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A PROSPECTIVE COMPARATIVE STUDY OF EFFECTIVENESS AND SAFETY OF INTRALESIONAL METHOTREXATE VERSUS TRIAMCINOLONE ACETONIDE IN THE TREATMENT OF LOCALIZED ALOPECIA AREATA

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INTRODUCTION: Alopecia areata (AA) is a common inflammatory disease causing unpredictable nonscarring form of hair loss. It may affect some or all areas of body especially the scalp and is usually reversible. It was first described about 2000 years ago by Celsus [AD 1437]. Its frequency ranges from 0.7% to 3.8% of patients attending dermatology clinics. The characteristic lesion of AA is circumscribed, hairless, smooth patch. Short, easily extractable broken hairs known as exclamation mark hairs are often seen at margins of bald patches during active phase of disease. Sparing of grey hair is a relative phenomenon. Severe and recurrent cases of AA can disturb quality of life of patients and may also lead to depression, changed self-image and interferes with social activities (**Masmoudi J et al., 2013**)[1]. Multiple therapeutic modalities for AA have been reported including immunosuppressive treatments as corticosteroids (topical, intralesional, systemic), photochemotherapy, immunomodulatory treatments as diphenylcyclopropenone and other treatment options as Anthralin or Minoxidil (**Hertl M et al., 2005**)[2]. AA continues to be a challenging disease with less than 20% of patients obtaining complete long-term hair regrowth (**Phan K et al., 2019**)[3]. Intralesional corticosteroid is considered drug of choice for localized AA with less than 50% of scalp involvement in adults followed by topical corticosteroids, topical minoxidil, and anthralin (**Ustuner P et al., 2017**)[4].

Methotrexate is folic acid antagonist that acts as immunosuppressant used in treatment of several skin diseases. (**Bressan AL et al., 2010**)[5]. Systemic methotrexate has been used in treatment of AA with satisfactory results (**Droitcourt C et al., 2012**)[6]. So intralesional methotrexate can be compared to triamcinolone as therapeutic option for localized AA in adults.

AIM AND OBJECTIVE: To compare the effectiveness and safety of intralesional methotrexate (MTX) versus triamcinolone acetonide (TrA) in the treatment of localized Alopecia Areata (AA).

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MATERIALS AND METHODS: It is an institution based, prospective comparative interventional study conducted in Department of Dermatology, Venereology and Leprology, BRD Medical College, Gorakhpur from July 2021 to September 2022. Sixty male and female patients in age group of 15-50 years with localized AA were selected after informed consent and divided into 2 groups. Diagnosis of Alopecia areata (AA) was made clinically. Meticulous history taking and clinical examination was performed taking care to note any other dermatoses in the patient. Nail changes and mucosal changes were noted. The location of patches of AA with reference to size, presence of hair in patches was also made. Complete blood count, liver function test, kidney function test, viral markers (HIV, HBsAg, HCV), thyroid function test, random blood sugar was carried out in all patients.

After completing the examination, 60 patients were taken in the therapeutic study based on following criteria:

Inclusion Criteria:

- Patients with localized AA on scalp (less than 50% of scalp surface area) and on beard
- Male and Female from age 15 to 50 years

Exclusion Criteria –

- pregnant and lactating women
- having chronic inflammatory diseases, renal or liver failure
- immunocompromised patients
- extensive lesions (alopecia totalis, universalis or surface area >50%)
- bleeding disorder history
- Infection or ulcer in or around lesion
- those not willing to take part in study
- Patients with ophiasis and sisaipho pattern

MATERIALS REQUIRED:

1. Betadine lotion
2. Gauze piece
3. Injection triamcinolone 5 or 10 mg/ml
4. Injection methotrexate 25 mg/ml
5. Insulin syringe (with 0.5-inch long 30-gauge needle)

METHOD:

Patients were divided into two equal groups:

MTX group:

MTX vial containing 25 mg/ml was used. Under complete aseptic precautions it was injected intradermally at 1 cm intervals with injection volume of 0.02 ml per site. Maximum of 2.5–5 mg was injected per session.

TrA group:

TrA vial containing 10 mg/ml (5mg/ml for face lesion) was used. TrA was injected intradermally at 1 cm intervals with injection volume of 0.05–0.1 ml per site. Maximum of 20 mg was injected per session.

Sessions were repeated every 3 weeks for maximum of four sessions. Patients were evaluated at baseline, each session and monthly upto 3 months after last session.

Clinical response to treatment was assessed by comparing pre and post treatment clinical photographs, SALT score, regrowth scale, side effects and patient satisfaction.

Severity of alopecia tool (SALT) score defined as: **S0** = no hair loss, **S1** = <25% hair loss, **S2** = 25%–49% hair loss, **S3** = 50%–74% hair loss, **S4a** = 75%–95% hair loss, **S4b** = 96%–99% hair loss, and **S5** = 100% total scalp hair loss.

Patients were evaluated for degree of improvement in hair regrowth using 5-point semi-quantitative score, **Re-Growth Scale (RGS)** defined as: **0 score** (regrowth <10%), **1 score** (regrowth 11%–25%), **2 score** (regrowth 26%–50%), **3 score** (regrowth 51%–75%) and **4 score** (regrowth ≥75%).

Patient satisfaction was assessed (as **High**, **Moderate**, **Mild**, **No**).

Patients were also evaluated for recurrence and side effects including pain, atrophy, hypopigmentation and hyperpigmentation clinically.

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STATISTICAL ANALYSIS: It was performed using SPSS software version 22. Quantitative data were presented as mean and standard deviations. Qualitative variables were presented as number and percentages. Comparison between groups with qualitative data was created by using chi-squared test. Correlation analysis was done using Spearman correlation test. p-value < 0.05 was considered significant.

RESULT: Mean age of patients was 28.87±9.42 years in MTX group and 25.00±7.73 years in TrA group. **(p-value = 0.088).**

Table 1: Comparison of mean age in between MTX group and TrA group

	MTX group (n=30)		**TrA group (n=30)**		t	p-Value
	Mean	±SD	Mean	±SD		
Age (years)	28.87	9.42	25.00	7.73	1.74	0.088

Male and female gender comprised 46.67% and 53.33% respectively in MTX group and 73.33% and 26.67% respectively in TrA group **(p-value = 0.065).**

Table 2: Comparison of frequencies of gender in between MTX group and TrA group

	MTX group (n=30)		**TrA group (n=30)**		Chi sq.	p-Value
	N	%	N	%		
Male	14	46.67	22	73.33	3.40	0.065
Female	16	53.33	8	26.67		

Number of patches were grouped as 1, 2 and more than 2. Sites of patches were - beard, frontal, occipital, parietal and combination of occipital-parietal, frontal-occipital and parietal-temporal in these patients. According to size, patches were grouped as 2x3cm, 2x3 to 3x5, more than 3x5 cm. Two or more than two patches were significantly more in TrA group as compared to MTX group **(p-value = 0.021).** On the basis of different sites and size, both groups were comparable.

Table 3: Comparison of frequencies of different patches no., site and size in between MTX group and TrA group

		MTX group (n=30)		**TrA group (n=30)**		Chi sq.	p-Value
		N	%	N	%		
	1	16	53.33	18	60.00	7.72	0.021*

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Patches no.	2	12	40.00	4	13.33		
	>2	2	6.67	8	26.67		
Site	Beard	2	6.67	10	33.33	9.89	0.139
	Frontal	8	26.67	7	23.33		
	Occipital	9	30.00	9	30.00		
	Parietal	5	16.67	2	6.67		
	Occipital, parietal	3	10.00	2	6.67		
	Frontal, occipital	2	6.67	0	0.00		
	Parietal, temporal	1	3.33	0	0.00		
Size (cm)	2x3	10	33.33	17	56.67	4.59	0.101
	2x3-3x5	16	53.33	8	26.67		
	>3x5	4	13.33	5	16.67		

*=Significant (p<0.05)

Frequency of SALT score between MTX group and TrA group was compared at baseline, after end of sessions (12 weeks), at 3 months follow up.

As SALT score is not applicable for beard lesions, such patients were excluded from calculation.

There was statistically insignificant difference between both groups regarding SALT score **(p-value = 0.634).**

Table 4: Comparison of frequencies of SALT score in between MTX group and TrA group

SALT score		**MTX group (n=28)**		**TrA group (n=20)**		Chi sq.	p-Value	
		N	%	N	%			
Baseline	S0	0	0.00	0	0.00	-	-	
	S1	28	100.00	20	100.00			
After sessions	S0	0	0.00	0	0.00	-	-	
	S1	28	100.00	20	100.00			
After 3 months follow up	S0	1	3.57	2	10.00	0.82	0.634	
	S1	27	96.43	18	90.00			

After sessions, targeted score of 4 for Regrowth was achieved by 3.33% patients in MTX group and 13.33% patients in TrA group **(p-value = 0.221)**. After 3 months follow up, targeted score of 4 was achieved by 16.67% patients in MTX group and 23.33% patients in TrA group **(p-value = 0.196).**

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Table 5: Comparison of frequencies of Regrowth scale in between MTX group and TrA group after sessions and after 3 months follow up

Regrowth scale		**MTX group (n=28)**		**TrA group (n=20)**		Chi sq.	p-Value
		N	%	N	%		
Regrowth scale after sessions	0 Score	10	33.33	4	13.33	5.73	0.221
	1 Score	6	20.00	8	26.67		
	2 Score	9	30.00	7	23.33		
	3 Score	4	13.33	7	23.33		
	4 Score	1	3.33	4	13.33		
Regrowth scale after 3 months follow up	0 Score	1	3.33	2	6.67	6.05	0.196
	1 Score	4	13.33	3	10.00		
	2 Score	4	13.33	10	33.33		
	3 Score	16	53.33	8	26.67		
	4 Score	5	16.67	7	23.33		

More patient satisfaction was observed at end of study in TrA group as compared to MTX group **(p-value = 0.048).**

Table 6: **Comparison of frequencies of patient satisfaction range in between MTX group and TrA group**

Patient satisfaction range	**MTX group (n=30)**		**TrA group (n=30)**		Chi sq.	p-Value
	N	%	N	%		
High	4	13.33	8	26.67	7.93	0.048
Moderate	9	30.00	10	33.33		
Mild	5	16.67	9	30.00		
No	12	40.00	3	10.00		

Side effects in both groups were few, transient and gradually disappeared during follow up period **(p-value = 0.071).**

Table 7: Comparison of frequencies of Side effect in between MTX group and TrA group

Side effect	**MTX group (n=30)**		**TrA group (n=30)**		Chi sq.	p-Value
	N	%	N	%		
None	27	90.00	26	86.67	7.02	0.071
Atrophy	0	0.00	2	6.67		
Hyperpigmentation	3	10.00	0	0.00		
Hypopigmentation	0	0.0	2	6.67		

Regrowth scale showed insignificant negative correlation with duration of disease.

There was **significant** negative correlation between Regrowth scale and SALT score, with **highly significant** negative correlation between Regrowth scale and SALT score after 3 months follow up.

Table 8: Correlation of regrowth scale with duration of disease MTX group and TrA group at regrowth scale after sessions and regrowth scale after 3 months follow-up

	Overall		**MTX group**		**TrA group**	
	Coefficient	**p-Value**	**Coefficient**	**p-Value**	**Coefficient**	**p-Value**
Regrowth scale after sessions						
Duration	-0.255	0.050*	-0.300	0.107	-0.106	0.579
SALT score baseline	0.038	0.797	-0.090	0.650	-0.343	0.139

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SALT score after sessions	-0.357	0.013*	-0.473	0.011*	-0.612	0.004*
SALT score after 3 months follow up	-0.319	0.027*	-0.562	0.002*	-0.552	0.012*
Regrowth scale after 3 months						
Duration	-0.205	0.116	-0.268	0.153	-0.058	0.761
SALT score baseline	-0.056	0.705	-0.058	0.771	-0.305	0.190
SALT score after sessions	-0.361	0.012*	-0.434	0.021*	-0.451	0.046*
SALT score after 3 months follow up	-0.491	0.001*	-0.597	0.001*	-0.646	0.002*

*=Significant ($p<0.05$)

DISCUSSION-

The response to treatment was evaluated on basis of photographic evaluation at each session and follow up; SALT score at baseline, after end of sessions and after 3 months of follow up; Regrowth scale after end of sessions and after 3 months of follow up; patient satisfaction range and side effects between both groups.

Intralesional TrA is first line of therapy for patchy and localized AA (**Shapiro J, 2013**)[7]. Intralesional route overcomes epidermal barrier, delivers drug directly into targeted area and minimizes possible side effects related to systemic therapy. Also penetration of drug is more expressive compared to topical route (**Melo DF et al., 2018**)[8]. Oral methotrexate has been used for AA as monotherapy or as adjunct, depending on its immunosuppressive and anti-inflammatory action (**Droitcourt C et al., 2012[6]; Phan K et al., 2019[3]**)

In our study, we compared intralesional MTX against TrA in localized patchy AA in scalp and beard area. After sessions (12 weeks), targeted score of 4 for Regrowth was achieved by 3.33% patients in MTX group and 13.33% patients in TrA group but with statistically insignificant difference between both groups (p-value = 0.221).

This was in contrast to **Hamdino M et al**.[9] study where clinical improvement at end of sessions (12 weeks) measured by regrowth scale was significantly higher in TrA group than MTX group, as targeted score of 4 (regrowth ≥75%) was achieved by 20% of patients after sessions in MTX group and in 40% of patients in TrA group.

Our results in TrA group are in contrast to **Ganjoo et al**.,[10] which showed complete hair regrowth (>75%) in 47% of patients at 12 weeks following intralesional TrA injection (5 mg/ml) at 4 weeks interval and also in contrast to **Kuldeep et al**.,[11] who reported hair re-growth (>75%, HRG IV) in 60% of patients at 12 weeks following intralesional TrA injection (10 mg/ml) at 3 weeks interval.

After 3 months follow up, targeted score of 4 was achieved by 16.67% patients in MTX group and 23.33% patients in TrA group (p-value = 0.196).

This was statistically similar to **Hamdino M et al**.,[9] where at 3-month follow-up after treatment, regrowth scale was improved in MTX group more than in TrA group as 65.0% of patients achieved score of 4 compared to 50% in TrA group but with statistically insignificant difference between both groups.

This is in contrast to other studies showing cumulative effect of TrA with passage of time like **Ganjoo et al**.,[10] who achieved RGS of 4 within 24 weeks of initiating therapy in 95% of patients. Similar effect was also observed by **Srivastava et al**.[12] with progressive increase of RGS of 4 from 9% of patients at fourth month, to 40% at fifth month and 60% at sixth month follow-up intervals. This might be explained by continuous injection of intralesional TrA up to maximum of 6 months at 4 weeks interval in their studies compared to 3 months of treatment in our study.

To degree that our study is concerned, only two studies have reported use of non-oral methotrexate in AA; first by **Hamdino M et al**.,[9] comparing effectiveness and safety of intralesional MTX versus TrA injection in treatment of localized AA in male patients, both clinically and trichoscopically which found higher Regrowth in MTX group compared to TrA group after 3 months of follow up (p-value = 0.153),

and second study by **Ahmed G et al**.,[13] which reported successful use of topical methotrexate 1% gel on 2 patients with localized patch of AA of scalp as monotherapy resulting in appearance of black terminal hairs with mild

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scaling at end of second month. Mild, self-limiting irritant effect of topical methotrexate was observed in their study and was considered beneficial in treatment of AA.

In our study, adverse events observed during sessions in both groups were transient and gradually disappeared during follow-up period. Side effects involved hyperpigmentation in 3 patients, in MTX group; hypopigmentation in 2 patients and atrophy in 2 patients in TrA group (p-value = 0.071). Our study suggests that use of intralesional MTX for AA in adults is safe and spares possible systemic adverse effects of MTX use.

Similar results were observed in study of **Hamdino M et al**.,[9] where adverse events were transient and gradually disappeared during follow up period. Study by **Srivastava et al**.,[12] also reported no substantial side effects of TrA. They reported telangiectasia in 7.5% of cases and 4.6% had atrophy**.** The study of **Kuldeep et al**[11] reported atrophy at injection sites of TrA. **Ganjoo et al.[10]** observed atrophy in 16% and telangiectasia in 3% by using dermoscopy.

No patient experienced recurrence after complete improvement of AA at site of injection in both groups.

This was in contrast to study by **Hamdino M et al**.[9] where no patients experienced recurrence after complete improvement of AA at site of injection in MTX group, compared to 1 patient in TrA group and 2 patients developed new lesions in MTX group compared to 5 patients in TrA group during course of treatment and follow-up period which might be explained by increased number of patients with progressive disease in TrA group more than in MTX group. This is also in contrast to **Trink et al.,[14]** who reported that 38% of intralesional corticosteroid-treated patients showed recurrence within 6-month follow-up.

In addition, more patient satisfaction was observed at end of our study in TrA group as compared to MTX group (p-value = 0.048). This was in contrast to study by **Hamdino M et al**.,[9] where higher patient satisfaction and lesser number of sessions in MTX group compared to TrA group was found but with insignificant difference.

In our study, regrowth scale showed **insignificant** negative correlation with duration of disease. There was **significant** negative correlation between Regrowth scale and SALT score, with **highly significant** negative correlation between Regrowth scale and SALT score after 3 months follow up.

This was in contrast to study by **Hamdino M et al.**[9] where significant negative correlation was found between regrowth scale and duration of disease in both groups. This is also in contrast with other studies evaluating intralesional corticosteroid in AA, as study of **Ganjoo et al.**, [10] which showed early response to treatment in patients with short duration of patches which could be due to various modifications that occur with long duration of AA like disappearance of terminal hairs, decrease in terminal to vellus hair ratio and development of more miniaturized hair follicles by chronic inflammatory infiltrate.

Our study is the first showing beneficial therapeutic effect of intralesional methotrexate in AA in comparison to TrA in both male and female patients and involving both scalp and non-scalp areas.

However, more randomized controlled researches are needed to validate its effectiveness in larger cohort of patients.

CONCLUSION-

In our study, we compared between intralesional MTX injection and TrA injection in localized AA.

MTX injection is cheaper and easily available than TrA injection.

Shortcoming of our study could be lack of dermoscopic evaluation which could have revealed early initial regrowth of hair or disappearance of AA's specific trichoscopic signs including yellow dots, black dots, exclamation mark hair and broken hair and early detection of adverse events.

Our study, first one of its kind investigating efficacy of intralesional MTX in AA in both males and females; scalp as well as non-scalp areas, suggests that intralesional MTX can be promising, therapeutic alternative for localized AA in adults compared to intralesional TrA in future.

Our results call for more controlled studies evaluating this therapeutic modality to validate its efficacy in larger cohort of patients and suggests increasing doses of methotrexate with short intervals and frequent monitoring and dermoscopic evaluation for more favourable results.

CONFLICT OF INTEREST- None

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