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Double-Blind Study of Variables Influencing the Clinical Effects of Solcoderm

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Abstract. Double-blind clinical studies of pairs of lesions were initiated to evaluate several components of Solcoderm treatment. The superiority of Solcoderm over plain nitric acid was as evident with plastic as with wooden applicators. A mixture of oxalic and nitric acid had effects similar to Solcoderm, while acetic and nitric acid was similar in effect to plain nitric acid.

The clinical superiority of topically applied Solcoderm as compared to plain nitric acid (N) in equivalent strength was clearly documented in an earlier report of a double-blind evaluation of the response of matched pairs of skin tumors in the same subjects [1]. Solcoderm superiority was apparent both in respect to the successful eradication of the tumor and minimal injury to the surrounding normal tissue. The studies now reported were designed to use the same clinical methodology with variants of Solcoderm to help define the factors critical to its clinical utility.

The possibility was considered that the wooden applicator stick used in prior studies may make a chemical, and not just a physical contribution to the treatment process. Therefore one objective of the study now reported was to determine whether the distinct differences between Solcoderm and N found with wooden applicators would also be apparent when acid-resistant plastic applicators were employed instead.

Another objective of these studies was to evaluate the contribution of the organic acids in Solcoderm. In vitro model studies suggest that the generation of nitrate reduction products by the interaction of oxidizable organic acids with nitric acid in Solcoderm may be critical to its clinical superiority [1, 2]. Since it is impractical to attempt to compare all possible combinations of all the ingredients of Solcoderm in one set of studies, selections of Solcoderm 'minus variants' were made for initial and subsequent comparison.

Methods and Materials

Initial comparisons were made of the following materials: (1) Solcoderm versus N using plastic applicators.

(2) Solcoderm versus nitric acid with two organic acids, oxalic and acetic, (NOA) in the concentrations contained in Solcoderm. (3) N versus NOA. After results of the above comparisons were available, the following set of variants were selected for the study.

(1) NOA versus nitric plus acetic acid (NA). (2) NOA versus nitric plus oxalic acid (NO). (3) NOA versus NA with acetic acid in double the concentration (N2A).

In the initial study, 30 patients with paired lesions having the same diagnosis and similar size, location and appearance were treated simultaneously by two therapists who exchanged places during the treatment to maximize the identity of all treatment factors for each lesion other than the material used. In each subject, one of the lesions was treated with material from a vial labeled A, and the other B. The identity of A and B were randomized by packagers who did not participate in the study, and the sealed code was broken by an independent evaluator after all case report data were tabulated, compared to serial color photographs, and acceptability of each case, as well as record deficiencies noted.

The case report forms were adapted from a protocol previously developed for clinical studies in North America. It permits the scoring of the nature and intensity of immediate and eventual responses of both the lesions and surrounding tissues to the treatment employed.

For ethical reasons, all lesions considered unsatisfactorily treated at follow-up visits, were retreated by standard methods and materials at that time, and the fact recorded.

The patients accepted for the initial study were adult volunteers (16 with nevi, 12 with basal cell epithelioma, and 2 with keratoses) who were randomly entered into 3 study groups of 10 each. The materials for treating each lesion were coded by patient number and letter so that each group of 10 would represent a comparison of 2 materials, with 2 subjects having both lesions treated with the same formulation, and in the other 8 each lesion in the pair would be treated with a different formulation. In the first group all lesions were treated with wooden applicators, and Solcoderm was compared with the simpler formulation, NOA. In the second group only plastic applicators were used to apply Solcoderm versus N. The third group compared NOA with N, using wooden applicators.

In the subsequent study, 30 other subjects were again divided into 3 groups of 10. In all subjects one lesion was treated with NOA and the other with a 2 ingredient variant as noted above. Wooden applicators were employed.

Results

In the initial study, the following significant observations were made prior to breaking the code. (1) In the 10 subjects comparing Solcoderm with NOA, essentially all lesions responded satisfactorily, consistent with the fact (not known to the observers) that none of these lesions were treated with N. (2) In the group comparing Solcoderm with N using plastic applicators, one subject showed poor results in both lesions and another good results in both lesions. The 8 other pairs all showed satisfactory results in one and poor results in the other. From these observations it was correctly predicted by the analyst which subject had both lesions treated with N, which with Solcoderm, and that in the 8 others the lesion with poor results had been treated with N, and the other with Solcoderm. (3) In the third group predictions again correctly identified the one patient treated only with N, and the one only with a satisfactory preparation. In all of the other 8 subjects, treated with 2 different preparations, the N treated lesion consistently yielded less satisfactory results.

The decoded global evaluations are summarized in table I. In general, these data confirm the prior conclusions about the superiority of Solcoderm over N alone, and indicate that the difference is fully apparent when plastic applicators are used. Efficacy largely persists when a formulation without lactic acid or copper (i.e. NOA) is employed.

In the subsequent study, analysis prior to decoding revealed 5 minor violations of protocol. In 16 of the 30 subjects, there was a global score difference of only 1 between the lesion pairs and in 4 of these 16 the lesion scored as being globally superior in response by the investigator could not be documented

Table I. Investigator's over-all preference (number of lesions with each score in the initial study)

Study number	Score			
	0	1	2	3
I (wooden)				
Solcoderm	0	0	4	6
NOA	0	0	4	6
II (plastic)				
Solcoderm	0	1	4	5
Nitric Acid	10	0	0	0
III (wooden)				
NOA	0	5	4	1
Nitric Acid	10	0	0	0

Scored from 0 (poor) to 3 (very good).

to be superior by the photographs or case report notes of individual parameters. Nevertheless the data in table II analyzed on the basis of judgmental factors established prior to decoding indicated quite clearly that: (1) Oxalic acid plays an important and perhaps critical role in achieving the advantages previously demonstrated for NOA and Solcoderm over N alone in the topical treatment of skin tumors. (2) NA preparations without oxalic acid are inferior to NOA. (3) NOA is not superior to NO alone. (4) Doubling the acetic acid concentration does not substitute for the positive contribution made by oxalic acid.

These conclusions apply both to superior lesion response ('mummification' and eradication of the lesion) and to lesser undesirable reaction of the surrounding tissue both initially and as regards final results.

The initial color reaction to the treatment was recorded for 105 of the 120 lesions in this study. Table III indicates a strong positive correlation of an initial yellow color reaction with satisfactory final results as scored on a scale of 0 (poor) – 3 (very good) regardless of treatment administered. Most lesions treated with an oxalate-containing formulation initially turned yellow and had good final results, while most lesions treated with formulations without oxalate did not turn yellow and had poor results. Even within each of these treatment groups, the lesions which initially turned yellow averaged better final scores than those which did not.

Discussion

Results of this study confirm the previously reported [1] superiority of Solcoderm over N and the correlation of an initial yellow reaction of the lesion to better final results. This study further indicates that use of acid-resistant plastic applicator sticks yields essentially the same results as wooden applicators. The oxalic acid in Solcoderm, which is significantly oxidizable by 6 *N* nitric acid, makes a far greater contribution to its desired action than the acetic acid, consistent with the previously presented theory that labile nitrate reduction products resulting from the interaction of nitric acid with oxidizable organic acids are largely responsible for the favorable action of Solcoderm. At ambient temperatures, the interaction between acetic acid and 6 *N* nitric acid is negligible.

The degree to which the full formulation of Solcoderm may be superior to an appropriate formulation of oxalic and nitric acids alone cannot be determined from these limited data. However, a review of pooled Solcoderm and NOA results to date suggests that the full Solcoderm formulation scores

Table II. Comparative results of paired lesion treatment (patient groups, 10 each)

	Agents compared					
	NOA vs. N2A		NOA vs. ON		NOA vs. AN	
Final visit						
By final evaluation as recorded						
Number equal	0		2		2	
Number superior	8	2	3	5	7	1
By predecoding evaluation of the full CRF						
Number equal	1		4		3	
Number superior	8	1	1	5	7	0
By final mummification score						
Number equal	0		2		0	
Number superior	10	0	2	6	7	3
By final surrounding tissue score						
Number equal	5		5		5	
Number superior (lower score)	4	1	2	3	4	1
Needed retreatment at the end	0	4	0	1	0	0
Initial reaction of lesion						
Intensity						
Equal	0		3		1	
Superior	10	0	2	5	8	1
Dehydration						
Equal	0		8		0	
Superior	10	0	1	1	9	1
Initial reaction of surrounding tissue						
Edema						
Equal	3		4		3	
Superior (less)	5	2	2	4	6	2
Erythema						
Equal	5		3		1	
Superior (less)	4	1	1	6	8	1
Burning						
Equal	2		3		2	
Superior (less)	8	0	1	6	7	1

Table III. Number of lesions by initial color and final score

	Final score						Good or very good (% 2+3)
	0	1	2	3	n	$\bar{X}$	
Initially yellow	3	11	24	16	54	1.98	74
Initially not yellow	23	13	11	4	51	0.92	30

somewhat better in essentially all parameters reflecting desired properties of a topical preparation for the ablation of skin tumors.

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