8 Randomized controlled trial to evaluate the effectiveness of topical use of salicylic acid for treatment of keratosis in arsenicosis patients

A.Z.M. Maidul Islam

Department of Dermatology and Venereology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka.

Mir Misbahuddin

Division of Arsenic Research
Department of Pharmacology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka.

Shahidullah Sikdar, Apurba Kumar Biswas, Zafrul Islam, Hadiuzzaman
Department of Dermatology and Venerology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka.

Salamat Khandker, Ifthaker-Al-Mahmud

WHO Arsenic Cell
DPHE Bahaban
Kakrail, Dhaka.

Sheikh Akhtar Ahmad

Department of Occupational and Environmental Health
National Institute of Preventive and Social Medicine
Mohakhali, Dhaka.

Abstract

To evaluate the effectiveness of topical salicylic acid in different concentrations (5, 10, 20 and 30%) for the management of keratosis, a total of 150 arsenicosis patients having different caregories (mild, moderate and severe forms) of keratosis were included in this study. After 1 month of using ointment, the improvement was found in 72.5% of cases of mild keratosis, 57.5% in moderate keratosis and only 20.0% in severe keratosis. On the contrary, after 3 months of application of ointment higher improvement was found among mild and moderate type of keratosis (92.5% and 77.5%, respectively) while in severe cases the improvement was only 45.0%. After 6 months of using salicylic acid ointment, almost all the mild

and moderate forms of keratosis were found to be improved (97.6 and 95.0% respectively) and in severe cases the improvement was less, which was 67.5%. Considering the effectiveness of different amounts of salicylic acid, 90% improvement was observed by 20 or 30% salicylic acid in mild keratosis within 1 month whereas 100% by 10, 20 or 30% within 3 months of treatment. In case of moderate keratosis, more than 90% improvement was found by 5% of salicylic acid or more after 6 months of treatment. More than 90% improvement was noted in severe form of keratosis only by using 30% salicylic acid for 6 months. The present study shows that topical use of salicylic acid has a significant role in the treatment of arsenicosis keratosis. However, the degree of keratosis (mild, moderate or severe), the amount of salicylic acid and duration of treatment are very crucial for getting optimal effectiveness.

Introduction

Topical use of salicylic acid has been reported to be effective in reducing pain and roughness of keratosis. Salicylic acid ointment is one of the most commonly used and oldest keratolytic agents in dermatology. Hippocrates used natural salicylic for various diseases including keratosis. Naturally salicylic acid is found in the fruit, leaves and bark of many plants. Modern purified salicylic acid is synthetically produced and has been used externally for various illness since the second half of the 19^{th} century.

For warts salicylic acid is most commonly used and principal keratolytic therapy for its treatment. It is considered as effective and relatively benign forms of treatment for most keratoic lesion of warts. This treatment relies upon chemical debridement of the epidermal layer of the skin. Usually salicylic acid in 15, 20, 40 or 60% concentrations in a variety of vehicles including flexible collodion, polyacrylic solutions or plaster pads used as keratolytic ointment. Though the term keratolytic indicates keratolysis, but the substances do not necessarily lead to lyses of keratin, rather act as squamolytic. Salicylic acid is also reported to be effective in keratotic lesions and scaling disorders of various skin diseases.

In Bangladesh and West Bengal for the treatment of arsenical keratosis, keratolytic ointment in terms of a combination of salicylic acid and urea is being used. In both the areas the application of keratolytic ointment was reported to improve keratosis lesions of arsenicosis. But in those studies the concentration of salicylic acid and the duration of use of ointment was not clearly mentioned and on the other hand they used in combination of urea.

The combination therapy of salicylic acid and urea as keratolytic ointment is said to be cause more side effects in human than use of salicylic acid alone. This study had been undertaken to find out the efficacy of salicylic acid in different concentrations with duration and side effect by the treatment of arsenical keratosis.

Method and Materials

Study areas: The study was conducted in two arsenic affected areas (Bhanga Upazilla of Faridpur District and Sonargoan Upazilla under Narayangonj District).

Duration of study: This placebo-controlled randomized double-blind study started in April 2003 and completed in February 2004.

Study population: Arsenicosis patients having keratosis and who didn't apply any keratolytic ointment for the treatment of keratosis were included in the study. The sample size was 150 of which 120 patients from Bhanga Upazilla and the rest 30 patients from Sonargoan Upazilla. Dhaka Community Hospital patients screening team identified 488 arsenicosis patients in Bhanga and submitted the patient's list to the Upazilla Health Complex. The researchers studied the patient's list and deputed one of the physicians to conduct preliminary survey on the number of arsenical hyperkeratosis patients. The physicians visited the patients, house-to-house, and conducted preliminary selection of hyperkeratosis patients. Our designated dermatologists confirmed the cases and made a list of mild, moderate and severe keratosis patients irrespective of age, sex and those who did not apply keratolytic ointment. For the study equal numbers of mild, moderate and severe keratosis patients were randomly selected from the list. Thus, a total of 123-hyperkeratosis patient were initially selected from Bhanga for this study. All selected hyperkeratosis patients were then informed of the objectives of the study, what outcome they could expect being a participant of the study and of their right to withdraw from the study at any point of time. Another 30 patients were randomly selected from the list of arsenicosis patients in Nilkanda village of Sonargaon Upazilla. The cases were selected following same criteria applied in Bhanga. Three patients from Bhanga didn't agree to participate in the study. So finally 120 cases continued with 40 cases each of the mild, moderate and severe groups. As for patients from 'Nilkanda' village each the group had 10 participants. Therefore, the total number of participants for this study was 150, with 50 participants in each of the mild, moderate and severe keratosis groups. Thereafter three separate sampling frames were prepared based on the severity of keratosis. By using this sampling frame in each group of patients, the cases were randomly selected for distributing 5 categories of ointment.

Development of questionnaire: The already developed questionnaire was field-tested at the time of orientation training of interviewer. The questionnaire was finalized after necessary amendment as per field test feedback.

Interviewers: Two physicians were selected for interviewing the patients. They were trained and instructed by the researchers on different techniques of interviewing procedure. A technician from International Development Enterprise, Dhaka provided training to the interviewers on installation of filter. The interviewers received orientation on quality testing of filtered water also.

Field staff: We divided the trial area in 21 zones and selected 1 field officer for each zone. There were 21 Field Officers who helped very actively to carryout this study properly. Most of the filed staffs were selected from the study area. At the beginning of the study we provided orientation training to the field staff regarding collection of information and interviewing procedure. The field staff were briefed on their specific job responsibilities e.g. monthly report to the local coordinator, monitor filtered water quality regularly, observe whether the selected patients were using filtered water for drinking and cooking purpose, check the compliance of drug used (local application of ointment twice daily in equal interval) and also report to the local coordinator if any side effects complained by patients.

Supervisors: The local supervisors were selected from the same locality where the patients live. Two local coordinators took the responsibility to follow-up the patients of Sonargaon. Health & Family Planning Officers (H&FPO) of the Health Complex in Bhanga was selected as focal person. Beside, local health staff of respective village/union were selected in Bhanga to conduct house visit of patients.

Procurement and distribution of filters: 153 water filter supplied by WHO were distributed among the selected patients. A team consisting of two trained physicians conducted active supervision on maintaining quality of filtered water. They took technical assistance of IDE personnel for water quality testing at the field and they used 'Hach Kit' for testing of water quality.

Ethical issues: The study was approved by the Ethical Committee of Bangladesh Medical Research Council (BMRC). All the participants were informed of the objectives of the study, what outcome they could expect being a participant of the study. In spite of taking care and monthly monitoring of the patients if any complication would arise the researchers were ready to treat the complications, even the participant could seek for further better treatment and after that they had also right to withdraw from the study. Besides, the participant had right to withdraw from the study at any point of time.

Preparation of medicine: The trial drug salicylic acid ointment in different concentrations e.g. 0%, 5%, 10%, 20% and 30% were prepared by a local pharmaceutical company and blinded and labeled as A, B, C, D and E without mentioning the concentration and the code kept with the pharmacist.

Assignment of participants into treatment groups: From each of the sampling frames, 10 participants were randomized into each of the 5 treatment groups (A, B, C, D and E). Finally the treatment groups were constituted, each group having 10 participants with the three different severity grades of keratosis. Ultimately each of the treatment groups were composed of 30 participants. The details of the assignment of the participants into the different treatment groups based on the severity grades of keratosis was only known to the principal investigator and was not disseminated to other investigators and staff of the project. The composition of a treatment was unknown to all the investigators and staff except the principal investigator.

Distribution of ointment among the patients: Relevant information comprising of names, addresses, identification number and assigned group were then passed over to the focal person for use when distributing the trial drug(s). The patients and the focal person did not know the concentration of ointment. Each patient was instructed to apply the medicine to the affected areas of palms and soles twice daily with proper washing of hands and feet with clean water prior to application of the medicine and the patient was also instructed to report for subsequent monthly follow-up visit up to 6 months of duration for clinical assessment. They

were further advised to report to the focal person if any problem / side effect faced to use this ointment. Each patient was asked to report to the office of the focal person on a fixed day of the subsequent month for clinical assessment.

Periodical clinical examination of patients: The patients were examined on monthly visit and note down the progress or any side effect of the treatment regimen. We follow the checklist for this purpose. Though the visits were made monthly basis by the researchers for regular monitoring, the analysis was mainly performed on the basis of the results after one month, three months and six months of the application of ointment.

Data collection: The interview and clinical examination for each of the patient was carried out properly by the investigator and the findings were noted in pre-design questionnaire and checklist. The patients were categorized in three grades, e.g. mild keratosis, moderate keratosis and severe keratosis and grouped them into I, II and III accordingly.

Mild keratosis (Group I): Hardening and roughness or gritty feeling of the skin of palm and sole or just palpable or just visible pinhead like keratosis scatteredly affecting the palm and sole.

Moderate keratosis (Group II): Palpable and visible wart keratosis affecting palm and sole

Severe keratosis (Group III): Wart like keratosis densely or extensively distributed in whole palm and sole

Each of the patients was provided with water filter as per project protocol to ensure arsenic safe drinking water. The filtered water was tested with field test kits to determine the efficacy and proper functioning of the filter in two occasions, one at beginning of the trial and second at 3 months interval.

The patients were evaluated by clinically in terms of change in severity of keratosis through comparing the state lesions as recorded in the checklist of previous visits of the patients by the same investigator. The evaluation was also done through comparing the patients' perception on changing in severity of their keratotic lesions as recorded in the previous visit. During recording the prognosis of changes of keratosis as observed by the investigator, the patients view on prognosis was also considered. Every month the same patient was examined by same investigator to evaluate the prognosis of keratosis. The efficacy of the medicine as indicated by prognosis of severity of keratosis was valuated as (0) = no improvement, (+) = mild improvement, (++) = moderate improvement and (+++) = excellent improvement, and recorded in the checklist at each follow up visit by the investigator. In every follow up visit the patients were examined and asked for any side effect such as pruritus, erythema, pain, blister, ulceration etc. and if any was also recorded in the checklist.

The recorded results at baseline, after first month, third months and sixth months of application of ointment were analyzed for evaluating the prognosis of patients.

Results and Discussion

Among the 150 subjects 90 were male and 60 female. The age of the patients varied from 11 to 75 years and the mean age was 35 (± 11) years. Maximum (64.6 %) patients were in the age group of 21 to 40 years.

In placebo group, only one patient showed improvement after 6 months of using ointment.

Table 1 shows the time-dependent improvement of keratosis. After one month of application of the salicylate ointment, the improvement was found in 72.5% in the mild keratosis, 57.5% in moderate and only 20.0% in severe cases. Continuation of drug for 3 months showed higher improvement amongst mild and moderate cases (92.5% and 77.5% respectively) while in severe cases the improvement was 45.0%. After 6 months of application of ointment almost all the mild and moderate cases were improved which were 97.5% and 95.0% and in severe cases the improvement was less, which was 67.5%. The difference in the improvement within the group was significantly associated with the extent of severity of the keratosis ($p < 0.05$). In relation with the severity of keratosis it was found that the improvement was higher in mild and moderate keratosis, in severe cases the improvement was lower, even after three months of use of ointment it was less than 50% and after six months of use the improvement was found in 67.5% of cases.

Table 1: Time-dependent improvement among different groups keratosis

Duration of Treatment	Improvement (in terms of percentage of population)						p value
	Mild keratosis (n=40)		Moderate keratosis (n=40)		Severe keratosis (n=40)		
	Nil	Yes	Nil	Yes	Nil	Yes	
One month	27.5	72.5	42.5	57.5	80.0	20.0	Chi Sq= 23.40; p <0.01
Three months	7.5	92.5	22.5	77.5	55.0	45.0	Chi Sq=23.22; p<0.001
Six months	2.5	97.5	5.0	95.0	32.5	67.5	Chi Sq=19.18; p<0.001

Table 2 shows the concentration-dependent improvement of keratosis by salicylate. The application of ointment for one month in mild group of patients the improvement was found in higher number of cases (90%) who used 20% and 30% ointment. In other mild cases who used 5% and 10% ointment the improvement was found in 30.0% and 80.0 % respectively. In moderate group also the initial improvement was found in 80.0 % of cases who used 20% ointment. After 3 months of ointment use in mild group, all cases (100%) who used 10, 20 and 30% ointment, was found to be improved. Amongst the cases that used 5% ointment the improvement was found in 70.0% of mild cases. Among the moderate group of cases who used 5, 10, 20 and 30% ointment, the improvement was observed in 70.0%, 70.0%, 80.0% and 90.0% of cases respectively. In severe cases the improvement was

higher among cases who used 30% ointment which was 80.0 %. Amongst the users of 5%, 10% and 20% ointment the improvement, was found in 10.0%, 40.0% and 50.0% respectively in severe cases. Similar to the findings after one month use of ointment the improvement was found higher among the mild and moderate cases of keratosis who used 20% and 30% ointment. After completion of 6 months ointment in mild group, all the cases were found to be improved who used 10%, 20% and 30% ointment. One case who used ointment 5% did not show any improvement.

Table 2: Improvement of the patients after using different concentrations of ointment in relation to severity of keratosis

Stages of keratosis	*Number of patients clinically improved*			
	5% salicylate	*10% salicylate*	*20% salicylate*	*30% salicylate*
After 1 month				
Mild	3	8	9	9
Moderate	3	5	8	7
Severe	0	3	2	3
After 3 months				
Mild	7	10	10	10
Moderate	7	7	8	9
Severe	1	4	5	8
After 6 months				
Mild	9	10	10	10
Moderate	9	9	10	10
Severe	3	7	8	9

Table 3 shows the degree of improvement after 1, 3 and 6 months of treatment with different concentrations of salicylate ointment. Moderate improvement was observed in 50% of cases after one month of treatment whereas excellent improvement was not seen in any case. Excellent improvement was observed in 36.7% cases after 6 months of treatment.

Table 3: Duration of ointment use and improvement status

Duration	*Mild or no improvement*	*Moderate improvement*	*Excellent improvement*	*Total*
After 1 month	60	60	0	120
	50%	50.0%	0%	
After 3 months	34	74	12	120
	28.3%	61.7%	10.0%	
After 6 months	16	60	44	120
	13.3%	50.0%	36.7%	

Regarding the side effects, none of the patients mentioned significant side effects due to use of salicylic acid ointment. Out of total cases 3 mentioned burning sensation and another 2 complained of pruritis.

This study found that the salicylic acid ointment has a significant role in the treatment of arsenical keratosis. For the mild and moderate cases the improvement of keratosis was excellent after six months of ointment use. Severe keratosis patients did not show much improvement after six months use of ointment. Only 7.5% of the severe patients had excellent improvement. The concentration of ointment, which had been found more effective in the treatment of keratosis was 20% and 30% of salicylic acids ointment. For the mild and moderate cases 10% salicylic acids ointment would be helpful but longer duration of ointment application might be required. In relation to the age of the patients it was found that significantly ($p<0.05$) higher improvement was observed among the users who were aged more than 40 years. No significant difference was found in the improvement of keratotic lesion in relation to sex of the participants. There was no significant side effect(s) due to use of different concentration of the salicylic acid ointments had been noticed by the users or observer during study period. But caution must be taken in case of longer use of keratolytic ointment particularly with high concentration of salicylic acid ointment.

Amongst all the cases the treatment might be continued even with high concentration of salicylic acid ointment for more than six months for persistence and/or further improvement or complete recovery from keratotic lesions of arsenicosis patients.

Recommendations

- Use of salicylic acid ointment in the treatment of keratotic lesion due to chronic arsenic toxicity could be useful particularly for mild and moderate cases of keratosis. In severe case it is also helpful but which might need a longer duration of use.
- For effective treatment of the keratosis the concentration of salicylic acid should be 20 to 30% depending upon the severity of keratosis and age of the patient.

References

Ahmad SA, Sayed MHSU, Hadi SA, Faruquee MH, Khan MH, Jalil MA, Ahmed R, Khan AW. Arsenicosis in a village in Bangladesh. Inter J Environ Health Res.1999; 9: 187-195.

Maidul AZM, Momn A, Akramullah SM, Ahmed Z, Afsar S, Salahuddin A, Tarafdar SA, Ali M. Arsenical keratosis (chronic arsenism): 22 cases study. Bangladesh J Dermatol Leprol 1996; 13: 1-4.

Ganmo A. Hereditary Ichthiosis, causes skin manifestaions, treatment and quality of life. A dissertation for degree of Doctor of Philosophy. Faculty of Medicine, Uppsala University, Sweden, 2002, p68.

Dockery GL. Key insights on mastering pedal warts. Podiatry Today. 2002; 16: 40-54.

Loden M et al: Distribution and keratolytic effect of salicylic acid and urea in human skin. Skin Pharmacol. 1995; 8: 173.

Baden HP, Baden LA. Keratolytic agents, pp 2352- 2354.

Fitzpatrick's Dermatology in general medicine, 6th edition, vol 2.

Ahmad SA, Faruquee MH, Sayed MHSU, Khan MH, Jalil MA, Ahmed R, Hadi SA. Chronic Arsenicosis: Management by Vitamin A, E, C Regimen. JOPSOM. 1998; 17: 19-26.

Saha KC. Arsenical dermatoses from the tubewell water in West Bengal, during 1983-87. Ind J Dermatol. 1985; 40: 1-11.