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Attempts using cryotherapy to achieve more rapid healing in patients with cutaneous leishmaniasis due to *L. braziliensis braziliensis*

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The use of cryotherapy as an adjunct to systemic antimonial therapy (Clucantime) was studied in 17 patients with a total of 23 skin lesions of leishmaniasis in an area where L. braziliensis braziliensis *is the species in circulation. Cryotherapy did not speed healing and has been discarded as an auxiliary therapeutic measure in our practice. However this technique may be suitable for species of* Leishmania *causing more limited superficial lesions in man without the danger of metastasis.*

Key words: Leishmaniasis. Leishmania braziliensis braziliensis. Cryotherapy.

Local treatments for cutaneous leishmaniasis are legion. In a review in 1912 Wenyon[7] gave a complete descripton of Broomes method of treating oriental sore with carbon dioxide snow. Recently very favourable results in this infection have been reported using this method[2].

Since *Leishmania braziliensis braziliensis* infections are said to frequently metastasise such local treatment is insufficient in contrast to most *Leishmania tropica* infections. The recommended therapy with antimonials is very difficult to administer under field conditions and often patients do not achieve the desired dose. In our attempts to offer more satisfactory therapeutic solutions to patients in an endemic area of *L. b. braziliensis* we have performed studies of combining systemic antimonial therapy with cryotherapy with the hope of speeding up skin healing. These studies are reported here.

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MATERIALS AND METHODS

Cryotherapy was applied using the Kryojet liquid nitrogen spray system[8]. For the lesions of 2cms or less a cone of rubber retained the liquid nitrogen facilitating freezing. Exposure times were dependent on the size of the lesion varying from 30-60 seconds in the majority of cases but for two to three minutes in some large lesions. A 5mm frozen "halo" to the lesion was taken as an indication to stop the application.

Glucantime therapy offered to all patients consisted of the standard recommended course of a total dose of 1 gram of drug (280mg Sb^{v}) per kilo body weight given over 10-12 day period followed by 10 days rest. Although three such courses were recommended often less was accepted. All individual course schedules were completed.

Patients attending the leishmaniasis clinic in the village of Três Braços, Bahia, with limited cutaneous lesions were offered cryotherapy plus Glucantime as an alternative to Glucantime alone. It was explained that cryotherapy was a supplementary procedure which might speed skin healing but did not imply the injections could be abandoned. Diagnostic procedures operative at the clinic, including routine methods for parasite isolation and immunodiagnosis utilising leishmanin skin testing and measurement of circulating antibodies[3].

Evaluation of cure consisted of clinical examination at one, two, three, six and twelve months after cryotherapy. Only firm scar formation without infiltration or satellite nodules was accepted as healing. Where possible sera were collected for antibody estimations.

RESULTS

Seventeen patients with a total of 23 lesions entered the trial. Fourteen lesions were frozen for 30-60 seconds, 6 for one to two minutes and only three for three minutes. Initially Glucantime therapy was offered two weeks after cryotherapy but since two patients refused on the grounds that the lesion appeared to be improving, injections were started simultaneously in later cases. One patient flatly refused all injections. Among the other 14 patients there was some variation in the time Glucantime therapy was initiated. Five patients had had previous courses without success. Seven started parenteral treatment at the time of therapy, five within a month of cryotherapy, while another two only began antimonial treatment 3 months after cryotherapy. These variations illustrate one of the basic problems of parenteral therapy in such field studies.

Initially we analysed the two groups of immediate and after one month parenteral therapy separately but since we could detect no difference in the parameters examined we have chosen to tabulate our results as patients with single lesions (Table 1), multiple lesions (Table 2), and those refusing parenteral treatment (Table 3).

Table 1 — *Results of eryotherapy plus glucantime in patients with single lesions of leishmaniasis*

Code Nº	*Age/Sex*	*Lesion*			*Parasite Recovered*	*Glucantime**		*Time When Observed Healed (months after cryotherapy)*
		Site	*Size (cm)*	*Duration (months)*		B	A	
202	3/F	shin	2.0	2	+		1	3
205	15/M	shin	3.7	2	+		3	6
200	15/F	knee	3.5	3	+		2	3
192	13/M	shin	2.0	1	-		1	3
189	15/F	shin	4.5	2	+	1	1	2
182	18/M	shin	1.5	5	+	2	2	12
266	14/M	shin	2.1	10	-		3	3
267	14/M	shin	1.7	6	-		2	12
144	16/M	knee	3.4	3	+		2	6

* Glucantime series are enumerated as before (B) and after (A) initial diagnosis

As evidence of cutaneous leishmaniasis all patients had compatible clinical lesions, histology, and a positive leishmanin skin test. In eleven patients parasites were detected and 9 isolated either in hamster (7) or culture (2). All four of the ulcers over 3cm in diameter occurred in a 3 month period. The term "shin" is used in the Tables to indicate the lower tibial half and knee the upper tibial half and knee joint.

Both Tables 1 and 2 show great variation in the time before healing was documented and usually this was not related to the size of the lesion, its duration or the duration of the combined treatment schedule. However patients who took 12 months to heal were irregular in their acceptance of Glucantime therapy. It appears that the site of the lesion may influence recovery since lesions in the lower limb healed in a mean of 5 months (68/14) in comparison to 2 (19/9) in other locations (p 0.001). Healing of the arms and face was rapid in the case documented in Table 2. In two cases

Table 2 — *Results of cryotherapy plus glucantime in patients with multiple lesions os leishmaniasis*

Code Nº	*Age/Sex*	*Lesion*			*Parasite Recovered*	Glucantime*		*Time When Observed Healed (months after cryotherapy)*
		Site	*Size (cm)*	*Duration (months)*		B	A	
194	12/F	shin	2.0	1	+		1	3
		shin	1.2	1				3
201	42/M	back	2.0	1	+		3	3
			2.0	1				3
179	23/M	face	1.0	5	+	3	3	1
		shin	1.5	5				3
		shin	1.2	5				3
FAS	30/M	arm	1.4	5	+	3	1	2
		arm	0.8	5				2
		finger	0.9	1/2				3
263	14/M	arm	1.2	8		1	1	3

* Glucantime series are enumerated as before (B) and after (A) initial diagnosis.

(Table 2 patients 201 and 263) lesions not receiving cryotherapy could be compared in the same patient to those in which it was applied. There was no difference in healing time. However in Table 3 we have two patients with longstanding lesions healing within a month on cryotherapy alone. Both lesions were small in size. In ten patients serology was available before and after cryotherapy. No rise in titre occurred after freezing and only three serologies had become negative by six months. The scar seemed to be more fibrotic after freezing than normal, possibly the result of more tissue necrosis from cold injury.

Table 3 — *Results of cryotherapy alone in three patients with leishmaniasis*

Code Nº	*Age/Sex*	*Lesion*			*Parasite Recovered*	*Time to Healing (months after cryotherapy)*
		Site	*Size (cm)*	*Duration (months)*		
204	22/M	pinna	1.2	24	+	1
032	46/F	elbow	0.8	48	-	1
199	15/F	knee	4.0	5	+	6

Comment: both rapidly healing lesions were small chronic ones.

The side effects of cryotherapy are listed in Table 4. Although pain was not felt at the time of freezing it appeared in 8 patients within 24 hours and lasted an average of 3 days. In only two pa-

tients was it described as severe. Blister formation worried the patients and was present in the majority. The serum discharge which resulted was an inconvenience. It lasted only three days on average but could continue for one to two weeks. Ten patients went on to develop a thick discharge which they interpreted as infection. Eight thought their lesion got larger and in 5 the side effects were enough to interfere with their daily work.

Table 4 — *Side effects of cryotherapy in 17 patients with leishmaniasis*

Complication	*Patients With Complaint*	
	Nº	*%*
Pain	8	47
Blistering	11	65
Serous discharge	12	71
Infection	10	59

These rather marked side effects of freezing resulted in a low preference for this technique. Only three patients preferred cryotherapy compared to eleven who opted for Glucantime injection alone. Three patients stated no preference.

DISCUSSION

While the patients were selected for the trial in terms of non extensive purely cutaneous lesions scrutiny of the clinical data presented shows features common to our experience of over 300 patients in the area. Leishmanial ulcers are most frequent in relatively young males and often occur on the lower leg[1]. While they are often of short duration, they rapidly ulcerate and are often large compared to lesions produced by other species causing South American cutaneous leishmaniasis.

Our results are in sharp contrast with the uniform success described by Bassiouny et al in Saudi Arabia[2], but then we are dealing with a very different disease to cutaneous leishmaniasis of the Old World. Of 54 isolates characterised from Três Braços 52 have been *L. braziliensis braziliensis* and it can be safely assumed that this is the infecting agent in our patients. One characteristic of this organisms growth in skin is that necrosis is a common feature[5] and the lesions were usually larger than those illustrated in the Saudis (precise measurements are not given in their paper). Also the majority of the Arab cases were on the head; a good healing site, and only 30-60 seconds cryotherapy resulted in a good response within 4-5 weeks in those patients. Our results utilising cryotherapy plus Glucantime show longer healing times with little difference from patients treated with Glucantime alone. Llanos (in preparation), in a careful study of 30 patients treated with Glucantime alone in the area, records the following healing times: at 2 months 23%, at 6 months 83%, and at twelve months 95%. Corresponding figures calculated, from the data reported here are very similar, namely: 26% at 2 months, 81% at 6 months, and 100% at a year. Freezing therefore has certainly not speeded healing of the skin sore as hoped and we have abandoned the procedure. Quite apart from the prolonged inflammation that occurs in the leishmaniasis present in our area it is perhaps unfortunate that the infected phlebotomine bite is so frequent on the anterior lower tibial third of the leg. This is a region notable for its poor vascularisation and delayed healing powers.[4]

Our high incidence of sideffects meant that the treatment was not popular with the patients which is perhaps the most important finding of the study. This is because the lesions we treated were really too large to be satisfactory for cryotherapy. The degree of sideffects correlates with the size of the lesion which governed application time to achieve a freeze halo of 5mm. The two cases which healed with cryotherapy alone were both small superficial lesions not unlike those seen in the Old World leishmaniasis.

Our standard treatment continues to be prolonged antimonial therapy. The logistical difficulties of ensuring correct application in our field area are formidable indeed and are discussed elsewhere (in preparation).

Recent recommendations regarding antimonial therapy indicate that longer schedules of higher dose antimony may be more efficacious[8] but he volumes of intramuscular Glucantime necessary are very difficult to achieve under field contitions.

It is notable that two of our smallest lesions healed with cryotherapy alone. Our failure does not imply that this technique might not be useful in infections with leishmanial species causing small granulomas.

RESUMO

O uso da crioterapia associada ao Glucantime na terapia da leishmaniose tegumentar foi estudado em

17 pacientes com um total de 23 lesões de pele por leishmaniose, em uma área onde Leishmania braziliensis braziliensis *é a espécie em circulação. A crioterapia não influenciou a rapidez da cicatrização. Ela foi abandonada como método de terapia auxiliar em nossa prática, embora possa ser útil para espécies de* Leishmania *causando lesões mais superficiais e limitads no homem, sem o perigo de metástase.*

Palavras chaves: Leishmaniose. Leishmania braziliensis braziliensis. Crioterapia.

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