

Topical Doxepin Cream is Effective in Relieving Severe Pruritus Caused by Burn Injury: A Preliminary Study

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Abstract: We studied the effect of a potent topical histamine H₁ and H₂ receptor blocker, doxepin, on severe burn wound pruritus. We compared the response of doxepin cream in 20 patients with healed itching burn wounds, using the standard of care, which included oral antihistamines, skin moisturizers, and sedatives. The patients (all outpatients) were first assessed as to the degree of itching using the 0 to 10 pain scale with an initial assessment and a take-home chart for a seven-day period after which all patients were placed on the topical doxepin alone, and a daily pruritus assessment was made for seven days. At the end of the doxepin-treatment period, wounds were assessed, after which the previous standard of care was resumed. The degree of pruritus decreased significantly with the use of doxepin cream, decreasing from a value of 7 ± 2 on standard care to a value of 3 ± 1 with the doxepin cream. The response was noted within 15 minutes, and no tachyphylaxis was noted. We also noted a significant decrease in wound erythema. Some somnolence was noted in 20 percent of patients, which decreased with two to three days of doxepin use. The degree of itching and degree of wound erythema returned to pre-doxepin levels with a return to standard care therapy. We concluded that a topical doxepin cream is effective in decreasing wound pruritus in burn patients with results superior to oral antihistamines, skin moisturizers, and sedatives.

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Severe pruritus or itching is a common and disabling problem in patients after burn injury.¹⁻⁵ The mechanism is not clearly defined, but increased histamine release from the healed wound appears to play a role. Current standard of care is the use of antihistamines. Wound erythema is also typically found.^{5,6} The increased mast cell population in the burn wound is likely the source.¹⁻⁵ It is known that histamine release occurs from a healed wound with minimal wound manipulation and is further

exacerbated by increased skin temperature.⁵⁻⁸

Histamine then appears to trigger local wound surface pain fibers, likely C fibers, through activation of H₁ receptors. Since itch is considered a form of pain, the same fibers are felt to produce both itch and burn wound pain.⁵⁻⁹ In addition, there are a number of studies indicating that histamine release in burn scar will actually increase the degree of erythema and scar, which appears to further increase itching.^{10,11}

The pruritus is often refractory to standard man-

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agement, which includes oral antihistamines, skin moisturizers, and often the addition of opioids, sedatives, and pressure garments, the latter felt to decrease histamine release.¹⁻³ Less than 20 percent of burn patients with severe itch obtain satisfactory control with these approaches, resulting in a significant level of discomfort and decreased quality of life. There is no current effective treatment for this problem.¹⁻⁵ Topical corticosteroids are not used on newly healed burns due to the risk of thinning of the skin and risk of infection.

Doxepin, a tricyclic compound, has been found to have potent histamine receptor blocking properties.¹²⁻¹⁴ Doxepin, currently available in a five-percent topical cream, has been found to be approximately 50 times more potent than hydroxyzine and nearly 800 times more potent than diphenhydramine as an antihistamine. Doxepin cream has been found to control the pruritus of atopic dermatitis, eczema, and urticaria—all histamine induced—with results superior to the use of steroid cream or oral antihistamines.^{10-12,15} Serum levels using the cream are usually immeasurable but when detected, are over 25 times lower than the serum level required for the doxepin to have any therapeutic central nervous system activity.^{16,17}

Our objective was to test the efficacy of doxepin cream* in patients with burn wound pruritus not controlled adequately by standard treatment modalities.

Methods

All burn patients initially admitted and now being followed as outpatients were considered candidates if inclusion criteria were met. The patient criteria included: age between 18 and 55 years and deep burns covering 10 to 40 percent of body surface. Deep burns larger than 40 percent of body surface are a much smaller patient group and have many more recovery issues. These patients typically require inpatient rehabilitation for the early burn scar period that we were testing. Secondly, the pruritic burn wound had to be totally reepithelialized for at least two months so as not to confuse pain of open areas with itching. Third, itching was present while using a standard care regimen, since this study focused on treatment not prevention. Finally, patients had to be

willing to completely stop one therapy, except pressure, while the effects of a second therapy were being tested.

Twenty patients with healed burn wounds that had been healed for two to six months, and were being managed in an outpatient setting, were studied. Fifteen had at least one excision and skin grafting procedure for deeper burn areas. All patients had significant pruritus in portions of their wounds for at least two weeks, despite standard care, i.e., skin moisturizers, oral antihistamines, and sedatives, and in 10 of the patients, pressure garments. Impaired physical activity, insomnia, and overall discomfort were reported in these patients, impairing quality of life.

Patients were then supplied with the five-percent doxepin cream to be applied as a thin layer, three to four times a day, on the itching wounds for a seven-day period. One tube of doxepin was provided per patient.** The oral antihistamines, sedatives, and other skin moisturizers were stopped for the seven-day doxepin trial. Use of pressure garments was continued in the 10 patients who were currently using them.

Measurements

Each participant was provided an evaluation form that quantified the degree of itching over the seven-day period. A scale of 0 to 10 was used, identical to the 0 to 10 pain scale with which all patients were familiar. A value of 0 indicated no itch, while a 10 was unbearable itching. This scale is currently the most common method of assessing itching in adults. Itching is a form of pain that can be assessed using a standard pain scale.¹⁸⁻²⁰ The degree of itching in patients with pressure garments was obtained with the garment on the wound.

The degree of wound erythema reflecting increased blood flow at this healing stage was assessed using the rating system described by the Vancouver scar scale.²¹ Erythema was graded 0 to 4, 0 being no redness or blanching with pressure and 4 being marked redness and warmth.²¹ The degree of erythema in patients with pressure garments was obtained 10 minutes after garment removal. Although some reactive hyperemia may occur, it should be comparable in both groups.

Table 1. Initial burn patient and wound characteristics

Patient Age	Burn Size % TBS		Pruritic Wound Days to Heal	Age of Healed Wound (months)	Pressure Yes/No	Itch 0-10	Erythema 0-4
	Initial Wound	Pruritic Wound					
24	18	10	15	2	N	7	2
28	24	12	20	6	Y	7	3
52	30	12	23	4	Y	7	3
45	12	8	20	3	Y	8	3
48	14	7	25	4	Y	7	4
35	30	12	16	2	N	6	2
37	10	6	17	2	N	8	3
50	14	7	22	5	Y	7	4
42	11	6	21	4	Y	7	3
33	24	12	15	5	N	7	3
36	20	11	23	2	Y	6	4
39	18	8	17	3	N	5	3
48	24	10	16	4	N	5	2
29	36	13	20	4	Y	6	3
51	18	9	23	6	Y	7	4
53	12	7	19	3	N	8	3
30	10	6	16	2	N	6	2
48	28	12	20	5	Y	7	3
44	14	8	19	5	N	6	3
46	24	13	15	3	N	6	2
44 ± 10	18 ± 9	9 ± 3	19 ± 4	4 ± 2	10Y 10N	7 ± 1	3 ± 1

mean ± SD

TBS = Total body surface

Demographics, e.g., the burn age, size, degree, etc., were obtained at day 0. Patients were seen weekly. For the first week, patients used their current regime and were assessed at the end of the week, then switched to the doxepin treatment and reevaluated at the end of one week. The doxepin was stopped, and the prior regimen was resumed.

At week three, another evaluation was obtained, after which patients had the option to remain on standard care or return to the use of the doxepin cream.

Statistical Assessment

The comparison of itch and wound erythema, using the two treatments, was performed using the Dunnetts T-test, a nonparametric test, which provides for group comparisons at different time periods.

Results

Day 1 (pre-doxepin). The description of the burns and patient population are presented in

Table 1 and Figure 1. All patients were suffering from itching on standard therapy. The pruritic wound was always the healed, nongrafted wound. These wounds were initially allowed to heal instead of being excised and grafted, as depth was typically mid-dermal with some small areas of deep dermal and reepithelialization. Healing time was felt to be less than four weeks. An absolute criteria for excision and grafting is a wound anticipated to exceed four weeks for healing, assuming adequate donor sites are available, due to increased risks of hypertrophic scar.

The baseline assessment of pruritus on standard care was very high at 7 ± 2. The itching wounds were noted to have significant erythema. The degree of itch was not significantly different in patients with and without pressure garments. We noted an increase in erythema in some patients with garment removal release but the value increased by a maximum of one point on the 0 to 4 scale in both groups. There did not appear to be a rebound increase in erythema above that seen prior to the use of pressure garments, as these values were monitored on each outpatient visit both before and after pressure garment use.

Day 1–7 (doxepin used). Mean data is presented in Table 1 and Figures 1 and 2. All patients described a significant decrease in itching beginning immediately after doxepin use, which persisted for the seven days. The mean itch value was 3 ± 1 beginning after the first application, a significant decrease from standard care.

The degree of wound erythema, assessed by the investigators, was also significantly less at day seven than the day one pre-doxepin assessment decreasing from a mean value of 3.2 (4 being the highest) to less than one with doxepin use.

The only complication or side effect reported was some somnolence in 20 percent of patients in the first day or two, after which it resolved. The initial somnolence was considered by these patients to be comparable to that noted with the standard care oral antihistamine use. There was no correlation between degree of somnolence and improvement in itching.

Day 7–14 (post-doxepin). Mean data \pm standard deviation is shown in Table 1 and Figure 1. The degree of itching returned to pre-doxepin levels by the second day of discontinuation and return of standard care and remained constant. There was no evidence of a rebound increase in histamine release over that of the initial pre-doxepin level.

The degree of erythema returned to pre-doxepin values but was not higher than baseline, reflecting no rebound increase in histamine activity over baseline.

Discussion

Burn wound itching remains a major problem for the recovering burn patient.¹⁻⁵ Itching in a burn wound usually begins at the time of wound closure then peaks at about two to six months. Typically, the itching persists at this level for months, markedly impairing quality of life.^{1-5,19,22} Resolution often occurs with scar maturation, which often takes 12 to 18 months.

The size of the burn is not a valid indicator of the degree of post-burn itch. As to depth, the longer the time to healing or reepithelialization, the higher the risk of significant itching. Burns healing in less than 10 days rarely itch. Burns

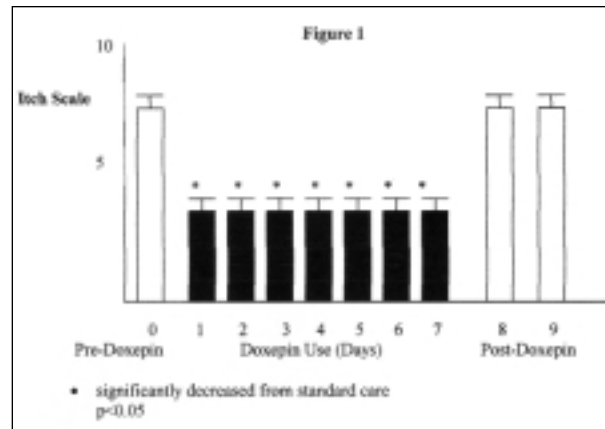


Figure 1. Mean \pm standard deviation responses for itching are shown for the 20 patients with use of standard care compared to topical doxepin. Significant itching was evident before doxepin application and immediately after doxepin was discontinued. Topical doxepin significantly and rapidly decreased itching to a very tolerable level, maintaining this degree of control over the seven-day period.

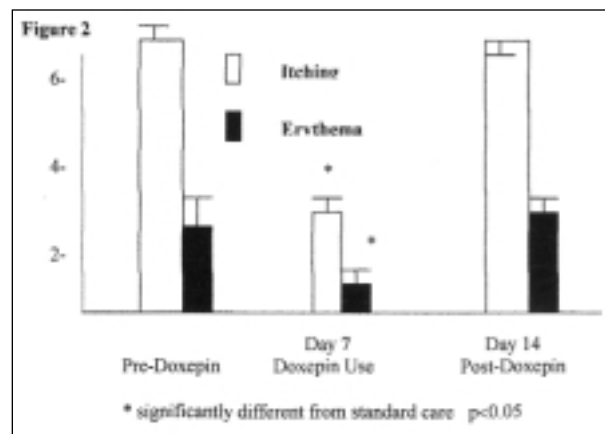


Figure 2. A comparison of the degree of itching and wound erythema is shown for the 20 patients between standard care, which includes oral antihistamines, and the use of topical doxepin. Itching is shown in the clear column (0–10), and erythema is shown in the solid column in a (0–4) scale. There was a significant improvement in itching, wound erythema, and wound edema with the use of the topical doxepin. There was no evidence of a rebound increase in histamine release upon discontinuation.

requiring over three weeks to heal usually have some degree of itching. Grafted burns are insensate for months and do not itch.

The degree of wound erythema and early scarring are good markers, but the itching usually

precedes the peak scar formation.¹⁻⁵ There is considerable variability in the degree of tissue reaction to any burn depth. Treatment for pruritus is initiated when itching begins, as there is no preventative measure, with the exception of skin moisturizers, to decrease dryness. Pressure garments are used to decrease wound blood flow, but the value of pressure garments in controlling itching is quite variable.¹⁻⁵

Recent studies indicate that the initially measured pressure of around 25mmHg with garments is only present for about seven days as the loss of edema decreases the pressure. In fact, a current hypothesis is that pressure garments control scarring by increasing skin temperature, which increases collagen lysis. We did not see a significant rebound in wound hyperemia 10 minutes after pressure garment removal indicative of the fact that there was not much pressure. In those patients where erythema did increase, the increase was no more than one point on the ranking scale and comparable at both study periods.²³⁻²⁶

Currently the standard measures at controlling itching using antihistamines, pain medication, skin moisturizers, and pressure^{1-5,19,20} are effective in less than 20 percent of burn patients who have severe itch.¹⁻³ Although the exact mechanism of post-burn itching is unclear, it is clear that histamine plays a major role as is the case in other forms of dermatitis-induced itch.^{1-5,9,27} Increased histamine release in the healed burn wound is well documented as is the increased number of wound mast cell histamine release.^{28,29} In addition, a host of other inflammatory mediators are present in an inflammatory wound, such as kinins and substance P, which increase histamine release and also can potentiate the pruritogenic effects of histamine.¹²⁻¹⁸

Itch is considered a form of pain, and both itch and pain are caused by activation of the C fibers in the skin and such dermal tissues.⁷⁻⁹ We therefore used a standard pain scale (0-10) with which all burn patients are familiar. In addition, most clinical studies on burn itch use a numerical scale.^{1-5,20}

Doxepin is a tricyclic compound found to have very potent H₁ and H₂ receptor blockade.¹⁰ The H₁ receptor blockade, which would control itch, is 775 times more effective than the commonly used

diphenhydramine.¹⁰ Topical doxepin provided as a five-percent cream has been shown to be extremely effective in controlling the itch caused by a number of types of dermatitis. There have been minimal side effects noted, the most prominent being a transient somnolence, which decreases even with continued doxepin use.¹⁰⁻¹⁴ In addition, there appears to be no rebound itching or wound erythema when topical doxepin is stopped. The serum levels from topical application are at least twenty five times lower than the levels needed for central nervous system modulation as a tricyclic agent.^{14,16,17}

We studied the effect of this potent histamine antagonist on patients with severe post-burn pruritus not responding adequately to current methods of treatment.¹⁻⁵ We found that the topical doxepin significantly decreased itching as soon as it was applied, and the control of itching continued as long as the cream was being applied. No tachyphylaxis was noted. In addition to controlling itching, the topical H₁ block also decreased wound blood flow as evidenced by the decreased erythema.¹⁸⁻²⁰

The effect of the doxepin was gone within 24 hours after the cream was stopped with return of the pruritus and wound erythema. However, no rebound increase in histamine release or any increase in symptoms above baseline were noted. Finally, minimal side effects were noted. Initial somnolence seemed to diminish by the second or third day of application, and degree of somnolence did not correlate with degree of itching.

Since we did not design a placebo control in this preliminary study in order to compare doxepin with standard care, a placebo effect is possible. However, this population with ongoing itching has used a variety of moisturizers and antihistamines, and although very hopeful, the group is also quite skeptical. A placebo effect would not have produced the dramatic decrease in itching in all patients nor the change in erythema.

In summary, we found that topical doxepin, a potent histamine receptor antagonist, was extremely effective in controlling severe pruritus in burn patients refractory to standard treatment measures.

*Prudoxin[®], HEALTHPOINT, Fort Worth, Texas

** HEALTHPOINT provided the doxepin cream for the one-week study only.

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