary markedly, even between different formulations of the same drug. This depends upon on the agent, the underlying disorder, and the site of application. It is therefore essential to consider the patient, the drug, and the drug delivery mechanism when selecting a topical preparation.

Topical pain creams are used commonly and require only a prescription, such as xylocaine 5% ointment, 4% xylocaine patches, and diclofenec 1% gel. NSAIDs such as diclofenac are primarily antiphlogistic agents and therefore only exert a secondary analgesic effect when inflammation is also present. C and Aδ polymodal nociceptors transmit signals from the periphery via the dorsal horn to higher cerebral structures. Topical pain can also be treated with preparations of combinations of medications put into topical form by a compounding pharmacy. One important consideration in the use of pain compounds is that insurances often will not pay for compounded pain medications. Table 2 outlines all the substance that been used topically to control pain, pruritus, and hyperhidrosis. Table 3 outlines topical pain medications, their receptors and comments on their use.

Table 2. Topical Medications Used in Compounded Preparations to treat Pain, Pruritus and Hyperhidrosis [7]

Local anesthetics	NSAIDs
Xylocaine 1.5%,	Diclofenac 1% gel
Xylocaine 3%	Diclofenac 1.5% solution
Xylocaine 4%	Ketoprofen 4% (not used in US)
Xylocaine 5%	Ketoprofen 5% (not used in US)
Xylocaine 7% & higher concentrations	Ketoprofen 10% (not used in US)
Bupivacaine[12,13]	Aspirin^{o}
oxybuprocaine [82]	
Tetracaine 1-7%	Flurbiprofen 5%
Benzoncaine 1-7%	Ibuprofen 2%
Etidocaine	Piroxicam 0.5%,
Prilocaine 2.5%	Piroxicam 2%
EMLA (lidocaine 2.5%& prilocaine 2.5%)	
	Anticonvulsants
Tricyclic Antidepressants	Carbamazapine 2%
Amitriptyline 2%	Topiramate 2%$^{\perp}$
Amitriptyline 3%	Gabapentin 6%
Amitriptyline 2.5%	Pregablin 10%
Amitriptyline 5%	
	Corticosteroids
Amitriptyline 7.5%	Dexamethasone 0.15%
Amitriptyline 10%	Hydrocortisone 10%
Nortriptyline	Others

Doxepin 3%	Baclofen 5%	
Doxepin 3.3%	Pramasone [46,47]	
Doxepin 5%	Glycopirrolate [63]	
Opioids	Orphenadrine*	
Fentanyl	Lecithin•	
Hydromorphone	Capsaicin 0.025%,	
Buprenorphine transdermal patch	Capsaicin 0.05%	
Morphine	Capsaicin 8% patch	
Sufentanil	Cyclobenzaprine 0.5%⊕	
Loperamide	Cyclobenzaprine 1%	
Tramadol	Cyclobenzaprine 2%	
Hydrocodone	Diphenhydramine 1%	
NMDA receptor antagonists	Nifedipine powder	
Ketamine 5%	Diltiazem	
Ketamine 10%	Guanethidine 2%♠	
Ketamine 15%	Guanethidine 1%,	
Ketamine 20%	Guaifenesin♦	
Methadone	Clonidine 0.1%	
Dextromethorphan♥	Clonidine 0.2%	
Amantadine	Haloperidol♣	
Memantine	Glyceryl trinitrate	Anal fissures
	Orphenadrine	

API indicates active pharmaceutical ingredient; NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug

Adapted from Zur E. Topical Treatment of Neuropathic Pain Using Compounded Medications. Clin J Pain. Clin J Pain. 2014 Jan;30(1):73-91.

⊣Orally has been used to treat diabetic neuropathic pain.[64]

*No reports of its topical use can be located in Pubmed but oral use with diclofenac have noted they act synergistically[65] and that low-dose intravenous orphenadrine had analgesic effects of in the state of capsaicin hyperalgesia.[66]

•Used to dissolve medication for topical compounds

⊕Orally used for fibromyalgia[67]

♦ Guaifenesin has been used to treat fibromyalgia. A study found it did not have any effect of fibromyalgia [68,69].

♣Topically used as an antiemetic with ativan and benadryl as topical gel; may act to control pain[70,71].

♠ Guanethidine acts to relieve dental hypersensitivity and pain [72, 73, 74].

♥Orally effective in patients with painful diabetic neuropathy and not post-herpetic neuralgia (PHN) and painful diabetic neuropathy [75].

ºMinimal effect in topical compounds

Table 3. Topical Pain Medications, Their Receptors and Comments on Their Use

Medication	Receptor	Comments
Ketamine	n-methyl-D-aspartate receptors	Can be combined with

		amitriptyline
Xylocaine	C Fibers	Mechanism of action an inhibition of the rapid Na+ ion influx into nerve fibers; that is, they act as sodium channel blockers [76]. Mechano-hyperalgesia but no effect on mechano-allodynia or heat-hyperalgesia [77].
EMLA(lidocaine 2.5% and prilocaine 2.5%)[82]	C Fibers	Methemoglobinemia
Amitriptyline	Inhibition of noradrenaline and 5-hydroxytryptamine reuptake, inhibition of NMDA, nicotinic, histamine, & 5-hydroxytryptamine receptors, & block of voltage-gated sodium channel antagonist.	At 10% lose can induce sleepiness like doxepin 5%. 10% formulation is much more potent than weaker concentrations
Gabapentin/Pregablin	blockade of calcium channels	Most effective as an oral medication
Diclofenac (and other topical NSAIDS not available in the United States)	polymodal nociceptors Aδ and C fibers	Also affect formation of cyclooxygenase products such as prostaglandins, thus reducing the enhanced responsiveness of nociceptors caused by local release of arachidonic acid metabolites from injured cells [78] 3% preparations can be systemically absorbed and cause systemic effects
Tramadol	Opiate receptors[79]	A weak μ-opioid receptor agonist, a serotonin releaser and a reuptake inhibitor of norepinephrine. Tramadol is metabolized to O-desmethyltramadol, a significantly more potent μ-opioid agonist. Tramadol and its major metabolite(s) are distinguished from other more potent opioid agonists by relative selectivity for μ-opioid receptors.
Capsaicin	Causes release of substance P from C fibers afferent neurons, and repeated application reversibly depletes stores of substance P and therefore reduces pain transmission from peripheral nerve fibers to higher centers	Has a burning sensation when put on the skin, not suitable for HS patients whose skin suffers from impaired barrier function.
Doxepin[80]	Inhibition of noradrenaline and 5-	5% cream can cause

	hydroxytryptamine reuptake, inhibition of NMDA, nicotinic, histamine, & 5-hydroxytryptamine receptors, and block of voltage-gated sodium channel antagonist.	drowsiness
Clonidine	May relate to reducing norepinephrine release presynaptic from sympathetic nerves.	More effective orally
Cannabinoids	Can act at peripheral sites to produce analgesia by action on CB1 and CB2 receptors.	Inhibit release of calcitonin gene–related peptide
Baclofen	$GABA_B$ receptor agonist	
Clonidine	α(2)-adrenergic agonist	Has synergistic antinociceptive effect with opioids
Nifedipine	Dihydropyridine calcium channel blocker	Calcium channel blocker
Diltiazem	Nondihydropyridine (non-DHP),	Calcium channel blocker
Orphenadrine	A strong muscle relaxant and pain relieving agent that provides both NMDA receptor and sodium-channel blocking properties	It provides additional benefits when combined with neuropathic and muscle relaxing agents.

The combination of these medications in topical preparations rests on the fact that they affect different components of pain signaling in the skin. NSAIDs act upon inflammation, whereas "caine" drugs block sodium channels even when no inflammation is present. Thus, combining them has a synergistic effects on controlling pain [10]. A list of some common analgesic combinations prepared by compounding pharmacies is found in Table 4. For example, amitriptyline affects different nerve actions than xylocaine-prilocaine [14]. Xylocaine-prilocaine cream displayed a short-lasting anesthetic effect for all sensations, although this was not significant for warm sensations. Amitriptyline, at the concentrations of 2%, 5%, and 10%, induces a mild and short-lasting increase of the tactile and mechanical nociceptive thresholds. Amitriptyline can significantly decrease cold thresholds and heat thresholds. It should also be remembered that itch and pain are related and medications that are anti- pruritic, such as doxepin, can also mitigate pain. The vehicle used in topical medication is important; this affects penetration. It is possible that as nanoparticle technology is perfected that topical pain control in nanoparticle form might improve the efficacy of such medications. The role of agents for pain type and disease state has yet to be defined, but the benefit of local anesthetics and capsaicin is well established. However, the efficacy of clonidine, tricyclic antidepressants, ketamine, opioids, and cannabinoids remains to be defined.

Table 4. Common compounds of pain medications in topical preparations[7]

General Neuropathies	General Joint and Musculoskel	Myofascial Pain Syndromes	Neuropathic Pain w/Large Inflammatory Component:
Amantadine 8%	Diclofenac 3%	Ketamine 10%	Ketamine 10%
Bupivacaine 1%	Baclofen 2%	Baclofen 2%	Bupivacaine 1%

Topiramate 2%	Gabapentin 6%	Bupivacaine 1%	Diclofenac 3%
	Bupivacaine 1%	Cyclobenzaprine 2%	Doxepin 3%
		Gabapentin 6%	Gabapentin 6%
		Orphenadrine 5%	Orphenadrine 5%

Xylocaine

Topical xylocaine is a mainstay of short term (1-2 hour) topical pain treatment. Monoethylglycinexylidide (MEGX), the primary active metabolite of xylocaine, is also active against pain. As a topical agent, xylocaine is a neural membrane stabilizing drug; it reversibly decreases the rate of depolarization and repolarization of excitable membranes (like nociceptors). The chief downside of topical xylocaine is its potential for cardiac side effects if systemically absorbed, but only a few such reports exist. Liposomal or micronized versions of xylocaine seem to maximize cutaneous affects and minimize system effects. Caine drugs are also causes of type I and type IV hypersensitivity reactions (anaphylaxis and allergic contact dermatitis, respectively) and assessment of this possibility should occur before they are applied to large areas of skin. I have found that the liposomal types of xylocaine (LMX4®, LMX5®) are more effective than the generic xylocaine 5% ointment and have not seen side effects in HS patients from the use of liposomal formulations. I do not use xylocaine patches because of the difficultly of adherence to areas of skin effected by HS and the potential when occluded for systemic absorption of the medication.

Another study characterized the absorption profile of and systemic exposure to xylocaine from patch and gel formulations in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster [15]. The bioavailability of xylocaine from the patch formulation averaged 3% and was similar after single and repeated doses. Systemic exposure to xylocaine after application of xylocaine gel or patches was minimal in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster. Considering the benefit versus risk of topical xylocaine, systemic absorption and toxicity of xylocaine seems not to be a significant risk. Because the barrier function of the skin is impaired in both herpes zoster and HS, this study substantiates the safety of using xylocaine gel in HS for the treatment of HS associated pain.

One study evaluated xylocaine absorption via oral mucosa following its topical application for symptomatic treatment of bone marrow transplantation-induced oral mucositis [16]. Five patients with high-grade oral mucositis after allogeneic bone marrow transplantation were entered consecutively into the study. Five healthy individuals served as controls. All 10 participants rinsed their mouth with 5 ml of a 2% xylocaine solution for 1 min, after which they expectorated the liquid. Blood samples were drawn at 1, 5, 10, 20, 30, and 60 minutes after rinsing. Plasma xylocaine levels were measured by fluorescence polarization immunoassay. In the bone marrow transplantation patients, plasma xylocaine levels were lower than the therapeutic range of this drug (0.2 µg/ml vs 1.5-5.5 µg/ml), whereas in the controls no detectable xylocaine levels were noted. The data from this preliminary study indicates that xylocaine prescribed as an anesthetic mouthwash in BMT patients with oral mucositis results in minor systemic absorption of the drug.

Nestor [12] evaluated the potential absorption and clinical toxicity of either 30 or 60 grams of occluded topical liposomal xylocaine (LMX4®) in 8 healthy volunteers. Blood was drawn to evaluate levels of xylocaine and monoethylglycinexylidide (MEGX) metabolites prior to application of the occluded cream at 1 hour, 2 hours, 6 hours, and 24 hours post-application. Additionally, the volunteers were assessed for any clinical signs of xylocaine toxicity. All patients' blood samples showed >0.5 µg/mL of xylocaine and MEGX metabolites in the serum. Patients reported no systemic effects and did not show any clinical signs of xylocaine toxicity. Nestor concluded that moderate amounts (30 and 60 grams-amounts used in a variety of cosmetic procedures) of occluded 4% xylocaine cream is safe; the test subjects showed no evidence of clinical toxicity and blood levels showed no evidence of significant xylocaine or xylocaine metabolites.

Serum levels of xylocaine remain low when used for cosmetic procedures.

However, some individuals have unpredictably high absorption levels. Oni [13] studied twenty-five subjects randomly assigned to one of five groups. The five topical anesthetics were LMX-4® (4% xylocaine; Biopelle/Ferndale Laboratories, Ferndale, Michigan), Topicaine® (4% xylocaine; Ebsa Laboratories, Jupiter, Florida), 2.5% xylocaine/2.5% prilocaine (generic EMLA preparation; High Tech Pharmaceuticals, Amityville, New York), LET (4% xylocaine, 1:2000 epinephrine, and 0.5% tetracaine), and BLT (20% benzoncaine, 6% xylocaine, and 4% tetracaine). After a patch test for adverse reactions, the topical anesthetic was applied to each patient's face and neck and covered with an occlusive dressing for 60 minutes. Blood was drawn at 90, 120, 150, 240, and 480 minutes to measure serum levels of xylocaine and monoethylglycinexylidide (MEGX). The average age of the 17 women and eight men included in the study was 26 years (range, 22-62 years) and the average weight was 70.9 kg (range, 46.4-96.4 kg).

Oni outlined his conclusions and found that the over-the-counter pain preparations had the highest serum xylocaine and MEGX levels. Topicaine® had the greatest serum levels of individual xylocaine absorption (0.808 µg/mL), followed by generic EMLA (0.72 µg/mL), LMX-4® (0.44 µg/mL), BLT (0.17 µg/mL), and LET (0.13 µg/mL). On average, topicaine had the highest serum xylocaine and MEGX levels: 0.438 µg/mL and 0.0678 µg/mL, respectively. There were significant inter-individual differences between the serum levels of MEGX and xylocaine in all groups except LET ($P<.0001$). There were significant differences between the 4% xylocaine-containing preparations ($P=.0439$). The 2.5% preparation had a greater absorption than the 4% xylocaine-containing preparation and the 6% xylocaine preparation. There were three adverse reactions in patients who received OTC preparations, one of which resulted in post-inflammatory hyperpigmentation. This study also demonstrates that the concentration of xylocaine, the formulation of the drug, and the individual patient characteristics all have significant effects on serum levels of xylocaine. The authors recommend that even over-the-counter topical anesthetics be used under the supervision of a healthcare professional to avoid adverse toxic effects, which rarely include death.

Topical xylocaine helps reduce pain of digital ulcers in systemic sclerosis (scleroderma) without systemic side effects [17]. The ulcers in this case may be comparable to the ulcers that are present in HS and gives more reassurance that topical xylocaine can be used safely on ulcers. One study [18] noted that 5% xylocaine helped thirty-five patients with postsurgical neuropathic pain, postherpetic neuralgia, or diabetic neuropathy with allodynia or hyperalgesia; 5% amitriptyline did not reduce pain.

There are no cases that I can locate involving topical liposomal xylocaine 4% cream (LMX4®) or xylocaine 5% cream (LMX5®) that have resulted in death, but this does not mean that LMX® is without side effects. This supports Nestor's observation that even using 60g of 4% topical liposomal xylocaine did not result in systematic absorption. The threshold for toxicity of “caine” type drugs is not clear. An article discussing the use of “caine” drugs in dentistry noted that adverse reactions to dental anesthetic might relate to true allergy, psychogenic reaction (syncope), normal toxic overdose, or idiosyncratic toxic overdose [17].

Preparations not recommended in HS

EMLA Cream (xylocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is a eutectic mixture of xylocaine and prilocaine in a ratio of 1:1 by weight. EMLA or prilocaine cannot be recommend for use in HS patients for pain control. A side effect of EMLA is methemoglobinemia that has occurred during endoscopic procedures and with circumcisions in infants; EMLA resulted in loss of consciousness, coma, and even death. In 2000, a 20-year-old Coast Guard cadet died owing to an allergic reaction and cardiac arrest after EMLA cream was applied to his back. A plastic surgeon in McLean, Virginia had applied a topical anesthetic to the back prior to planned laser hair removal. His parents filed a wrongful death lawsuit and settled the case for $725,000 [21].

Xylocaine/tetracaine mixes and tetracaine itself cannot be recommended for pain control of HS owing to possible side effects related to systemic absorption. Patient deaths have been reported in the literature regarding high concentrations of topical anesthetics put on legs under the occlusion of plastic wraps [21]. One of the women received a preparation of 10% xylocaine and 10% tetracaine, whereas the other woman’s medication contained 6% of each anesthetic [21].

Diclofenac

The anti-inflammatory activity of the non-steroidal anti-inflammatory, diclofenac, is primarily attributed to inhibition of distinct steps in the arachidonic acid cascade, particularly the cyclo-oxygenase pathway. Diclofenac sodium, a compound of this class of drugs, appears to have a dual effect because it also regulates the lipoxygenase pathway. A study of appropriate cell systems (leukocytes and whole blood in rats) demonstrated that diclofenac's potent inhibition of cyclo-oxygenase activity causes a sharp reduction in the formation of prostaglandin, prostacyclin, and thromboxane products, all key mediators of inflammation. Recent work disclosed that at higher concentrations, diclofenac sodium also reduces the formation of products of the lipoxygenase

pathway (5-hydroxyeicosatetraenoic acid, leukotrienes). The mechanism, by which this occurs, however, appears to be unrelated to direct inhibition of lipoxygenase. Instead, by enhancing its reincorporation into triglycerides, diclofenac sodium reduces the intracellular level of free arachidonic acid [22].

The topical preparations currently approved in the United States are diclofenac sodium 1.5% topical solution (containing dimethyl sulfoxide as a penetration enhancer), diclofenac sodium gel 1%, and a diclofenac hydroxyethylpyrrolidine 1.3% patch [23]. Other topical NSAID preparations approved in the European Union include ibuprofen creams and gels, ketoprofen gel, felbinac gel and cutaneous foam, and piroxicam gel (which might have more side effects than other topical NSAIDS). Rubbing in diclofenac 1% gel for 45 seconds seems to increase its penetration into the epidermis. It is also not clear from the literature whether the strong evidence that supports pain control for osteoarthritis can be extrapolated to other painful conditions of the skin [24].

I have found that most patients find topical diclofenac gel 1% more effective and long lasting at relieving pain than xylocaine ointment 5%. I do not use diclofenac solution or patches or xylocaine patches in HS patients. This utility of diclofenac gel is based on the fact that HS is an inflammatory disease and diclofenac gel affects polymodal nociceptors Aδ and C fibers; it inhibits the formation of cyclooxygenase products such as prostaglandins, thus reducing the enhanced responsiveness of nociceptors caused by local release of arachidonic acid metabolites from injured cells [25].

Several studies demonstrate that, perhaps because of low systemic concentrations, topical NSAIDs have a reduced risk of upper GI complications, such as gastric and peptic ulcers, and GI nuisance symptoms, such as dyspepsia, as compared to oral NSAIDs. GI adverse drug reactions are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs. Like oral NSAIDs, topical NSAIDs have a black box warning for increased risk of cardiovascular events and serious GI adverse affects. Two meta-analyses in 2004 by Mason *et al* [26,27] that combined information from 2,853 patients showed topical NSAIDs to be effective and safe in treating acute painful conditions for 1 week. This systemic review of 26 double-blind, placebo-controlled trials showed clinically significant efficacy in 19 of 26 trials, with a pooled relative benefit of 1.6. Heyneman *et al* [28] reviewed both single- and multiple-dose NSAID absorption studies. After topical NSAID administration, studies showed that peak plasma levels of the NSAID moiety were less than 10% of those obtained after oral administration. After topical NSAID administration, studies showed that peak plasma levels of the NSAID moiety were less than 10% of those obtained after oral administration. Treatment of chronic knee pain with topical ibuprofen provided comparable clinical efficacy and patient satisfaction as oral ibuprofen in this pilot study [29]. The pharmacological action of topical NSAIDs is exerted at the local level and is not dependent on systemic absorption [27].

Indirect comparisons of individual topical NSAIDs showed that ketoprofen, banned in the United States and a potent photosensitizer, was significantly better than all other topical NSAIDs, whereas indomethacin was barely more effective than placebo. Three trials, with 433 patients, compared topical with oral NSAID (two trials compared the same drug; one compared different drugs) and found no difference in efficacy. Local adverse events, systemic adverse events, or withdrawals owing to an adverse event were rare. There were no differences between topical NSAID and placebo. Thus, one can conclude that topical NSAIDs are effective and safe in treating acute painful conditions for at least one week and perhaps longer if not indefinitely [27].

The safety of topical NSAIDs for short-term use has been further established. Topical NSAIDs were effective and safe in treating chronic musculoskeletal conditions for two weeks. Larger and longer trials are necessary to fully elucidate the place of topical NSAIDs in clinical practice for the treatment of pain in HS. Adverse effects secondary to topical NSAID application occur in approximately 10-15% of patients and are primarily cutaneous in nature (rash and pruritus at site of application). Available clinical studies suggest, but do not document, equivalent efficacy of topical over oral NSAIDs in rheumatic diseases [30].

The lack of system absorption of topical diclofenac has been demonstrated in other studies. Systemic bioavailability and pharmacodynamics of topical diclofenac sodium gel 1% were compared with those of oral diclofenac sodium 50-mg tablets. In a randomized, 3-way crossover study, healthy volunteers (n = 40) received three 7-day diclofenac regimens: (A) 16 g gel applied as 4 g to 1 knee 4 times daily (4 g on surface area 400 cm2), (B) 48 g gel applied as 4 g per knee 4 times daily to 2 knees plus 2 g gel per hand applied 4 times daily to 2 hands 12 g on 1200 cm^2, and (C) 150 mg oral diclofenac applied as 50-mg tablets 3 times daily. Thirty-nine participants completed all 3 regimens. Systemic exposure was greater with oral diclofenac than with topical treatments. Oral diclofenac inhibited platelet aggregation, cyclooxygenase-1 (COX-1), and COX-2. Topical diclofenac did not inhibit platelet aggregation and inhibited COX-1 and COX-2 less than oral diclofenac. Treatment-related adverse events were mild and limited to application site reactions with diclofenac sodium gel 1% (n = 4) and gastrointestinal reactions with oral diclofenac (n = 3). Systemic exposure with diclofenac sodium gel 1% was 5- to 17-fold lower than with oral diclofenac. Systemic effects with topical diclofenac were less pronounced.

A study of diclofenac solution (1.5% percentage weight/weight) has been reported. The solution base contains 45% w/w dimethyl sulfoxide (DMSO) to enhance the absorption of diclofenac through the skin. Using 50 drops three times daily was as effective as oral diclofenac 150 mg/day for improving osteoarthritis knee pain. This was assessed in a 12-week, double-blind study using the

Western Ontario and McMaster Universities Osteoarthritis Index pain and physical function, patient global assessment, and/or patient overall health assessment scores from baseline to the final assessments. Topical diclofenac solution was generally well tolerated. The most common treatment-emergent adverse event experienced by topical diclofenac 1.5% solution recipients was dry skin at the application site, which would make unhelpful for sensitive HS's erosions and ulcerations. Gastrointestinal adverse events and abnormal laboratory parameters were less common with topical diclofenac solution than with oral diclofenac.

Amitriptyline

Amitriptylinoxide (amitriptyline N-oxide) is a tricyclic antidepressant (TCA), which was introduced in Europe in the 1970s for the treatment of depression. It has been noted to have anti-pain and anti-pruritic properties. Topical amitriptylinoxide has been found helpful for post-traumatic neuropathic pain.

Kopsky [32] investigated the analgesic effect of topical amitriptyline 5% and 10% cream in a patient with central neuropathic pain related to multiple sclerosis. The analgesic effect of topical amitriptyline cream on neuropathic pain was dose related. Kopsky [33] also described two different cases treated effectively with topical amitriptyline 5% and 10%. The first patient was a 39-year-old man, suffering from severe intractable neuropathic pain in feet and hands related to diabetes mellitus type II. After application of amitriptyline 5% the patient experienced complete relief only in the hands, whereas after application of amitriptyline 10%, a total reduction of pain occurred within 20 minutes, which lasted the whole day. The second patient was a 57-year-old man suffering for 10 years from progressive sensory disturbances in both feet and increasing pain related to chronic idiopathic axonal polyneuropathy. Amitriptyline 5% cream reduced pain in the toes nearly completely, but this was not the case in the heels. Amitriptyline 10% reduced pain in the feet, but systemic adverse effects occurred, mainly drowsiness. The patient decided to stop topical treatment because of these adverse effects. These two cases suggest an analgesic dose-response effect of topical amitriptyline in painful neuropathy. Like xylocaine, systemic adverse effects should be taken into account when using topical amitripyline.

Other researchers have found topical amitripyline to be less effective at treating pain and changing neural thresholds. Dualé [34], in a double-blind study, examined the effects of transcutaneous amitriptyline diluted in hydroalcoholic solution in healthy young male volunteers. Six treatments were randomly applied on different areas of the skin of the back: amitriptyline at 0 (vehicle), 25, 50, and 100 millimolar; saline (control); and xylocaine-prilocaine cream as a positive control. Up to 24 hours after application, mechanical thresholds for touch and nociception and thermal thresholds for cold, warm, and heat sensation were recorded for each area. Blood samples were collected to assess plasma levels of amitriptyline. A late recording of the tactile thresholds was performed 1 and 3 weeks after the treatment session The thresholds for all sensations did not differ between the vehicle and saline. Xylocaine-prilocaine cream (EMLA) displayed a short-lasting anesthetic effect for all sensations, although this was not significant for warm sensation. Amitriptyline, at the three concentrations studied, induced a mild and short-lasting increase of the tactile and mechanical nociceptive thresholds. EMLA significantly decreased cold thresholds (down to 21.8 degrees C, $P = 0.01$ vs. 27.5 degrees C for control) and heat thresholds (down to 40.1 degrees C, $P = 0.004$ vs. 43.4 degrees C for control). These two effects were no longer significant after the fourth hour of observation. Amitriptyline did not change warm thresholds. There was no apparent systemic absorption effect of the drug.

Ketamine

When given locally, ketamine acts to block, in a non-competitive fashion, n-methyl-D-aspartate receptors. Pain modulation then occurs via the blocking of glutamate production. Other NMDA antagonists include dextromethorphan, methadone, memantine, and amantadine. These seem to be effective in the management of hyperalgesic neuropathic states poorly responsive to opioid analgesics [35,36]. Although, amitriptyline serves primarily as a voltage-gated sodium channel antagonist, ketamine, acts synergistically with amitriptyline. Modulators of nerve transmission like amitriptyline and ketamine may act in pruritus by inhibiting nerve transmission of sensitized Aδ- and C-fibers. Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia [37]. Topical ketamine cream was studied in the treatment of painful diabetic neuropathy. In this randomized, placebo-controlled double blind initial study of 17 patients, it was found ineffective [38]. Another study found that both ketamine 1% cream and 1% gel could be found in the blood after application, but the adverse effects of this did not seem to be significant [39].

Finch [40] noted that patients with recalcitrant localized pruritus caused by various skin disorders reported a response to a topical combination of amitriptyline and ketamine. Specifically, Finch used a double-blind placebo-controlled crossover trial to determine the effects of topical ketamine on the sensory disturbances in 20 patients with complex regional pain syndrome. On two occasions separated by at least one week, sensory tests to light touch, pressure, punctate stimulation, light brushing, and thermal stimuli were performed in the symptomatic and contralateral limb and on each side of the forehead, before and 30 minutes after 10% ketamine cream was applied to the symptomatic or healthy limb. Venous blood for the plasma estimations of ketamine and nor-ketamine was obtained 1 hour after application of the creams. Ketamine applied to the symptomatic limb inhibited allodynia to light

brushing and hyperalgesia to punctate stimulation. Systemic effects of the ketamine are unlikely to account for this because the plasma levels were below detectable limits. Touch thresholds were unchanged, suggesting that NMDA receptors may contribute to the sensory disturbances in CRPS via actions at cutaneous nociceptors [41]. Allodynia and hyperalgesia were detected in the ipsilateral forehead to a range of stimuli (brushing, pressure, punctate stimulation, cold, heat, and warmth). In several patients, ketamine treatment of the symptomatic limb inhibited allodynia to brushing the ipsilateral forehead, suggesting that the mechanism that mediates allodynia in the symptomatic limb contributed to allodynia at more remote sites. Finch's study shows promise for the use of topical ketamine as opposed to parenteral and oral forms, which often result in undesirable side effects.

Because amitriptyline and ketamine have different mechanisms of action, researchers have combined them to see if a combination was superior to either agent alone in treating pain and itch. Lynch [42] studied twenty eight subjects with refractory, moderate-to-severe, peripheral neuropathic pain in an open label prospective trial examining perceived analgesic effect, patient satisfaction, and safety of topical amitriptyline 2%/ketamine 1% cream. Outcome measures included an 11-point numerical rating scale for pain intensity (NRS-PI), a 5-point satisfaction scale, blood chemistry screen, drug and metabolite levels, urinalyses, electrocardiogram (ECG), and physical examination. Adverse events were monitored. Twenty-one subjects completed the trial. At 6 months, subjects reported an average long-term reduction in pain of 34% (standard deviation [SD] = 37%). Of the 25 subjects, 5 (25%) achieved 50% or greater reduction in pain and 1 subject (5%) achieved 100% reduction in pain. At 12 months, the average reduction in pain was 37% (SD = 40%); 7 subjects (40%) achieved 50% or greater pain reduction. At the end of the study, 89% of subjects rated their satisfaction as 3/5 or greater and 2 subjects (10%) were pain free. Minimal adverse events were reported and there were no serious medication related adverse events. Blood levels revealed minimal systemic absorption. In conclusion, topical 2% amitriptyline/ 1% ketamine cream was associated with long-term reduction (6-12 months) in perceived pain and moderate to complete satisfaction. The preparation was well tolerated in treatment of neuropathic pain. There was no significant systemic absorption of amitriptyline or ketamine.

Antidepressants and ketamine both produce multiple pharmacologic effects that may contribute to peripheral analgesia. Such actions include block of peripheral N-methyl-D-aspartate receptors, local anesthetic properties, and interactions with adenosine systems. Similarly combinations of topical amitriptyline combined with topical ketamine are useful for the management of recalcitrant localized pruritus. Topical amitriptyline-ketamine has been found effective for treatment of rectal, genital, and perineal pain and discomfort. In a retrospective study of 36 erythermalgia patients at Mayo Clinic, 75% reported improvement in pain with topical application of a compounded amitriptyline-ketamine formulation [43].

Capsaicin

Capsaicin, extracted from the capsicum plant, is used for a variety of painful conditions, such as musculoskeletal pain and peripheral neuropathies. It selectively binds to the receptor, vanilloid receptor 1 (TRPV1), a ligand-gated, non-selective cation channel, primarily expressed on C-nerve fibers, that releases substance P [44]. It also inactivates voltage-gated Na+ channels in peripheral nociceptors and promotes extracellular spill of intracellular calcium, which potentiate activation of calcium-dependent proteases and cytoskeleton breakdown. Capsaicin inhibits electron chain transport in the mitochondria at higher concentrations contributing to their loss of function. It tends to burn when put on the skin and likely does not have a role in the treatment of the pain of HS, and I have not used it for the treatment of HS.

Tramadol compared to Ketamine

Tekelioglu [45] compared topical tramadol (a μ opiod receptor agonist with additional analgesic effect is associated with inhibition of reuptake of norepinephrine and serotonin) and ketamine in pain treatment after tonsillectomy and found them equally efficacious. The tramadol was compounded in a saline solution. Because tramadol is available only in a liquid solution it might only be useful for pain when HS that occurs in the anal area and drops of it are applied.

Pramoxine hydrochloride

Pramoxine hydrochloride is a local anaesthetic [46,47]. Pramoxine stabilizes the neuronal membrane by an uncertain mechanism. Pramoxine hydrochloride is also known for it anti-pruritic effects and is widely used in this capacity. Whereas soothing in some conditions, pramoxine has little role in the treatment of the pain of HS. Preparation H® cream used for treatment of hemorrhoids contains phenylephrine/pramoxine in a topical preparation but is likely not of real use for the more intense and complicated pain of HS. I have not used it for the topical treatment of the pain of HS.

Piroxicam

Topical piroxicam is available in the European Union but not the United States. A study [48] compared the efficacy of topical piroxicam and EMLA cream on pain control and subsequent inflammation in neodymium:yttrium-aluminum-garnet (Nd:YAG) 1,064 nm laser hair removal in female volunteers. Fifty female volunteers were enrolled in this prospective, randomized, double-blind, clinical study over a 6-month period. It was found that topical piroxicam was associated with fewer inflammatory side effects than was EMLA cream, because of its anti-inflammatory effect after the procedure.

Bupivacaine and Ketoprofen

Bupivacaine is mostly used topically for surgery on the eyes and tonsils. Bupivacaine is longer acting than xylocaine and has an effect for 4-8 hours. A patient of mine with intact skin and subcutaneous hidradenitis particularly was happy with a xylocaine 7%/ bupivacine 7% mixture, a mixture that mimics Pliaglis® (xylocaine and tetracaine) Cream 7% / 7%. It is likely best to combine it with other pain medication if used to treat the skin pain of HS. In one study [49], two groups of six patients each received either bupivacaine gel (2.5 mg/ml) or ketoprofen gel (1.6 mg/ml). The mean surface area for bupivacaine was 106 cm^2 (range 64-160) and the mean for ketoprofen was 130 cm^2 (range 64-180). Blood samples were obtained before application and at 10, 20, 30, 60, 120, 240, and 480 minutes after application. Serum levels were assayed using gas liquid chromatography and high pressure liquid chromatography. Bupivacaine levels peaked at 120 minutes; the mean level obtained was 0.07 µgram/ml (range 0.03-0.1). Ketoprofen levels also peaked at 120 minutes and the mean level obtained was 0.20 µgram/ml (range 0.12-0.27). The reported toxic serum level for bupivacaine was 4 micrograms/ml and for ketoprofen is 1128 µgrams/ml. The Pliaglis® warns against using it in patients with liver disease and it should only be used on patients with subcutaneous HS and not HS with open wounds [81].

Additional topical investigation has been done on bupivacaine. Topically applied oxybuprocaine provides sufficient anesthesia during cataract surgery with scleral incision. A combination with mild systemic analgesia (tramadol) helps to minimize pain and discomfort. Retro-bulbur injection yielded only in the postoperative period significantly better analgesia. In the operating room full cooperation of the patient is required. Therefore I do not recommend the use sponge anesthesia in cases when communication between surgeon and patient is insufficient.

In conclusion, these preparations, when applied to denuded dermis of a split skin donor sites, are unlikely to result in toxic levels. Such denuded skin mimics the condition of the skin found in HS and it is reassuring that using topical medications like bupivacaine or ketoprofen should not result in toxic systemic levels of medications. Bupivacaine at higher concentrations (which last 4-8 hours) compounded with other agents for a combination will HS likely has role in the control of HS skin pain

Gabapentin and Pregablin

In my previous paper on pain and oral treatment of HS pain, I discussed a large body of evidence for the use of gabapentin and pregabalin for the treatment of HS related pain. Thus, it unsurprising that physicians have used gabapentin and pregabalin (which can be broken down into powder) compounded topically to treat neuropathic pain [50,51]. Topical gabapentin, 2–6%, reduced pain in 80% of patients with vulvodynia [50]. In an animal model, a combination of pregabalin 10% and diclofenac 5% cream reduced infraorbital nerve pain with minimal plasma concentrations [51]. Gabapentin and pregabalin tablets or capsules (when pulverized) can be mixed with other topical analgesic agents by a compounding pharmacy to create topical preparation that have increase analgesic effect.

Clonidine

Clonidine is a sympatholytic medication used to treat high blood pressure, anxiety/panic disorder, and certain painful conditions. Clonidine is classified as a centrally acting α2 adrenergic agonist. An alternative hypothesis that has been proposed is that clonidine acts centrally as an imidazoline receptor agonist. It is likely that clonidine locally blocks the release of norepinephrine via activation of alpha 2 receptors on the sympathetic terminals [52]. Topical clonidine gel significantly reduces the level of foot pain in painful diabetic neuropathy subjects with functional (and possibly sensitized) nociceptors in the affected skin as revealed by testing with topical capsaicin [53]. Screening for cutaneous nociceptor function may help distinguish candidates for topical therapy for neuropathic pain. In a study of 17 patients [54], 10 were diagnosed with neuropathic pain and 7 with neuralgia. Two of the 17 patients had complaints overlapping both neuropathic and neuralgic pain. All were treated with 0.2% clonidine cream. In the patients with neuropathic pain, an overall mean reduction in severity of burning of 36% (on a 10-point visual analogue scale) was reported. Of the patients with characteristics of neuralgia, 57% improved. In those who reported improvement, a mean reduction of approximately 54% was reported. In the 4 patients with neuralgia who responded, a 94% reduction in pain was reported, with complete resolution of pain in 2 patients. Finally, in patients with oral neuropathic pain or neuralgia involving the oral cavity treated with 0.2% clonidine cream, 50% of patients reported clinical improvement. However, no patients reported complete resolution of symptoms. Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain [55].

Animal studies have supported the use of topical clonidine in controlling neuropathic pain. In a rat study topical clonidine was shown to be effective for treatment of neuropathic pain, but only partly effective for inflammatory pain (days reducing thermal hyperalgesia, but not mechanical allodynia) and not effective for postoperative pain [56]. In a mouse study [57], researchers showed that topical administration of clonidine to mice (via tail immersion) elicited anti-nociception in the radiant heat tail-flick test. The magnitude of anti-nociception was dependent upon the duration of exposure to the clonidine solution. Tolerance to the anti-nociceptive actions of clonidine was not blocked by topical administration of the NMDA antagonist, ketamine. As many other options are available, topical clonidine is not a preferred agent for the pain of HS.

Other combination therapies

Combination of topical amitriptyline, ketamine, and xylocaine

Because of the different mechanisms of action of agents, Uzaraga [58] combined topical amitriptyline, ketamine, and xylocaine (AKL) to treat neuropathic pain involving radiation dermatitis. Eligible subjects had radiation dermatitis with dry or moist desquamation with neuropathic pain and were intolerant or allergic to standard intervention. AKL was applied to painful sites three times a day, every day, until 2 weeks post-radiotherapy. Subjects were monitored every 2-5 days during radiotherapy and at 2 and 6 weeks after completion of radiotherapy. The University of Washington Neuropathic Pain Scale was used to grade the neuropathic pain before and after use of the interventional gel. Compliance was assessed by asking subjects at each visit how frequently they were using the interventional gel. Over a 14-month period, 16 subjects met eligibility criteria. 82% of subjects used the AKL as directed. Five subjects (32%) reported fatigue and three subjects (19%) reported site irritation from the gel. AKL was shown to significantly reduce pain intensity, sharpness, burning, sensitivity, itchiness, and unpleasantness on a short-term basis (i.e., between pre-treatment and 30 min post-treatment). AKL was shown to significantly reduce burning levels on a long-term basis (i.e., between pre-treatment and 2 weeks post-treatment).

Baclofen 10 mg, amitriptyline 40 mg, & ketamine 20 mg in a pluronic lecithin organogel

Baclofen is a derivative of gamma-aminobutyric acid (GABA). It is primarily used to treat spasticity and is in the early research stages for use in the treatment of alcoholism. Orally it is used as a muscle relaxant. Baclofen is also used by compounding pharmacies in topical pain creams as a muscle relaxant. Baclofen is an agonist for the $GABA_B$ receptors ($GABA_BR$) [59]. Baclofen produces its effects by activating the $GABA_BR$, similar to the drug γ-Hydroxybutyric acid, which also activates this receptor and shares some of its effects. However, baclofen does not have significant affinity for the $GABA_BR$ and has no known abuse potential. The beneficial effects of baclofen in spasticity result from actions at spinal and supraspinal sites. Baclofen has been shown to prevent rises in body temperature induced by the drug 3,4-methylenedioxy-N-methylamphetamine in rats.

In a patient population prone to polypharmacy and systemic toxicity, topical amitriptyline and ketamine were combined in a double blind, placebo-controlled trial. A topical gel (made of baclofen 10 mg, amitriptyline HCL 40 mg, and ketamine 20 mg in a pluronic lecithin organogel (BAK-PLO)) versus placebo was studied for the treatment of chemotherapy-induced peripheral neuropathy (CIPN) [59]. These three agents were chosen because they have different and complementary mechanisms of action. Baclofen acts as a $GABA_BR$ agonist, amitriptyline HCL affects both sodium channels and adenosine A receptors, and ketamine inhibits N-methyl-D-aspartate receptors. The trial involved 208 patients with the primary end point being the change in the European Organization for Research and Treatment of Cancer Qualify of Life Questionnaire. Chemotherapy-induced peripheral neuropathy was assessed in a 20 part series of questions regarding sensory scale at 4 weeks. The treatment group showed a greater improvement in the sensory scale as compared with the placebo group, the greatest of these improvements was in reducing tingling, cramping, and shooting/burning pain in the hands. The BAK-PLO group also showed an improvement in Cancer Qualify of Life Questionnaire - Chemotherapy-induced peripheral neuropathy 20 part series motor subscales. There were no apparent toxicities with the BAK-PLO treatment. Although the results of this trial were encouraging, further investigation of these topical agents in the treatment of chemotherapy-induced peripheral neuropathy or neuropathic pain is needed. Such investigation could focus on different dosing regimens and higher doses, given that the BAK-PLO treatment was well tolerated.

Xylocaine 5%, capsaicin 0.025-0.075% and doxepin 3.3% and other combinations

One study noted that application of a combination of xylocaine 5%, capsaicin 0.025-0.075%, and doxepin 3.3% is effective, although moderately, in peripheral neuropathic pain with allodynia and should be considered as a therapeutic option; the efficacy of a topical amitriptyline/ketamine combination was not demonstrated [60] Topical application of 3.3% doxepin, 0.025% capsaicin and 3.3% doxepin/0.025% capsaicin produces analgesia of similar magnitude. The combination produces more rapid analgesia [82]. Superficial sponge anesthesia in cataract surgery with oxybuprocaine and tramadol was superior to oxybuprocaine alone [83].

Table 5. Pearls for Pain Control

Cold suppresses pain while some suggest patient drawing out puss with warm compress this actually makes pain worse
Ice packs can be used to control the pain of HS*
Preparation for pain in any form can have their effect augmented by being put in the refrigerator
The lotion from of a pain medication is preparation to best suit augment its analgesic effects
Lidocaine in particular the microsomal lidocaine works immediately to control pain with a duration usually on one hours but up to two
Subcutaneous HS or keloidal HS but not eroded HS might benefit from lidocaine patch which lasts much up to 72 hours.
Duration of effect is longest with compound that include bupivacaine which lasts for 4-8 hours
Compound containing prescription medications that are controlled like ketamine or pregablin require a written prescription
The compound of ketamine 10%, bupivacaine 1% diclofenac 3%, doxepin 3%, gabapentin 6%, with or with out orphenadrine 5% and others in Table IV usually lasts 8 hour for TID
Medications that have cardiac side effects tetracaine, bupivacaine should not be occluded
Dicofenac gel can be occluded with serum level still only 5-15% of oral dicofenac
Patients with cardiac or liver problems should use compounds with care as the medications are broken down in the liver and bupivacaine and tetracaine can have cardiac side effects.

*ice is effective but short acting and inconvenient to use

Conclusions

As is true for the disease of HS itself, the pain of HS requires a combination approach. Oral and topical anti-pain medications have a role. Xylocaine should not be used over large areas under occlusion as this can result in death. A patient who presents with HS and complains of pain centered on the skin should first be offered topical 1% diclofenac. In my experience patients prefer it to generic topical 5% xylocaine ointment. If the patient can afford special preparations of liposomal xylocaine such as LMX4 or LMX5, these will likely offer better control of skin pain, but will likely not be covered by insurance and xylocaine is short acting. Its application under heavy occlusion in concentration above 5% can lead to death and this should be discussed with patients [84]. The use of topical ketamine, which blocks n-methyl-D-aspartate receptors in a non-competitive fashion, might be a useful tool for the treatment of pain. Topical 3% or 3.3% doxepin, which less frequently causes drowsiness than available in the 5% commercial preparation can also be used to control pain when used compounded with other agents. Doxepin is preferred over use of topical amitriptyline. If these are inadequate, other compounded preparations of topical pain medications can be used. The compound of ketamine 10%, bupivacaine 1% (with a longer duration of action as compared to xylocaine), diclofenac 3%, doxepin 3% or 3.3%, and gabapentin 6%, owing to the many combined mechanisms of action, seems to be the most effective in my experience. Topical analgesics hold promise as safe and effective adjuncts in the care of HS patients, but further research into details that can enhance the benefit of these is essential.

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