SEEJPH Volume XXVI, 2025, ISSN: 2197-5248; Posted:04-01-25

Cryotherapy with intralesional steroids versus intralesional pentoxifylline in the treatment of Recalcitrant Alopecia areata- a Randomized Control Trial.

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KEYWORDS

Recalcitrant alopecia areata, cryotherapy, intralesional pentoxifylline.

ABSTRACT

BACKGROUND: In clinical practice, recalcitrant alopecia areata is common, and most conventional therapies have either failed to treat the condition or caused recurrence in certain patients. Recalcitrant alopecia areata is characterized by a disease duration of more than six months and no response to more than three different forms of treatment.

Few studies have evaluated the effectiveness of cryotherapy and intralesional pentoxifylline as a monotherapy in treating alopecia areata. The purpose of this study was to compare cryotherapy with intralesional steroids with that of intralesional pentoxifylline.

METHODOLOGY: A Randomized Control Trial (RCT) was conducted on 50 patients with Recalcitrant scalp alopecia areata. They were divided into 2 groups (Group A & Group B).25 patients in (Group A) received cryotherapy with intralesional triamcinolone acetonide 5mg/ml over the alopecic patch. 25 patients in Group B received 1ml(20mg) of intralesional pentoxifylline(100mg/5ml) over the alopecic patch. Their efficacy and adverse effects were documented and compared once in 2 weeks for a total of 5 sittings.

RESULTS: According to the GPA scale and LAD score, the effectiveness of the treatment approach indicates significant improvement in both the groups initially but drastic improvement and patient satisfaction was observed in Group A with subsequent sittings.

CONCLUSION: This study showed that intralesional pentoxifylline is less efficacious when compared to cryotherapy with intralesional

steroids. However, Intralesional pentoxifylline has lesser adverse effects when compared to cryotherapy with intralesional steroids.

INTRODUCTION

Alopecia areata is a chronic, immune-mediated autoimmune disorder which presents with non-scarring hair loss.[1] Geographical location and ethnicity have an impact on the estimated 0.1-0.2% global prevalence of alopecia areata.[1]

Alopecia areata has a complex etiopathogenesis that includes environmental variables, autoimmune, and genetic predisposition.[2] In Alopecia Areata, scalp is more commonly involved. It typically appears as one or more well-defined, hairless patches on the scalp that are free of erythema and have preserved follicular ostia.[5] Recalcitrant alopecia areata is characterized by a disease duration of more than six months and no response to more than three different forms of treatment.[1]

Topical drugs including tacrolimus, steroids, minoxidil, anthralin & psoralen with UVA solution and NBUVB are common forms of treatment, as are systemic treatments such oral corticosteroids, methotrexate, azathioprine, levamisole.[2]

With promising clinical results, cryotherapy is used to treat recalcitrant alopecia areata. The process by which it encourages hair growth is said to be immune-related. Cryotherapy is associated with decreased T cell & monocyte activation response, as well as decreased IL-17 and IL-1b/IL-23 secretion.[3]

Pentoxifylline, a methylxanthine derivative is an FDA approved drug for intermittent claudication. However, it exerts anti-inflammatory effects by inhibition of several cytokines including TNF-alpha, IL-1,6 which plays a role in alopecia areata.[4]

MATERIALS AND METHODS

This study was done in Dermatology, venereology and leprosy OPD at R.L Jalappa Hospital and Research Centre, Tamaka from May 2024 to October 2024 after obtaining ethical clearance from Central Ethics Committee (CEC).

STUDY DESIGN: Randomized Control Trial (RCT)

This study includes patients aged 18-55 years with clinical features suggestive of Recalcitrant alopecia areata over the scalp (who did not respond to different topical and systemic treatments for 6 months)

Patients with systemic illness – cardiac, hepatic and renal disorders, cold intolerance, pregnant and lactating women, patient not willing for study, severely immunocompromised individuals were not included in the study.

Sample size is 50.

Sample size per group is 25. 25 patients in Group A will be treated with Cryotherapy with intralesional triamcinolone acetonide 5mg/ml and 25 patients in Group B will be treated with 1ml(20mg) of pentoxifylline (100mg/5ml) given intralesionally every 2 weeks for maximum of 5 sittings.

The treatment modality's efficacy was graded using Global Photograph Assessment (GPA)scale and Lesional Area Density (LAD)score.

Serial photographs were taken to document the objectory post procedural side effects such as erythema, edema, skin atrophy, post inflammatory hypo/hyperpigmentation and any other peculiar features and it will be evaluated by a blinded third observer.

STATISTICAL ANALYSIS

Based on the previous survey on proportion of highest combined drug usage followed by single drug usage two group comparison with minimum difference of 25.0% maintains statistical power above 90% while achieving significance at type 1 error (α error) of at least 5% and type 2 error (βerror) of at least 10%. For a two-group assessment randomized clinical investigation, the sample size of 50 (25+25) is sufficient after considering withdrawals, dropout rates, and lost to follow-up.

RESULTS

Out of total 50 patients in this study, the majority of patients belong to 18-30 years (52%) followed by 31-40 yrs (34%) followed by 41-50 yrs (12%).

Amongst study population, 68% cases were men (34 cases) and 32% of cases were women (16 cases).

Table 1: The assessment of efficacy using GPA scale:

	MEAN SCORE				
GROUP	1st sitting	2nd sitting	3rd sitting	4th sitting	5th sitting
GROUP A	0.35	1.12	2.24	2.89	3
GROUP B	0.66	1.56	2	2	2.54
P Value	<0.001	<0.001	<0.001	0.112	<0.001

Blinded Third Observer gave a score of 3 (> 75% improvement) to all cases in Group A (100% - 25cases), 60% of cases in Group B (15 cases) after complete evaluation.

Blinded Third Observer gave a score of 2 (50-75% improvement) to 40% of cases in Group – B (10 cases).

Table 2: Assessment of efficacy using LAD score and LAD score percentage of improvement

	MEAN SCORE					
GROUPS	1st sitting	2nd sitting	3rd sitting	4th sitting	5th sitting	LAD score %improvement >90%
GROUP A	20.7	39.1	64.1	81.5	94.6	72%
GROUP B	27.7	49.1	59.1	69.2	74.8	32%
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	

> 90% LAD Score Improvement percentage seen in 72% of cases in Group A (18 cases), 32% of cases in Group – B (8 cases).

28 % of cases in Group A (7 cases), 68 % of cases in Group B showed a 70 to 90 percent LAD Score Improvement percentage (17 cases).

Table 3: Adverse effects:

Groups	Erythema	Edema	Atrophy of skin	Post inflammatory hyperpigmentation
Group A	7 (28%)	6(24%)	6(24%)	7(28%)
Group B	10(40%)	5(20%)	0	3(12%)

The most common adverse effect observed in Group – A was Erythema (28%)-7cases. In our study, 24% of individuals (6 cases) in Group A had skin atrophy documented, while there were no cases in Group B. Atrophy of the skin is the most frequent significant cosmetic side effect of steroids. The other adverse effects documented in both groups include edema, post inflammatory hyperpigmentation.

FIGURE 1: GROUP A: Patient treated with cryotherapy combined with intralesional triamcinolone acetonide(5mg/ml)

1st sitting

GPA – 0

LAD – 9.3cm^2

2nd sitting

GPA- 1

LAD – 7.1cm^2

3rd sitting

GPA-2

LAD- 4.7cm^2

4th sitting

GPA- 3

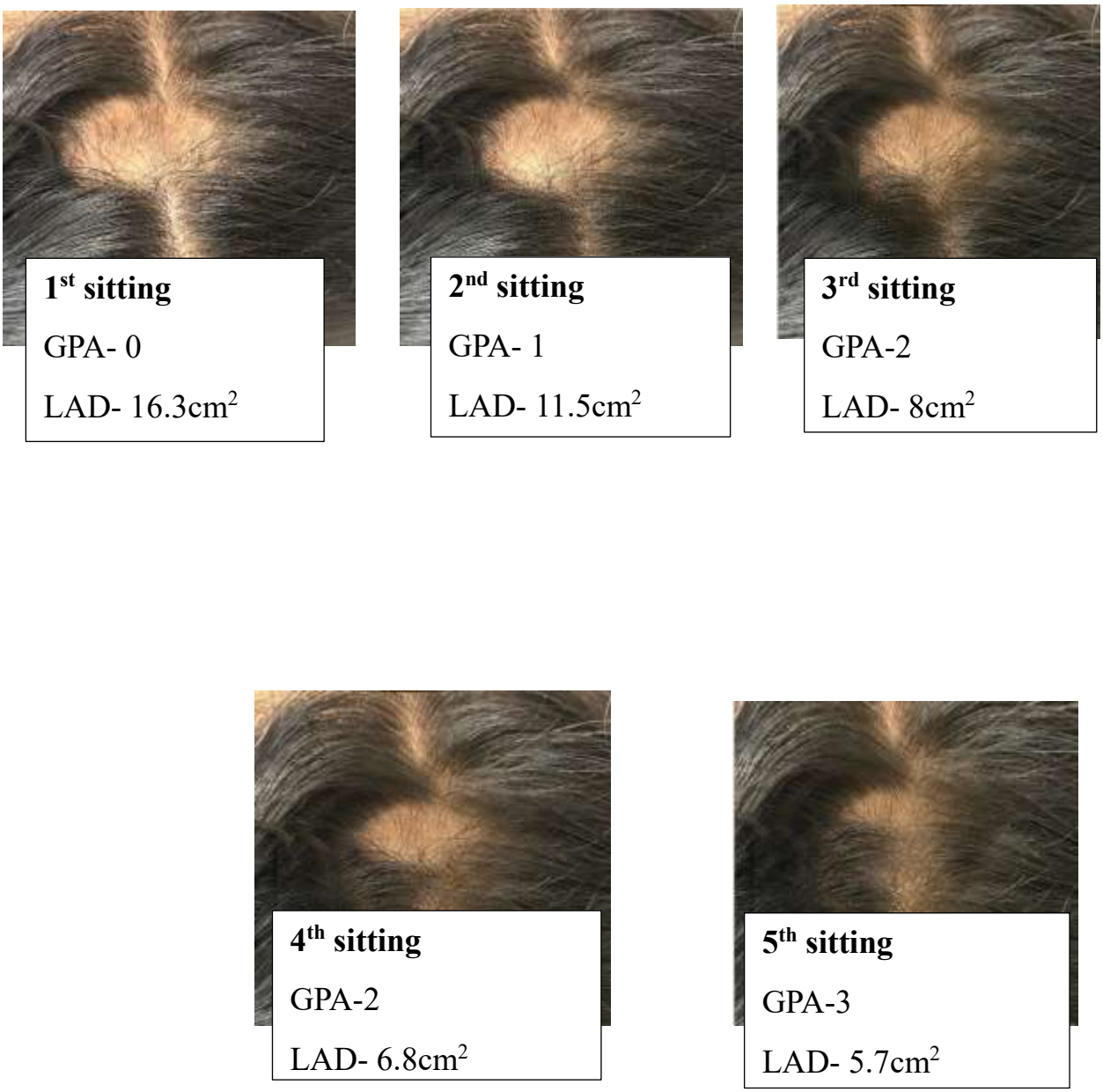
LAD- 3.1cm^2

5th sitting

GPA- 3

LAD- 1.8cm^2

FIGURE 2: GROUP B: Patient treated with 1ml (20 mg) intralesional Pentoxifylline



DISCUSSION

Alopecia areata is an autoimmune disorder which causes non-scarring alopecia of the scalp and other areas of the body with hair.[1] A person's quality of life can be greatly impacted by this disorder, which frequently affects emotional and mental health.[6]

While many AA patients may have spontaneous remission, other AA patients are fairly resistant to one or more forms of treatment. Despite there are numerous topical and systemic treatment options

available, some individuals may still not respond to those treatments. Therefore, it becomes difficult to treat recalcitrant alopecia areata.

AA patients may experience hair regrowth as a result of cryotherapy by following mechanisms: Cryotherapy causes initial vasoconstriction, but as the temperature drops to 0 degrees Celsius during the thaw period, there is pronounced local vasodilatation.

Accordingly, it is hypothesized that cryotherapy dilates the blood vessels surrounding the damaged hair follicles, thus increasing blood flow and promoting hair regrowth.[8] Cryotherapy may damage antigenic elements of the hair follicle, keratin16, trichohyalin.

Since white hairs are known to be spared in AA, melanocytes may be involved in its etiopathology. Therefore, cryotherapy might work by destroying melanocytes, which would prevent their part in initiating AA.[8]

Steroids are utilized to treat AA in topical, systemic, injectable forms. When compared to topical steroids, corticosteroids given intralesionally is said to have greater efficacy. Despite the fact that betamethasone has been used and also has lesser side effects, triamcinolone acetonide is the most widely used steroid for this purpose.[7] Though, there are various concentrations employed, studies have not reported that higher concentrations (10 mg/mL) are efficacious than most widely used 5 mg/ml.

Pentoxifylline has several anti-inflammatory properties, been effectively used to treat a variety of dermatological problems of which alopecia areata is one.[9]

It reduces inflammation by inhibiting cytokines that promote inflammation, such as IL-1, IL-8, TNF-alpha, IL-6. It inhibits fibroblast production triggered by TNF-α.

In our study, we compared the treatment modality of recalcitrant alopecia areata using cryotherapy with triamcinolone acetonide(5mg/ml) given intralesionally to (Group A) versus intralesional pentoxifylline 1ml(20mg) (Group B)

Most of the patients (52%) were of 18-30 years of age 24-30 years followed by 31-40 years (34%). This finding is consistent with observations of Mohammad Radmanesh et al[8] in their study where they concluded that patients belonging to 18-30 years are having the highest prevalence.

Amongst the study population, 68% of cases were men (34 cases) and 32% of cases were women (16 cases) which is consistent with the observations of Mehdi Amirnia et al.[10]

LAD score & GPA scale were used to evaluate the effectiveness of both treatment modalities. By the end of the fifth session, all cases treated with cryotherapy combined with intralesional triamcinolone acetonide(5mg/ml) showed a GPA score of 3(>75% improvement). This finding is consistent with observations of Doaa S. Sayed et al.[3]

The patients who had been treated with cryotherapy with intralesional triamcinolone acetonide(5mg/ml) had adverse effects such as Erythema (28%), edema (24%) skin atrophy (24%) and post inflammatory hyperpigmentation (28%) This result is in line with the observations of Seyed-Sajjad Mahmoudi in their research.[10]

Those patients in Group B who had been given pentoxifylline intralesionally had lesser adverse effects compared to Group A. The side effects were erythema (40%) followed by edema (20%) and Post

inflammatory hyperpigmentation (12%). No cases showed atrophy of the skin. This result is line with the observations of Hader Mohammed Ibrahim et al.[11]

CONCLUSION

Thus, it was concluded that cryotherapy with intralesional triamcinolone acetonide is efficacious when compared to intralesional pentoxifylline in the treating recalcitrant alopecia areata.

However, in terms of adverse effects, patients in Group B treated with intralesional pentoxifylline had no atrophy of skin and also had other minimal adverse effects which were reversible. Because of this, pentoxifylline would be a better treatment option, particularly in cases where intralesional corticosteroids are contraindicated.

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