

ORIGINAL ARTICLE

Treatment Outcome of Liquid Nitrogen (LN) Cryotherapy in Patients Presenting Recalcitrant Alopecia Areata (AA) at Tertiary Care Hospital, Karachi

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ABSTRACT

Objective: To determine the treatment outcome of liquid nitrogen (LN) cryotherapy in patients presenting with recalcitrant alopecia areata (AA) at tertiary care hospital, Karachi.

Material and Methods: This Descriptive study was conducted in the department of Dermatology, JPMC, Karachi. The duration of study was Six months after the approval of synopsis from 15 December 2021, to 14 June 2022. Total 88 patients were included in the study. The patients were assessed for treatment outcome at 8 weeks and were labeled as having excellent, good, moderate, poor and no response.

Results: Total 88 patients were included in the study. Mean \pm SD of age was 38.3 \pm 12.5 years. In distribution of gender, 58 (65.9%) were male while 30 (34.1%) were female. Outcome of liquid nitrogen showed excellent response in 5 (5.7%), good response in 29 (33.0%), moderate 19 (21.6%), poor 9 (10.2%) while no response of liquid nitrogen was noted in 26 (29.5%) patients.

Practical implication: The treatment given is mainly for cosmetic reasons and to halt the progression of the disease. Previously, therapeutic outcomes of these treatment options were dealt with in many studies. At the same time, long treatment duration, high cost, invasiveness and inconvenience of application have hindered the utmost treatment outcome and patient satisfaction.

Conclusion: It is to be concluded that good response of liquid nitrogen was noted in most of the patients followed by moderate and poor response. More prospective and well-controlled trials are needed to validate the current findings.

Keywords: Alopecia Areata, Cryotherapy, Liquid Nitrogen, Prevalence

INTRODUCTION

Alopecia areata (AA) or patchy, focal alopecia is the most common form of hair loss seen in dermatology outpatient department comprising of 25% of all the alopecia cases ⁽¹⁾. It is a T-cell mediated autoimmune disease characterized by a patchy, nonscarring hair loss affecting the scalp and other body parts ⁽²⁾. In the most frequent and benign forms, patients have one or more discrete round patches of hair loss that often resolves within a few weeks or months ⁽³⁾. The rare and severe forms of AA with complete and persistent hair loss seem to occur more frequently in children and young adults, especially those with a history of atopy or family history of alopecia and in adults with autoimmune disorders ⁽⁴⁾. One of the most intriguing features of hair biology is the immune privilege of the anagen hair follicle.

Hair loss that is characterized by an immunosuppressive milieu around the hair bulb ⁽⁵⁾. The unique microenvironment of this immune-privileged site protects the organs from deleterious immune reactions and loss of function ⁽⁶⁾. The hair loss immune privilege is present during anagen but is lost during the resting (telogen and regression (catagen) phases of the hair cycle ⁽⁷⁾. Common modalities of treatment include topical medications as steroids, tacrolimus, anthralin, minoxidil, and psoralen with ultraviolet 4 A solution, narrow band ultraviolet B, immunotherapy with diphenylcyclopropenone or squaric acid dibutyl ester (SADBE), and systemic therapy such as oral corticosteroids, levamisole, methotrexate, azathioprine, and others ⁽⁸⁻⁹⁰⁾. The treatment given is mainly for cosmetic reasons and to halt the progression of the disease. Previously, therapeutic outcomes of these treatment options were dealt with in many studies ⁽¹⁰⁾. At the same time, long treatment duration, high cost, invasiveness and inconvenience of application have hindered the utmost treatment outcome and patient satisfaction ⁽¹¹⁾. Although spontaneous remission may occur in a good number of AA patients, there are certain patients of AA who are fairly resistant to one or more type of treatments ⁽¹²⁾. This poses a challenge to treat such recalcitrant AA patients ⁽¹³⁾. Superficial cryotherapy with liquid nitrogen is a

minimally invasive treatment option ⁽¹⁴⁾. Radmanesh et evaluated treatment outcome of liquid nitrogen (LN) cryotherapy in patients presenting with recalcitrant alopecia areata and found excellent (4.55%), good (34.09%), moderate (18.18%), poor (9.09%) and no response (34.09%) respectively ⁽¹⁵⁾.

Significance of the Study: this study was designed to determine the treatment outcome of liquid nitrogen (LN) cryotherapy in patients presenting with recalcitrant alopecia areata in order to establish local perspective as there is paucity of local as well as international data.

MATERIAL AND METHODS

This Descriptive study was conducted in the department of Dermatology, JPMC, Karachi. The duration of study was Six months after the approval of synopsis from 15 December 2021 to 14 June 2022. The sample size for the study was n=88 patients. This sample size was calculated using the WHO sample size calculator. Non-Probability, Consecutive Sampling technique was applied.

Inclusion Criteria

- Patients with recalcitrant alopecia areata
- Either gender.
- Age 20-60 years.
- No simultaneous immune suppressive therapy and discontinuation of any other treatment for at least 4 weeks.

Exclusion Criteria

- Non-consenting.
- Pregnant patients
- Patients with history of bleeding tendency or any documented hypersensitivity to the procedure (e.g., intolerance to cold).
- Patients with history of systemic illness such as thyroid, vitiligo, autoimmune diseases, and psoriasis.
- Patients with history of congestive cardiac failure, chronic liver disease, COPD, and stroke.

This study was conducted after approval from College of Physicians and Surgeons Pakistan. Recalcitrant alopecia areata patients visiting Outpatient Department of Dermatology, JPMC,

Karachi, were enrolled in this study who fulfilled the inclusion criteria. Permission from the institutional ethical review committee was taken prior to conduction of study. Brief history of demographic information (age, gender, and place of residence) and written informed consent were taken from each patient. All cases were examined and procedure was done by the researcher in the presence of the supervisor with over 10 years of 56 experience. All patients were managed according to a standard protocol. The pain was minimized in patients by application of topical local anesthetic agent (2.5% lidocaine and 2.5% prilocaine) 1 h prior to therapy. A handheld cryo unit containing LN as a cryogen was used. The cryo unit comprised of a vacuum insulated container of 500 ml with a brass spray tip of 1 mm. The spray tip was held over the alopecic patch kept at a distance of 1 cm and sprayed the lesion with liquid nitrogen for 2–3 s till the appearance of mild frost and after the frozen area thaw (3-5 s), a second spray was done in the same manner. The development of a skin-colored edematous wheal within 30 minutes after cryotherapy was signed for sufficient cryotherapy. Each lesion was treated with LN cryotherapy every 2 weeks for maximum five sittings (at 0, 2, 4, 6, and 8 weeks). The patients were assessed for treatment outcome at 8 weeks and were labeled as having excellent, good, moderate, poor and no response as per operational definition. The findings of quantitative variable (age and duration of alopecia areata) and qualitative variables (gender, place of residence, diabetes mellitus type II, smoking status and treatment outcome (excellent, good, moderate, poor and no response) was entered in Performa attached as annexure.

Data was analyzed on SPSS Version 20. On the basis of normality mean and standard deviations or median (IQR) were calculated for the quantitative variables like age and duration of alopecia areata. Normality of data was assessed by using Shapiro Wilk test. Frequencies and percentages were calculated for the qualitative variables like gender, place of residence, diabetes mellitus type II, smoking status and treatment outcome (excellent, good, moderate, poor and no response (Yes/No). Effect modifiers were controlled through stratification of age, gender, place of residence, diabetes mellitus type II, smoking status and duration of alopecia areata to see the effect of these on the outcome variables (treatment outcome). Post stratification, Chi square/Fischer Exact test was applied taking p-value of ≤ 0.05 as statistically significant.

RESULTS

There were statistically insignificant differences found in proportion of mean stratification of confounders / effect modifiers with respect to liquid nitrogen outcomes, noted in age group (P=0.473), gender (P=0.700), duration of AA (P=0.740). Whereas significant difference was noted in diabetes mellitus (P=0.002) and smoking status (P=0.011).

Table 1: Stratification of Age Group with Outcomes of Liquid Nitrogen n=88

Liquid Nitrogen	Age Group 20-40	(In Years) > 40	P- Value
Excellent	2 (2.3%)	3 (3.4%)	0.473
Good	19 (21.6%)	10 (11.4%)	
Moderate	11 (12.5%)	8 (9.1%)	
Poor	3 (3.4%)	6 (6.8%)	
No response	14 (15.9%)	12 (13.6%)	

Table 2: Stratification of Gender with Outcomes of Liquid Nitrogen n=88

Liquid Nitrogen	Gender		P- Value
	Male	Female	
Excellent	2 (2.3%)	3 (3.4%)	

Good	10 (11.4%)	19 (21.6%)	0.700
Moderate	6 (6.8%)	13 (14.8%)	
Poor	1 (1.1%)	8 (9.1%)	
No response	7 (8.0%)	19 (21.6%)	

Table 3: Stratification of Duration of Aa with Outcomes of Liquid Nitrogen n=88

Liquid Nitrogen	Duration In Months		P- Value
	3-24	>24	
Excellent	1 (1.1%)	4 (4.5%)	0.740
Good	12 (13.6%)	17 (19.3%)	
Moderate	8 (9.1%)	11 (12.5%)	
Poor	2 (2.3%)	7 (8.0%)	
No response	9 (10.2%)	17 (19.3%)	

Table 4: Stratification of Diabetes Mellitus Type II with Outcomes of Liquid Nitrogen n=88

Liquid Nitrogen	Diabetes Mellitus		P- Value
	Diabetic	Non-Diabetic	
Excellent	3 (3.4%)	2 (2.3%)	0.002
Good	3 (3.4%)	26 (29.5%)	
Moderate	2 (2.3%)	17 (19.3%)	
Poor	4 (14.8%)	5 (5.7%)	
No response	13 (14.8%)	13 (14.8%)	

Table 5: Stratification of Smoking Status with Outcomes of Liquid Nitrogen n=88

Liquid Nitrogen	Smoking Status		P- Value
	Smoker	Non-Smoker	
Excellent	4 (4.5%)	1 (1.1%)	0.011
Good	18 (20.5%)	11 (12.5%)	
Moderate	10 (11.4%)	9 (10.2%)	
Poor	4 (4.5%)	5 (5.7%)	
No response	5 (5.7%)	21 (23.9%)	

DISCUSSION

Alopecia areata (AA) is a common type of hair loss or alopecia in humans; it is an autoimmune disease with a variable, typically relapsing or remitting, course that can be persistent – especially when hair loss is extensive. Alopecia areata is the second-most frequent nonscarring alopecia, after male and female pattern alopecia. Clinical patterns of hair loss in alopecia areata are usually very distinct. The most common pattern is a small annular or patchy bald lesion (patchy alopecia areata), usually on the scalp, that can progress to total loss of scalp hair only (alopecia totalis), and total loss of all body hair (alopecia universalis) (16-18).

Current treatment strategies of hair loss are mainly focused on promoting cellular proliferation and differentiation during the hair growth cycle. It has been postulated that minoxidil prolongs anagen and increases hair follicle size through stimulation of potassium channels and prostaglandins endoperoxide synthase-1 (18,19). The main etiology for the occurrence of AA is not clear, the evidence is in favor of an autoimmune disease. Disease changes with genetic factors and is exacerbated by stress. Conventional

treatments of AA include intralesional, photochemotherapy and systemic steroid therapy⁽²⁰⁾. Cryotherapy can also be useful in the treatment of AA⁽²¹⁾. Cryotherapy leads to local edema, inflammation, and blister formation; hence, like other sensitizers and irritants, it increases the local blood flow⁽²²⁾. Although cryotherapy has been reported for the treatment of AA, it is not popular in this field. In previous reports, the authors conducted research on cases with limited involvement or in combination with other modalities⁽²³⁾. Cryotherapy leads to local edema, inflammation, and blister formation; hence, like other sensitizers and irritants, it increases the local blood flow. The increase in local blood flow cannot be the sole mechanism because the inflammation and edema subside within a week, while the hair starts to grow 1-2 months later. The cellular components of hair follicles are epithelial, melanocytes, T cells, and Langerhans cells⁽²⁴⁾. All these cellular structures are altered in AA⁽²⁵⁾. The hair follicle components involved in the pathogenesis of AA are antigenic structures, the cellular immune system including T cells and langerhans cells, and hair follicle melanocytes. Cryotherapy may damage one or all of these components as its mechanism for hair regrowth. The hair follicles in active AA are in the telogen state with little T cell infiltration. So, damage to T cells which are surrounding the hair follicles in the anagen phase is less likely to have a role⁽²⁶⁾.

The findings of this study are comparable with multiple studies conducted worldwide. In this study, mean age was 38.3±12.5 years. Whereas another study found mean age to be 30.2±6.8 years⁽⁹⁾. Abdel-Majida e, et al reported as 26.55±8.54 years⁽¹⁴⁾. In current study, mean duration of alopecia areata was 25.6±4.1 months. Abdel-Majida e, et al noted duration of alopecia areata <6 months in 14 (70%) while ≥6 months in 6 (30%) patients⁽¹⁴⁾. In this study, distribution of gender, 58 (65.9%) were male while 30 (34.1%) were female. Jun M, et al noted to have 53.3% males and 46.7% females⁽¹⁰⁾. The study of Radmanesh M, et al documented 37 (62.7%) males and 22 (37.3%) females⁽¹⁵⁾.

In current study outcomes of liquid nitrogen showed excellent response in 5 (5.7%), good response in 29 (33.0%), moderate 19 (21.6%), poor 9 (10.2%) while no response of liquid nitrogen was noted in 26 (29.5%) patients. Abdel-Majida e, et al noted to have 25% excellent response, good response in 30%, moderate 10% while poor outcomes of liquid nitrogen were noted in 35% patients⁽¹⁴⁾.

In a study conducted by Radmanesh M et al, excellent response was noted in 2 (4.55%), good response in 15 (34.09%), moderate 8 (18.18%), poor 4 (9.09%) while no response of liquid nitrogen was noted in 15 (34.09%) patients⁽¹⁵⁾. It has shown that superficial cryotherapy could be a meaningful adjuvant treatment option for AA patients through the prospective study. Considering that it is less painful and easier to perform, superficial cryotherapy is especially worthy of application to patients with mild AA who have difficulty with conventional treatment such as intralesional steroid injection. Further studies with a larger subject group and more investigations focused on the pathophysiology in treatment of AA are necessary⁽²⁷⁾. Cryotherapy can be considered as an alternative method particularly for those who do not respond to topical or intralesional steroids⁽²⁸⁾.

CONCLUSION

It is to be concluded that good response of liquid nitrogen was noted in most of the patients followed by moderate and poor response. More prospective and well controlled trials are needed to validate the current findings.

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