DERMATOLOGICAL CRYOSURGERY IN PRIMARY CARE WITH DIMETHYL ETHER PROPANE SPRAY IN COMPARISON WITH LIQUID NITROGEN

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CUTANEOUS CRYOSURGERY IN FAMILY MEDICINE: DIMETHYL ETHER PROPANE SPRAY VERSUS LIQUID NITROGEN

Objective. To compare the efficacy, tolerance and safety of two types of cryotherapy, performed by family physicians, for benign cutaneous lesions: low freezing (-57°C) with dimethyl ether propane cryogenic spray (DMEP) and intense freezing (-196°C) with conventional liquid nitrogen (LN).
Design. A randomized, multi-centered, controlled clinical trial, with single-blind assessment.
Setting. Three primary care teaching teams in the Community of Madrid.
Patients and other participants. Ten MIR from family & community medicine intervened. There were 124 patients, who had 174 benign cutaneous lesions, suitable for cryotherapy. There were 3 voluntary withdrawals, none because of an adverse reaction.
Interventions. In each case there was local application for a standard time of the randomized agent. Control-group intervention, 81 cases: swab soaked in LN. Study-group intervention, 93 cases: swab saturated with DMEP spray. Maximum of three freezings per case, at weekly intervals.
Measurements and main results. A doctor made a blind assessment of the results (elimination, adverse reaction, aesthetic result) 15 days after treatment.
Conclusions. No clinically relevant differences between the efficacy, tolerance and safety of the two cryogenic agents used in primary care were found. The low freezing of DMEP was sufficient for the cryotherapy of benign lesions.

1. INTRODUCTION

Dermatological cryosurgery enables destruction of a wide variety of superficial skin lesions by controlled freezing. Because of its safety and high level of effectiveness (1-4) and because it is easy to learn to use the method, it is widely used in Anglo-Saxon countries by doctors who are not dermatological specialists (5-7).

The simplest method of freezing is topical application on lesions which one wishes to destroy of a cottonwool swab saturated by immersion in liquid nitrogen (LN). This cryogenic agent, having a temperature of -196°C, is very effective in elimination of a large variety of very common benign and premalignant skin lesions (verrucas, molluscum contagiosum, seborrheic and actinic keratoses...). Unfortunately, because of its extremely low boiling point, the substance has to be stored in special containers which are not available in the Health Centers in our environment. An infrastructural deficiency is therefore the main limiting factor for cryosurgery in general medical practice in Spain.

In our Teaching Unit, a regular supply of small quantities of the cryogenic agent in portable, domestic type thermos flasks from the reference Dermatological Department (Puerta de Hierro Hospital) has enabled us to carry out cryosurgery with liquid nitrogen for the past few years, as a routine method and with good results. Because of the rapid evaporation of the product transported in this way, it is essential to use it within a few hours of receipt of the same. In order to make the method cost-effective, therefore, it is necessary to gather together patients to be treated on the days on which one will be receiving the product.

Since the treatment is excessively dependent on the willingness of participants, this experience is still an exceptional situation in Primary Care in this field of medicine. In fact, in June 1994, only 0.8% of tutors and third year resident general practitioners of the 26 Primary Care Teams of the Community of Madrid were regularly practicing cryosurgery, the usual practice being to use less decisive alternatives (keratolytics) or, unnecessarily, to refer patients to busy departments specializing in minor pathology.

A coolant mixture of dimethyl ether and propane (DMEP) has recently been marketed in aerosol form, which is easy to administer and also to store; its small container makes it easy to transport and keeps it stable for three years with no special precautions. Through evaporation this product reaches -57°C in its applicator swab. Our theory was that if this temperature, which is markedly higher than that obtained with liquid nitrogen, was found to be adequate for destruction of skin lesions, this kit would represent an answer to logistic problems standing in the way of practicing cryosurgery in the consulting rooms of general practitioners.

The bibliography available to date on DMEP spray (11) describes some small trials using the product without control groups; the real effectiveness of this low freezing cryosurgery is therefore as yet unknown. In this study, we present the results of the

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first clinical trial of the product in comparison with standard cryotherapy with liquid nitrogen in elimination of benign skin lesions, for the purpose of providing the doctor with scientific criteria on the basis of which to assess the advantage of the new therapeutic alternative in his daily practice.

2. MATERIAL AND METHOD

Design of the Study. A controlled, randomized, parallel experimental trial, with blind assessment of the main result, to compare the effectiveness of DMEP in elimination of benign skin lesions with standard cryotherapy (LN). Tolerance and safety of both systems are analyzed secondarily. The trial was designed and monitored in the Family and Community Medicine Teaching Unit of Madrid Area 6, with the mandatory approval of the Clinical Research Ethics Committee of Puerta de Hierro Hospital.

Scope and Period of the Trial. The field work was carried out in the clinics of three Primary Care Teams of the Teaching Unit (Majadahonda PCT [=Primary Care Team], Arguelles PCT and Pozuelo de Alarcón PCT) by 10 third year house physicians assigned to the said centers during 1995, supervised by their respective tutors, between June and October 1995. All these doctors had prior experience of conventional cryosurgery with LN.

Selection of Study Subjects. Out of the complete range of benign skin lesions suitable for cryotherapy diagnosed in the clinics during the period of the trial, the following 5 complaints were accepted as study subjects, after separate confirmation of the diagnosis of two researchers: verruca plana, verruca vulgaris, verruca filiformis, molluscum contagiosum and seborrheic keratoses. Recruitment of cases continued until a minimum of 80 lesions per treatment group had been obtained, representing a sample of adequate size to enable detection of a difference equal to or greater than 15% between the percentage of lesions eliminated by each agent (95% cures expected with LN, assuming a bilateral contrast having a level of significance of 0.05 and a study power of 0.80). Absence of the exclusion criteria stated in Table 1 was confirmed in each case, and each patient's specific consent was requested after they had received oral and written information.

Procedures Compared. Freezing was carried out by contacting the skin lesions with identical cottonwool swabs (the swabs supplied in the DMEP kit) saturated in the cryogenic products by immersion for a minimum of 10 seconds in LN (reference procedures) or by spraying with the DMEP spray in accordance with the manufacturer's specifications (index procedures). Freezing times (swab-skin contact) were standardized in accordance with standard recommendations in the bibliography for each type of lesion: 20 seconds for verruca plana and molluscum contagiosum, 40 seconds for verruca vulgaris, verruca filiformis and seborrheic keratoses, ensuring in each case that a perilesional halo of healthy skin measuring from 1 to 3 mm was covered. In the event of incomplete elimination of the lesion, repetition was permitted up to a maximum of three freezings (or until such time as the cure enabled assessment of the need for retreatment).

Allocation of Procedural Methods. Allocation of treatment according to centers was stratified in such a way that each PCT had a single list of randomized treatments allocated to it correlative to the cases as included in the trial. It was permitted for one and the same patient to contribute up to a maximum of three different lesions to the trial, treated simultaneously or one after the other. In this situation each lesion was considered as one case, receiving its randomized treatment according to a correlative cranio-caudal order of anatomical location.

Trial Variables and Assessment Criteria. Clinical assessment of the patient was carried out at the time of inclusion in the trial, with recording of the characteristics of the skin lesion (diagnosis, size, location, number) and the characteristics of the carrier patient (sex, age, concurrent cutaneous pathology, previous treatments) which might influence the treatment result. Follow-up of the cases was carried out, as a minimum, one week after each freezing and during an extra end-of-trial appointment 15 days after the last application.

A cure was considered obtained if a lesion was eliminated after freezing, i.e., if no vital skin findings compatible with the original skin lesion were detected, even though after-effects of the therapy applied still persisted (necrotic residues of ampullae, epidermal denudation, depigmentation or other changes of coloration, cicatricial tissue). This judgment was made by the blind method in each case by a researcher other than the physician who had performed the therapy, the patient's group being unknown to the assessing

Table 1. **Criteria for Exclusion of Study Cases**

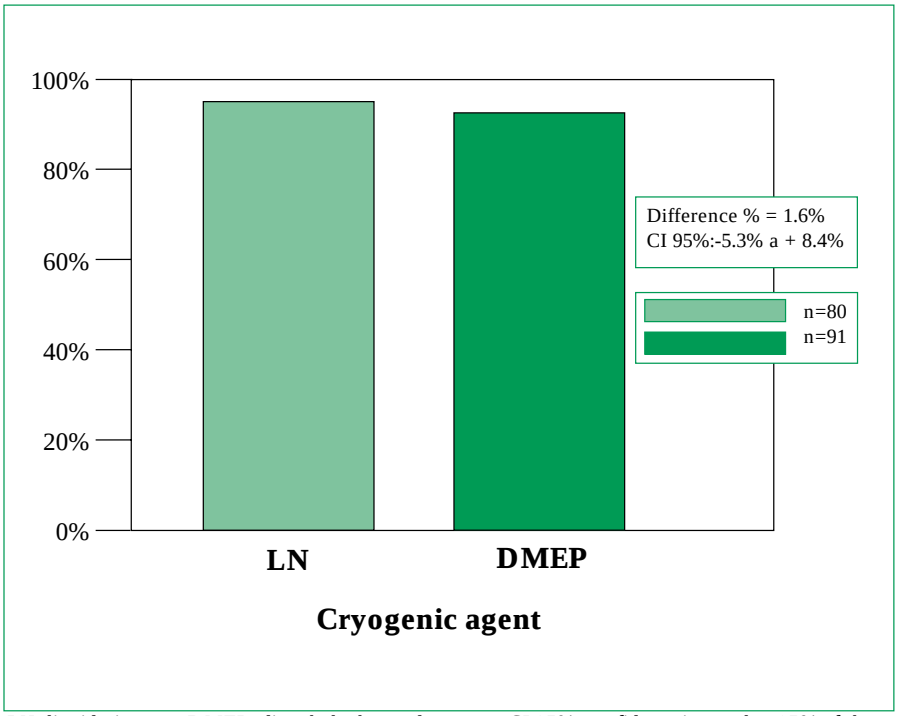
1. -Criteria relating to the site of the lesion
-Area with active skin infection -Areas of potential aesthetic (face) or functional risk (lateral surface of the fingers) -Plantar and genital verrucas
2. -Criteria relating to the diagnosis of the lesion
-Doubtful or discrepant diagnosis in the opinion of two assessing doctors -Pigmented lesions (except for seborrheic keratoses)
3. -Criteria relating to patient's circumstances
-Age less than 6 years or greater than 85 years -Clinical or pathological circumstances which in the operator's opinion render cryotherapy inadvisable (cutaneous or generally important disorder, rough vasculopathic area, cryoagglutinins, terminal patient...) -Other previous, recent treatment of the lesion (in the past 15 days) -Significant adverse effect after other previous cryotherapy

Table 2. **Comparability of the Study Groups**

Characteristics	Liquid Nitrogen (n=80)	Dimethyl Ether Propane (n=91)	p [1]
Characteristics of the patient			
- Sex (male)	52.5%	53.8%	0.86
- Age (average / SD)	24 (15.2)	32.1 (17.3)	<0.01 [2]
Characteristics of the lesion			
- Size (average / SD)	3.9 (3.4)mm	3.2 (1.6)mm	0.54 [2]
- Single lesion	18.7%	17.5%	0.84
- Clinical diagnosis			
Verruca vulgaris	61.2%	56%	0.49
Verruca plana	20%	31.8%	0.07
Molluscum contagiosum	11%	1%	<0.01 [3]
Verruca filiformis	3.7%	6.5%	0.31 [3]
Seborrheic keratoses	3.7%	4.3%	0.57 [3]
- Site			
Head and neck	10%	9.9%	0.98
Upper limbs	61.2%	70.3%	0.21
Lower limbs	11.2%	8.7%	0.59
Trunk	17.5%	14.2%	0.56

SD: standard deviation in mm. (1) p value in chi-square test. (2) p value in Mann-Whitney U test. (3) p value in Fisher's exact test.

Figure 1. **Effectiveness of each cryogenic agent**



LN: liquid nitrogen. DMEP: dimethyl ether and propane. CI 95%: confidence interval at 95% of the difference in percentages. n: lesions treated with each cryogenic agent.

researcher. The aesthetic result was likewise assessed by this dichomotized method at the end of the trial (satisfactory or unsatisfactory). The number of freezings necessary to eliminate the lesion was quantified in each case.

Tolerance of cryotherapy was assessed by asking the patient to describe discomfort perceived during the freezing (none, paresthesia, pruritis, smarting, pain, etc.) quantified in intensity according to a typical scale (none, bearable, treatment interrupted because of discomfort). Safety of the treatment was assessed by recording adverse effects occurring during freezings, identified by questioning the patient and physical examination of the area treated.

In each also the total duration of treatment time was recorded (days elapsing from the start of treatment until restoration of normal skin continuity).

Statistical Analysis. The chi-square test was used for comparison of the proportions of qualitative variables (or Fisher's exact test in the necessary cases). Where necessary, the 95% confidence interval (CI 95%) of the difference of the said percentages was estimated. Mean values of quantitative variables were compared by the Mann-Whitney U test. In all the tests of hypothesis a 95% level of significance was used. Absence of factors of confusion in effectiveness obtained was explored for both types of cryotherapy by means of an unconditional logistical regression model, with the possible modifiers of effectiveness (the aforementioned characteristics of lesion and patient) and the product used taken as independent variables, and elimination (yes / no) of lesions taken as a dependent variable. The computer programs EPIINFO 6.02, SAS for Windows and ENE 2.2 were used for determination of the sample size.

3. RESULTS

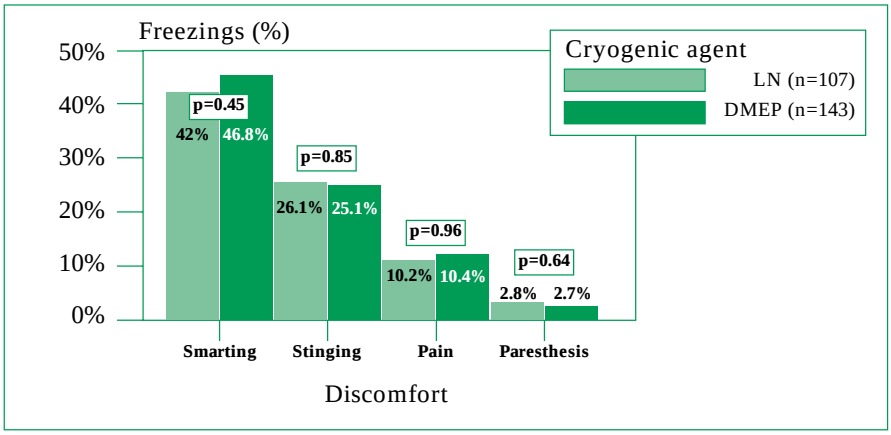
Of the skin lesions potentially suitable for treatment with cryotherapy attended to during the study period, for the exclusion reasons specified (Table 1), 15 cases were not included in the study, 2 refusals to participate being recorded.

Table 3. **Result of each cryogenic agent according to lesion treated**

Lesions	Cases treated with LN %		Cases treated with DMEP %	
	Successes	Failures	Successes	Failures
Verruca vulgaris	46 (94%)	3	48 (94%)	3
Verruca plana	16 (100%)	0	27 (93%)	2
Molluscum contagiosum	9 (100%)	0	1 (100%)	0
Verruca filiformis	3 (100%)	0	5 (83%)	1
Seborrheic keratoses	2 (66%)	1	4 (100%)	0
Total	76 (95%)	4	85 (93%)	6

LN: liquid nitrogen, DMEP: dimethyl ether and propane spray.
Success: lesion eliminated, Failure: lesion persistent after three freezings.

Figure 2. **Characteristics of types of discomfort perceived during freezings**



LN: liquid nitrogen. DMEP: dimethyl ether and propane spray. n: number of freezings with each cryogenic agent. p: value in Fisher's exact test. The figures printed in the bars above represent, for each agent, the % of freezings in which a patient presented the discomfort stated.

Treatment of 174 lesions as study cases was initiated, finally ending with a follow-up of 171 lesions (91 treated with DMEP spray, 80 with LN). The 3 abandoned treatments (two with DMEP, one with LN) were discontinued because it was not possible for the patient to complete the trial protocol [program]. In no case did withdrawal occur for the expected reasons for withdrawal (serious adverse effect or at the patient's express request).

Comparability of the groups resulting after the randomized allocation of treatments was confirmed by univariant analysis of the distribution of characteristics of lesion and carrier patient in each group as summarized in Table 2, no differences of any interest being found. Nor were any significant differences detected in the number of cases treated by each operating physician.

After the complete treatment in accordance with the protocol, 85 lesions treated with DMEP (93.4% of the cases treated) had been eliminated as compared with 76 lesions treated with LN (95% of the cases treated). Contrast of these values by Fisher's exact test gives a p=0.75. Figure 1 gives a graphic representation of the difference between these effectiveness percentages and their corresponding confidence interval. Table 3 summarizes the results obtained by each cryogenic agent on the different types of lesions in the study.

For successfully treated cases an average of 1.26 freezings per lesion destroyed with LN were found in comparison with 1.48 freezings with DMEP (Mann-Whitney U test, p=0.06). Comparison of the distribution of lesions cured by one, two and three freezings with each cryogenic agent (57.18 and 1 with LN, as against 54.21 and 10 with DMEP) showed no differences between the two with a chi-square test with two degrees of freedom corrected by continuity (p>0.05).

In 81.3% of the 107 freezings applied with LN, the patient perceived some discomfort, as compared with 85.33% of the 143 DMEP applications (Fisher's exact test, p=0.39). The CI 95% of the difference found (4%) fluctuated between -5.4% and +13.4%. In no case did the intensity of discomfort prevent completion of the therapy allocated. Figure 2 summarizes the distribution of the types of discomfort perceived by the patient in a comparison of both treatment groups.

Table 4 gives a summary of the 5 cases of minor adverse effects recorded. All cases were healed in a few days of conservative treatment. Of the total number of freezings carried out with each cryogenic agent the complications described represent 1.3% of the DMEP applications as compared with 2.8% of the LN applications. The difference between these percentages (1.5%) lies within the CI 95% range from -2.2% to +5%.

The average time spent on cryotherapy of a skin lesion by each method was 10.2 days with LN and 10.3 days with DMEP (Mann-Whitney U test, p=0.49).

Adjusted by all the variables which could act as possible modifiers of the cryosurgical therapy result (type, size and location of the lesions; age and sex of the patient), by means of an unconditional logistical regression model, non-dependence of the cases of therapy failure on the cryogenic agent applied was confirmed.

4. DISCUSSION

The hypothesis investigated that skin cryosurgery with DMEP spray can be as effective as conventional cryotherapy with liquid nitrogen (LN) cannot be rejected in the light of the results obtained. The differences in percentages of skin lesions cured with one or the other method are neither statistically significant nor clinically relevant.

In consideration of the methodological precautions specified in the design stage, the possibilities of systematic error in the study are low. Firstly, the randomized allocation of the treatments, the homogeneity of the resultant groups and the minimal losses of patients rule out the possibility of gross errors of selection bias. Secondly, and even though it was not possible to hide the treatments from the patients or the operating physicians, the main result of the study (whether the lesion was eliminated or not) can certainly be considered to be blind, since the treatment applied was not revealed to the assessing physician (who was not the operating physician). In this way, the possibilities of information bias were minimized. Similarly, because of their previous experience in conventional cryosurgery, the clinical judgment of the researchers was considered sufficiently capable and specific for measurement of the said main result. In addition to verifying total agreement (100% agreement) between observers in assessment of the results of a pilot sample of 25 lesions having received cryo-treatment, the precaution was taken of reassessing each study case in a final appointment 15 days after application of the final freezing.

Furthermore, the calculations of sample size made beforehand were carried out on the basis of a bibliographic hypothesis of expected results in the control group which totally corresponded to the results obtained in our study. In this way the precautionary measures for sufficient power in the study to detect differences judged as clinically relevant were confirmed.

For all the above reasons, we consider our study to be a true negative result which has not detected differences in the cures achieved by the two methods tested. In both cases over 90% of the skin lesions treated were eliminated, a figure similar to the results obtained with LN by other authors. The temperature reached by the new DMEP spray (low freezing cryosurgery) appears adequate for effective cutaneous destruction of the complaints treated.

Nor did we detect differences in the secondary comparisons of the study, either with regard to discomfort produced in the patient by the one or the other method, or with regard to the adverse effects which occurred. Leaving aside considerations of sample size (which was calculated for the main objective of the study), the good tolerance formerly known for LN is confirmed for DMEP; even though it is usual to feel smarting during the technique, it is perfectly bearable for the majority of patients. It is nevertheless necessary to remember that the freezing of certain areas of the body can be particularly painful (fingernails and toenails, lips, eyelids...). The extremely few complications which occurred were slight and healed spontaneously.

Given these results, the safety of cryotherapy appears manifest. Despite this, a new clinician must guarantee adequate knowledge of the method, as well as of the necessary basic precautions and the few contraindications for the treatment before commencing to practice the same. Various of the bibliographic references of this article are perfectly adequate for these purposes. Even more important than the above-mentioned technical capabilities of execution, which can be acquired by any professional person, is reliability of the doctor's diagnosis, in order to guarantee certain diagnosis of the skin lesion before freezing it. Adequate further training and nearby availability of advice of a dermatologist should prevent destruction of lesions for which histological examination is necessary to enable correct clinical management.

Together with the above-mentioned precautions, even in optimum circumstances of mutual doctor-patient trust, the necessity to obtain the patient's formal consent to the cryosurgery should not be forgotten. This is a legal precaution of a universal nature for any procedure in which clinical risks different from the conventional risks of daily practice can be assumed. Amply distributed printed forms can be used for this.

Table 4. **Adverse effects occurring after 107 freezings with LN and 143 freezings with DMEP.**

Case	Group	Skin Lesions	Complication	Action
1	LN	Seborrheic keratoses	Local infection	Local antiseptic
2	LN	Verruca vulgaris	Hypersensitivity in area treated observation (7 days) (*)	Kept under observation
3	LN	Verruca vulgaris	Hypersensitivity in area treated (5 days) (*)	Kept under observation
4	LN	Verruca plana	Local infection	Local antiseptic
5	DMEP	Verruca vulgaris	Inflammation (superimposed traumatism)	Local antiseptic

LN: liquid nitrogen, DMEP: dimethyl ether and propane spray, (*) healed spontaneously within the period stated.

If we take into consideration, together with all their limitations, the cases not included in the study and the refusals to participate as a sure way of exploring the feasibility of cryosurgery in primary care and the acceptability of patients for this practice by their family doctor, the results discussed would appear to confirm its nature as a suitable method for carrying out in family medicine and as a method which would be well received by patients. This being so, DMEP would provide an answer to a care requirement which is at present not well covered because of lack of infra-structure in Primary Care for handling LN. The DMEP spray kit provides all the necessary equipment for cryosurgery, whilst being small in size and available at a reasonable cost. Also because of its portability, it has enabled us to treat immobilized patients at home during visits to their homes. Combined with good clinical results, we have obtained excellent aesthetic results in all patients, and healing of our cases with a rapidity comparable to that obtained with LN.

These clinical results should be completed by future analyses concerning cost-efficiency between both cryogenic methods. In this way, Anglo-Saxon authors with experience by using the DMEP spray consider it, because of its low infra-structure cost, as the most efficient cryogenic potential in general medical practice.

On the other hand, after our experience with DMEP, together with its obvious advantages we have found a certain disadvantage: the type of ready-made swab fitted on the spray kit, which is supplied in a single, 5mm diameter size, is too big for freezing the smallest lesions. Although the appropriate cryosurgical technique requires inclusion of a perilesional halo in the area to be frozen, this problem which we have encountered can be a source of certain amounts of discomfort which would be avoidable with more accurately sized swabs. This situation has now been rectified by the manufacturer of the product by distribution of different types of applicators.

It must also be pointed out that this study has included exclusively 5 types of specific benign skin lesions, probably those with the highest morbidity rate of the pathologies treatable with cryotherapy in primary care. Until it is irrefutably confirmed, it would not be scientifically permissible to extend the indications of DMEP spray to other types of lesions apart from those referred to here, and especially to premalignant conditions (actinic keratoses, Bowen's disease, ...) which are routinely treated with LN. In experimental cryosurgery a different destruction temperature has been found for normal, dysplastic and cancerous skin cells. As a new research prospect derived from this trial, we shall in the near future study the subject of clinical translation of these data, by means of a new trial with DMEP, to other, different skin lesions.

Likewise, our results can definitely not be extrapolated to other cryogenic sprays of different formulation and physical properties which have not been tested in controlled form for skin freezing: ethyl chloride, Verruca Freeze (not available in our country), etc.

Finally, and in order to provide information which is complementary to this study, we expect to be in a position in a few months' time to provide an analysis of the possible differences of the long term result (rate of relapses) between the two cryogenic agents studied.

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