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Original Article

Efficacy of topical Doxepin in the treatment of eczematous dermatoses.

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ABSTRACT

Background: Doxepin hydrochloride is a dibenzoxepin tricyclic, has a potent H_1 & H_2 receptor blocking actions. If topical doxepin can effectively control pruritus associated with eczematous dermatoses, we can use it as adjunctive therapy and can reduce the drawbacks of topical steroids and antihistamines.

Methods: An interventional study from january 2010 to june 2010 has done in the department of dermatology and venereology, Faridpur Medical College Hospital, Bangladesh to evaluate the efficacy of topical doxepin cream in eczematous dermatoses. We included moderate to severe pruritic eczematous dermatoses patient in this study.

Results: Improvement of pruritus was assessed at day 3 and at day 7 by both Visual analogue scale (VAS) and Itch severity scale (ISS). At day 3 by VAS 61.3 %(57) patients showed improvement and at day 7 improvement rate increases to 84.9% (79). By ISS improvement at day 3 was 68.9% (64) and increased to 90.3% (84) at day 7. Improvement was experienced by all types of eczema patients. An average of 27.27% (29.88% by VAS and 24.65% by ISS) reduction of pruritus noticed at the end of day 3 and at the end of study, response increases to 55.58% (57.10% by VAS and 54.06% by ISS). Paired sample t test was done both for visual analogue scale (VAS) and itch severity scale (ISS) that compare the mean pruritus reduction at day 3 and day 7 with baseline pruritus (day-0). Pruritus reduction was statistically significant at day 3 and day 7 both by VAS & ISS.

Conclusion: Doxepin cream is highly effectively in relieving pruritus associated with eczematous dermatoses but it has little effect on eczema itself.

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Introduction

The term eczema is broadly applied to a range of persistent skin conditions. These include redness, swelling, itching, dryness, crusting, flaking, blistering, cracking, oozing, or bleeding and areas of temporary skin discoloration[1]. In most eczematous reactions, severe pruritus is a prominent symptom. Scratching induces lichenification and may lead to secondary infection, which in themselves cause itching. A vicious cycle may be established[2].

Cessation of pruritus is the goal in eczema treatment and it is important to break the habitual itch-scratch cycle. There is no universal remedy, which is effective in every form of pruritus. Topical steroids and systemic antihistamines are widely used to treat the pruritus. These modalities need more time to control pruritus[3]. Topical steroid cause atrophy, striae, easy bruising of the skin and many systemic antihistamines have sedative property and hampered daily activity of the patient. Different studies showed that topical doxepin is effective in histamine induced pruritus. Doxepin hydrochloride is a dibenzoxepin tricyclic compound structurally related to amitriptyline. It has a potent H_1 & H_2 receptor blocking actions. Oral doxepin is effective in the treatment of acute, chronic and cold induced urticatia; however, systemic adverse effects limit the usefulness of this therapeutic approach. Topical doxepin is expected to act by competing with histamine at the receptor sites, thus inhibiting their biologic effects. If topical doxepin can effectively control pruritus associated with eczematous dermatoses, we can use it as adjunctive therapy and can reduce the drawbacks of topical steroids and antihistamines[4]. Topical doxepin has recently introduced in Bangladesh. Unfortunately there is no data base study with this drug over Bangladeshi people. The present study was designed to assess the effect of topical doxepin in the treatment of eczema.

Materials and Methods

An interventional study was carried out in the department of dermatology and venereology, Faridpur Medical College Hospital from january 2010 to june 2010. Patients with eczematous dermatoses attending at out patient department of Faridpur Medical College Hospital, Faridpur were selected for the study. Within this period ninety three patients with eczematous dermatoses were assigned purposively, considering exclusion criteria like children aged below 12 yrs, presence of secondary infection and patient with untreated narrow angle glaucoma and considering inclusion criteria like patients presented with moderate to severely pruritic eczematous dermatoses such as lichen simplex chronicus, nummular eczema and contact dermatoses for at least one week, willing to participate in the study, adult and children older than 12yrs of age of both sexes, patient who did not use any topical medication within last one week, patients who can understand visual analogue scale of pruritus & pruritic severity scale etc

Procedures of treatment: Data were recorded in a pre-designed format after taking history, clinical examination and doing necessary investigations. Patients with lichen simplex chronicus, nummular eczema, or contact dermatoses were diagnosed by at least one qualified dermatologist. Patients satisfying all inclusion criteria was given doxepin 5% cream and instructed to apply the cream to designated areas twice on the day of the baseline visit (day 0) and four times daily for the remainder of the study. Patients were instructed to return to the hospital for evaluation of efficacy on days 3 and 7 of treatment. At each follow up visit, we completed an itch severity scale (ISS). ISS scores correlated moderately with physical (r=-0 x 483) and mental (r=-0 x 492) health composite scores of the RAND-36 and strongly with Dermatology Life Quality Index scores (r=0 x 628), evidence of construct validity. It had an internal consistency reliability of 0 x 80 and a test-retest reliability of 0 x 95 [9, 11].

Pruritus relief assessed by patients were done by using a 100-mm horizontal Visual Analogue Scale (VAS) for pruritus relief, which was

labeled "complete relief from itching" and "no relief from itching" on oppositee xtremes. Operationally a VAS is usually a horizontal, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the line point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient markss[7].The evaluation of eczema severity (worse: —1; same: 0; and better: +1) were based on the following signs of eczematous dermatoses: erythema, induration, oozing, crusting, lichenification, excoriations, and scaling. Statistical package for social science (SPSS) software (version-12) was used to analyze the data. Data were expressed as mean ± standard deviation. Paired sample t test was used to test whether the therapeutic outcome is significant or not. Observation and results of the clinical study and statistical analysis were presented by suitable chart, tables, graphics and diagram. P value 0.05 was considered significant.

Ethical consideration: Procedures of the study were described elaborately to every patient. They were assured about the confidentiality of the information concerning to them. They were also assured that, they reserve the right to withdraw themselves from this study at any time, without any explanation. The medications that would be used in this study were found safe in different study in different country. After explanation all the things, written informed consent was taken from the entire patient or their guardian.

Results

Table I showed that the mean age of the patients was 35.26 ± 10.55 years and their age ranged from 16 to 62 years. Among the 37 patients, highest percentage of patients, 28(30.1%) were in between the 31- 40 years old. Table II showed that mean pruritus in Lichen simplex chronicus (LSC) patients by Visual analogue scale (VAS) was 7.50(±0.968), 5.08(± 1.609), 3.17(± 1.629) at day 0, 3 and 7 respectively. In patient with Contact dermatitis (CD) mean pruritus by VAS at day 0 was 7.60(± 0.957), at day 3 was 5.52(± 1.447) and at day 7 was 3.56(± 1.895). Mean pruritus in Nummular eczema (N. eczema) patient by VAS was 7.50(± 0.827), 5.45(± 1.605) and 2.95(± 1.050) at day 0, 3 and 7 respectively. This result shows that pruritus relief was noted in each types of eczema. Mean pruritus in LSC patients by Itch severity scale was 15.40(±1.106), 11.46(± 3.235), 6.83(± 3.257) at day 0, 3 and 7 respectively. In patient with CD mean pruritus by ISS at day 0 was 15.56(± 1.044), at day 3 was 11.68(± 2.897) and at day 7 was 7.40(± 3.571). Mean pruritus in N. eczema patient by ISS was 13.95(± 0.887), 10.75(± 2.149) and 6.65(± 2.870) at day 0, 3 and 7 respectively. This results clearly showed that pruritus reduction was noted in each types of eczema (table III**).** We included moderate to severe pruritic eczematous dermatoses patient in this study. Severity of pruritus was measured by patients through Visual analogue scale of pruritus (VAS), and also by physician, through Itch severity scale (ISS). At the beginning of treatment (day-0) mean pruritus by VAS was 7.53 (± 0.928) and by ISS was 15.13(± 1.209). At day 3 mean pruritus by VAS was 5.28 (± 1.563) and by ISS was 11.37(± 2.933). At the end of the study (day 7) mean pruritus by VAS was 3.23(± 1.63) and by ISS 6.95(± 3.245) (figure I & II**).**

Improvement of pruritus was assessed at day 3 and at day 7 by both Visual analogue scale (VAS) and Itch severity scale (ISS). At day 3 by VAS 61.3% (57) showed improvement and at day 7 improvement rate increases to 84.9% (79). By ISS improvement at day 3 was 68.9% (64) and increased to 90.3% (84) at day 7. Results showed all types of eczema were improved (table IV & V**)**. By visual analogue scale (VAS) mean pruritus reduction at day 3 was 2.25 (± 1.93) and at day 7 was 4.30 (± 1.99). By Itch Severity Scale (ISS) mean pruritus reduction at day 3 was 3.76 (± 2.91), and at day 7 was 8.18 (± 3.42). An average of 27.27% (29.88% by VAS and 24.65% by ISS) reduction of pruritus noticed at the end of day 3 and at the end of study, response increases to 55.58% (57.10% by VAS and 54.06% by ISS) (table VI &VII**)**.

Paired sample t test was done both for visual analogue scale (VAS) and itch severity scale (ISS) that compare the mean pruritus reduction at day 3 and day 7 with baseline pruritus (day-

0). Pruritus reduction was statistically significant at day 3 and day 7 both by VAS & ISS (table VIII & IX**).** At the end of study (day 7) severity of eczema was same in 76 patients (81.7%), 11 patients (11.8%) showed improvement & only 6 patients (6.5%) noticed worsening of severity of eczema (Figure III**).**

Table I: Age and sex distribution of patients (n=93)

Age group	Sex		Total
	Female	Male	
11-20	6	2	8 (8.6%)
21-30	15	10	25 (26.9%)
31-40	13	15	28 (30.1%)
41-50	12	14	26 (28.0%)
>50	4	2	6 (6.5%)
Total	**50**	**43**	**93 (100%)**

Table II: Mean pruritus in different eczema by VAS

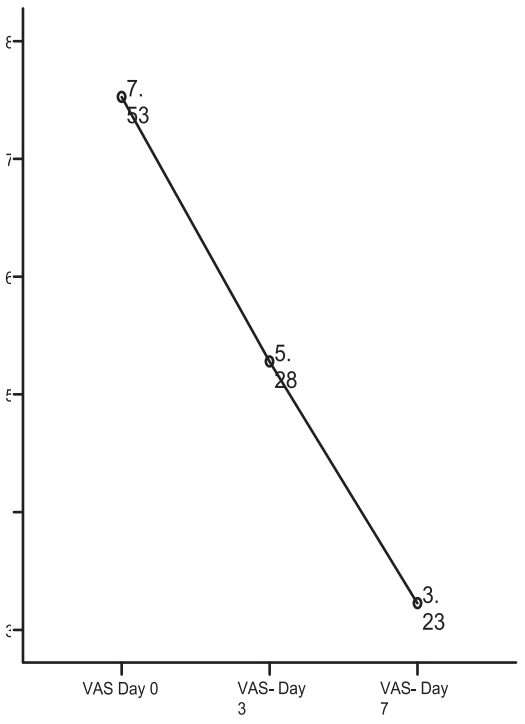
Type of eczema	Number	Visual analogue scale of pruritus		
		Day - 0	Day - 3	Day - 7
LSC*	48	7.50 (± 0.968)	5.08 (±1.609)	3.17 (±1.629)
CD**	25	7.60 (±0.957)	5.52 (±1.447)	3.56 (±1.895)
N. Eczema***	20	7.50 (±0.827)	5.45 (±1.605)	2.95 (±1.050)
Total	93	7.53 (±0.928)	5.28 (±1.563)	3.23 (±1.603)

*LSC : Lichen simplex chronicus,
**CD: Contact dermatitis,
*** N. Eczema : Nummular eczema

Table III: Mean pruritus in different eczema by ISS

Type of eczema	Number	Itch severity scale		
		Day - 0	Day - 3	Day - 7
LSC*	48	15.40 (± 1.106)	11.46 (± 3.235)	6.83 (± 3.257)
CD**	25	15.56 (± 1.044)	11.68 (± 2.897)	7.40 (± 3.751)
N. Eczema***	20	13.95 (± 0.887)	10.75 (± 2.149)	6.65 (± 2.870)
Total	**93**	**15.13 (± 1.209)**	**11.37 (± 2.933)**	**6.95 (± 3.245)**

Figure I - Mean pruritus at day 0, day-3 and day-7 (Visual analogue scale)



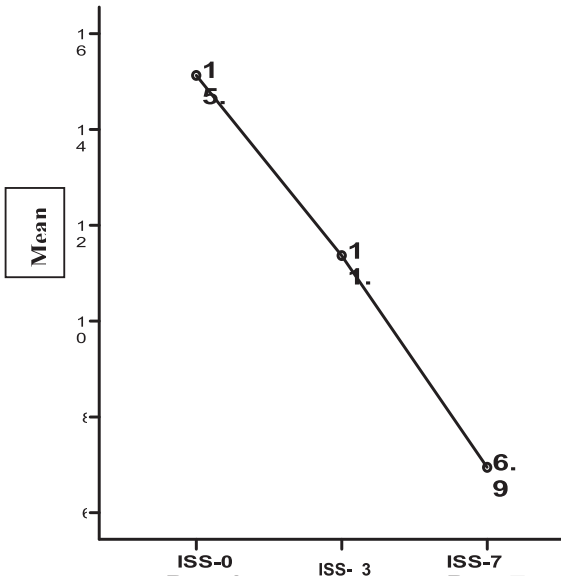


Figure II - Mean pruritus at day 0, day-3 and day-7 (Itch severity scale)

Table IV - Improvement of pruritus by Visual analogue scale (VAS)

Types of eczema	Day-3		Day-7	
	Improved	Not improved	Improved	Not improved
LSC*	31 (33.3%)	17 (18.3%)	41 (44.1%)	7 (7.5%)
CD**	15 (16.1%)	10 (10.7%)	20 (21.5%)	5 (5.4%)
N. Eczema***	11 (11.9%)	9 (9.7%)	18 (19.3%)	2 (2.2%)
Total	**57 (61.3%)**	**36 (38.7%)**	**79 (84.9%)**	**14 (15.1%)**

*LSC- Lichen simplex chronicus,
**CD- Contact dermatitis,
***N. Eczema- Nummular eczema

Table V- Improvement of pruritus by Itch severity (ISS)

	Mean pruritus		Reduction	Percentage	Average
	Day- 0	Day - 3			
VAS	7.53 ± 0.93	5.28 ± 1.56	2.25 ± 1.93	**29.88 %**	**27.27%**
ISS	15.13 ± 1.21	11.37 ± 2.93	3.76 ± 2.91	**24.65 %**	

Table VI: Reduction of pruritus at day-3

Types of eczema	Day - 3		Day - 7	
	Improved	Not improved	Improved	Not improved
LSC*	33 (35.5%)	15(16.1%)	44 (47.3%)	4 (4.3%)
CD**	18 (19.4%)	7 (7.5%)	22 (23.7%)	3 (3.2%)
N. Eczema***	13 (14.0%)	7 (7.5%)	18 (19.3%)	2 (2.2%)
Total	**64 (68.9)%**	**29 (31.1)%**	**84 (90.3%)**	**9 (9.7%)**

Table VII – Reduction of pruritus at day 7

	Mean pruritus		Reduction	Percentage	Average
	Day-0	Day - 7			
VAS	7.53 (± 0.93)	3.23 ± 1.60	4.30 ± 1.99	**57.10 %**	**55.58 %**
ISS	15.13 ±1.21	6.95 ± 3.25	8.18 ± 3.42	**54.06 %**	

Table VIII- Paired sample t test (By Visual analogue scale)

	Paired Differences				t
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference	
				Lower-Upper	
Pair 1 day-(0-3)	2.247	1.926	.200	1.851-2.644	11.252
Pair 2 day-(0-7)	4.301	1.988	.206	3.892-4.710	20.865

*VAS- Visual analogue scale

Table IX- Paired sample t test (By Itch severity scale)

	Paired Differences				t
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference	
				Lower-Upper	
Pair 1 day (0-3)	3.763	2.906	.301	3.165-4.362	12.490
Pair 2 day (0-7)	8.183	3.417	.354	7.479-8.886	23.097

* ISS- Itch severity scale

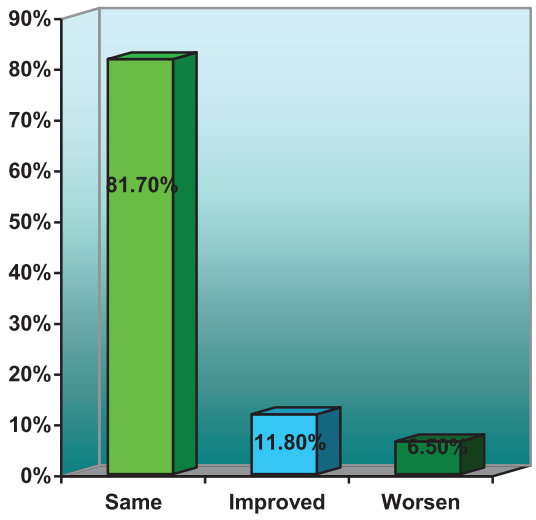


Figure III – Effect of topical doxepin on eczema severity at day 7

Discussion

The objective of this study was to evaluate the anti-pruritic efficacy of topical doxepin cream in eczematous dermatoses. In this prospective clinical trial ninety three patients were included and female to male ratio was 1:1.16. Majority of the patients (30.1%) were in between 31-40yrs. This study documents that eczema affects sexes and lichen simplex chronicus, nummular eczema and contact dermatitis common in early adult life. Mean age of the patients were 35.26 years, that is similar with the study conducted by Drake L.A. [5] Lichen simplex chronicus (LSC) were found most common (52.6%) eczema in this study followed by contact dermatoses (26.9%) and N. Eczema (21.5%). Number of LSC patient were higher may be due to this study was conducted in govt. hospital where mainly low incoming people come who do not treat their disease in time. Number of LSC patients was also highest in study conducted by Drake L.A [5].
In this clinical trial 5% topical doxepin cream provide statistically significant pruritus relief in the patients with eczematous dermatoses. Improvement of pruritus was assessed by visual analogue scale (VAS) and itch severity scale (ISS) at day 3 and day 7. At day 3 average 65.05% patients (61.3% by VAS and 68.8% by ISS) showed at least some degree of pruritus reduction and the rate increased to 87.6% (84.9% by VAS and 90.3% by ISS) at day 7. Improvement was increases in continued application of doxepin cream. Not only this, majority of patients experienced pruritus reduction irrespective of types of eczema. These results consistent with the study conducted by drake LA, where he found 84% patients experienced reduction of pruritus at day 7 [5]. In another study with doxepin cream on atopic eczema patients, 85% patient showed pruritus reduction at day 7 [6].
Mean reduction of pruritus 27.27% (29.88% by VAS and 24.65% by ISS)) noted at day 3 and it was increased to 55.58% (57.10% by VAS and 54.06% by ISS) at day 7. This results clearly documents that topical doxepin has antipruritic effect irrespective of types of eczema [10]. Studies of Drake L.A. have shown that 52% mean pruritus reduction achieved after 24hrs and it reached to 75% at day 7 [4,5]. Improvement was little beat lower in present study that may be due to small sample size or may be due to different genetic constituents of patients. Paired sample t test was done and there was statistically significant ($p<0.05$) pruritus improvement noted at day 3 and 7 both by VAS and ISS. So null hypothesis is rejected and alternate hypothesis is retained.

Conclusion

Doxepin cream is highly effective in relieving pruritus associated with eczematous dermatoses. Doxepin cream provide symptomatic relief of pruritus associated with eczema but it has little effect on eczema itself. So if we use topical doxepin cream along with corticosteroid, this will optimize patient compliance.

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