Section: Skin & VD

Original Research Article

EVALUATION OF THE EFFECTIVENESS OF INTRALESIONAL INTRAVENOUS IMMUNOGLOBULIN FOR THE TREATMENT OF MORPHEA AMONG CHILDREN ATTENDED AT TERTIARY CARE HOSPITAL IN THE STATE OF BIHAR, INDIA

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ABSTRACT

Background: Morphea is an inflammatory, fibrosing skin disorder,with increased collagen deposition. When children are affected it is also known as juvenile localised morphea. Girls are at seen to have higher risk of having morphea and it typically appears around the age of 5 to 7 years. The present study is aimed at assessing effectiveness with intralesionalIVIG therapy in case of failure of standard protocol of treatments. **Materials and Methods:** This is a prospective interventional study based on 20 children with morpheawho were previously treated with a range of topical and systemic treatments with limited success. After obtaining clearance from IEC and after written consents from the parents or guardian of the affected children all the selected patients were administered intralesional IVIG at a dose of 10mg/ml/cm2 of 5% IVIG in every 2 weeks. The study recorded regression of lesions both clinically and ultrasonological parameters over the period of one year. **Result:** Following six months of therapy, a very good response was observed in twelve patients (60%), and a good response in eight patients (40%), with no treatment failures reported. Patients were monitored over an average period of three months. Throughout this time, no serious adverse events were noted. **Conclusion:** The results of this study revealed that intralesional IVIG monotherapy is a safe and effective approach for managing this particular subset of morphea in children.

INTRODUCTION

Morphea is a rare autoimmune condition that causes sclerosis of the skin and subcutaneous tissue. The incidence of rates of Morphea may vary from 3.4 to 27 per 100,000. Higher rate of morphea among women is observed in the ratio 2.5 to 5:1 compared to men. Among children the peak incidence of morphea is reported to happen between 7 and 11 years.[1-6] Another study reported that it primarily occurs in children aged between 2–14 years.The estimated annual incidence rate of juvenile localized scleroderma was 3.4–9.0 cases per million children per year.[7,8]

In patients with morphea there is an increased presence of vascular cell adhesion molecule 1 (VCAM1) and intracellular cell adhesion molecule 1 (ICAM1), which facilitate the recruitment of T lymphocytes in the acute phase. CD-4 T helper cells have significant role in producing IL-4 cytokine. IL-4 cytokine causes the up-regulation of TGF-B. TGF-B, helping as a stimulator of fibroblast production of collagen and other extracellular matrix proteins.[8,9] About half of patients may experience spontaneous remission approximately 2-3 years after first appearance of symptoms. However other cases may extend causing substantial atrophy,joint contractures,and psychological impairment. Epidemiological studies shows 0.9-5.7% of morphea can progress to systemic sclerosis.

Treatment options ranges from Topical and oral corticosteroids as 1st line treatment.Topical tacrolimus 0.1% is also being used as an alternate choice for superficial circumscribed morphea.[10-13]Other options include PUVA, phototherapy with ultraviolet A1 (UVA1) for the patients with more

widespread lesions and deep morphea.[14]Cyclosporin, Methotrexate, penicillamine and other anti malarials have also been tried with limited success. Despite suggested treatment algorithms for different morphea subtypes by Fett and Werth, there remains a lack of consistent treatment guidelines tailored for the disease.

The present study aims to assess the effectiveness of using intralesional IVIG alone in treating stubborn localized morphea.

MATERIALS AND METHODS

Materials

This prospective study was carried out during the period from February 2023 to March 2024 at the Department of Skin and Venereal diseases, Nalanda Medical College and Hospital(NMCH), Patna. 20 patients were selected randomly from all the patients aged <18 years withconfirmed diagnosis as plaque scleroderma through histology and sonological testing and cases of morphea not responded to topical treatments (such as corticosteroids, calcineurin inhibitors, and vitamin D analogs), PUVA, oral corticosteroids, and methotrexate who attended the department for their treatments.

Methods

Clinical characteristics, duration of disease, history of previous treatments, and extracutaneous manifestations were obtained from each patient.

Diagnosis was confirmed through skin biopsy for histologic examination, and lesioned ultrasound was conducted. Prior to initiation of treatment with IVIG standard screening including a full blood count, liver biochemistry, serum urea, creatinine, IgA level, and serology tests for HBV, HCV, HIV and chest X-ray and Mantouxwere also performed for tuberculosis.

Patients were treated with intralesional IVIG at a dosage of 10mg/ml/cm2 of 5% solution biweekly. Disease activity was assessed monthly, along with adverse events, if any. Treatment was discontinued in cases of very good improvement, lack of improvement, disease progression after 3 months of intralesional IVIG or unmanageable adverse events.

The detailed histories of the patients were noted with well-designed pre-tested questionnaire through direct interview. The progression of recovery and side effect, if any, were also noted. Severity of morphea was assessed as per Modified Localized Scleroderma Skin Severity Index (mLoSSI) and improvement of morphea was assessed as per Physicians Global Assessment Scale (PGA)

Compliance with ethics guidelines: This study was conducted after getting approval from the Institutional Ethics Committee of the hospital, and written informed consent was obtained from the parents or guardians of the patients.

RESULTS

The study was based on 20 patients with Morphea. The mean (mean±s.d.) age of the patients was 10.20±3.66 year with range 3 – 16 years and the median age was 10.5 years. 75.0% of the patients were with age between 5 – 14 years. Girls (70.0%) were significantly higher than boys, in the study.

The mean (mean±s.d.) duration of disease of the patients was 26.55±4.61 months with range 20 – 36 months and the median duration of disease was 25 months. 60.0% of the patients were with duration of disease between 24 – 31 months. Thigh was the most common site of Morphea (35.0%) followed by leg (25.0%) and abdomen (25.0%). Thus, in overall lower part of the body of the patients (60.0%) was seen more affected in our study.Plaque type (65.0%) was the most common form noted, followed by Linear type (30.0%) and Pansclerotic (5.0%)

Improvement of severity of disease was significant after the initiation of treatment.One-way analysis of variance showed that there was significant difference in mean mLoSSI at different time interval ($F_{3,76}=5.37$ $p=0.002$). Also, Tukeys post hoc test confirmed that mean mLoSSIdeceased significantly at different time interval after the imitation of treatment with intralesional IVIG ($p<0.01$) [Table3].

The patients enrolled in this study had average disease duration of 24 months prior to starting IVIG treatment. Clinically, most patients began to experience marked or moderate improvement within the first month of therapy, which continued over the subsequent months. This improvement was evident in various scoring systems for disease activity like modified localized scleroderma index (mLoSSI) which includes erythema, skin thickness, and new lesion or extension of previous lesion.

According to the PGA assessment, there was no case of treatment failure. Also, improvements of morphea at post-treatment different time intervals were observed ($p<0.001$). At 12 month very good response was observed in 60.0% of the cases which was significantly higher than very good response at 3 month (5.0%). During follow-up till the end of the study no new skin lesion of generalized morphea was observed among the patients and there was no observed exacerbation of the disease [Table4].

Table 1: Site of involvement of Morphea

Site of involvement	Number	%
Thigh	7	35.0%
Leg	5	25.0%
Abdomen	5	25.0%
Forearm	4	20.0%
Face	3	15.0%
Arm	2	10.0%

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Forehead	1	5.0%
Hands	1	5.0%
Back	1	5.0%

Table 2: Type of morphea.

Type of morphea	Number	%
Plaque type	13	65.0%
Linear type	6	30.0%
Pansclerotic	1	5.0%
Total	20	100.0%

Table 3: Severity of morphea as per Modified Localized Scleroderma Skin Severity Index (mLoSSI)

Severity of morphea	Baseline		At 3 month		At 6 month		At 9 month		At 12 month	
	Number	%	Number	%	Number	%	Number	%	Number	%
Mild	0	0.0%	2	10.0%	6	30.0%	11	55.0%	14	70.0%
Moderate	12	60.0%	10	50.0%	11	55.0%	7	35.0%	5	25.0%
Severe	8	40.0%	8	40.0%	3	15.0%	2	10.0%	1	5.0%
Total	20	100.0%	20	100.0%	20	100.0%	20	100.0%	20	100.0%
Mean±sd	12.85±7.02		10.35±6.43		7.85±5.72		6.45±5.08		3.75±3.63	
Median	9		7		5		4		2	
Range	7 - 32		4 - 28		2 - 26		2 - 22		1 - 16	

Table 4: Improvement of morphea as per Physicians Global Assessment Scale (PGA)

PGA	At 3 month		At 6 month		At 9 month		At 12 month	
	Number	%	Number	%	Number	%	Number	%
Treatment failure	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Fair response	7	35.0%	2	10.0%	1	5.0%	0	0.0%
Good response	12	60.0%	10	50.0%	9	45.0%	8	40.0%
Very good response	1	5.0%	8	40.0%	10	50.0%	12	60.0%
Total	20	100.0%	20	100.0%	20	100.0%	20	100.0%

DISCUSSION

Juvenile localized scleroderma is a rare disorder. But it was observed that 20–30% of patients with localized scleroderma were found in childhood. Also, a higher incidence at the menarche was observed. The average age of onset was around 13 years of age. It is more common in girls and typically appears around the age of 5 to 7 years. This study also revealed that the mean (mean±s.d.) age of the patients was 10.20±3.66 year with range 3 – 16 years and the median age was 10.5 years. Girls (70.0%) were significantly higher than boys (30.0%) similar to previous studies.[15]

Poojary et al. Also mentioned that it was more common in girls and typically found around the age of 5 to 7 years. Vildan also reported among 19 patients 63.2% were female and 36.8% were male. The female-to-male ratio was 1.7:1.0. The mean age of onset of symptoms was 8.2±5.5 years and the mean age of diagnosis was 9.4±4.9 years.[16]

Jindal et al. from North India reported that the median age of disease onset was 5 years with the median age at diagnosis was 8 years. Thus, the mean and median age of the patients of different hospital-based studies were more or less equal.[17]

According to a recent classification system, morphea is divided into 5 types: circumscribed (plaque), linear, generalized, pansclerotic, and mixed. Approximately 40% of patients present extracutaneous manifestations. Childhood morphea is treated with phototherapy, oral or topical calcitriol, topical tacrolimus 0.1%, methotrexate, topical or systemic corticosteroids, mycophenolatemofetil, bosentán, and topical imiquimod 5, among others.[18]

Chiu et al. conducted study on 2522 lesions. As per them the trunk was the most commonly affected site overall with 46.9% of the lesions with neck (4.3%) was the least frequently affected site. In our study Thigh was the most common site of Morphea (35.0%) followed by leg (25.0%) and abdomen (25.0%).

The study from North India by Jindal et al. describes the clinical, immunological titre profiles and treatment outcomes in a cohort of 84 patients.3 The study includes patients from paediatric dermatology clinic and paediatric rheumatology clinic and has compared management aspects in the two clinics. Amongst the clinical subtypes, linear scleroderma constituted 67.9% reaffirming predominance of linear type in childhood. In our study we had plaque type as the most common followed by linear type as the commoner variants of morphea.

Immunosuppressants which have been recommended for use in localized scleroderma include methotrexate, mycophenolatemofetil. Other drugs used in limited cases include tocilizumab, abatacept, infliximab and JAK inhibitors.

Methotrexate is the first recommended choice of systemic treatment. Steroids are effective in the early inflammatory stage and are used in combination with methotrexate.5 MMF has been used in methotrexate resistant morphoea. The study by Jindal et al. has shown significantly higher remission with combination therapy of methotrexate

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and steroids in comparison to methotrexate alone. They also found that the combination of oral pulse steroids and methotrexate was more commonly prescribed in the dermatology clinic than in the rheumatology clinic.

The study by Martini et al. revealed that most patients with JLS have a good prognosis and achieve remission. Activity of disease was observed in 12.5% of patients with linear variant even after 10 years of follow up. It was observed that the delay in start of therapy was associated with longer disease activity. Functional damage was more prevalent in pansclerotic, linear, and mixed types of morphea. Also, disease reactivation was observed most often within 2 years of discontinuation of treatment warranting close follow up during that period.

In a study by Lisa et al they enlisted 7 patients of morphea for treatment with intravenous IVIG after treatment failure with other modalities and significant improvements was seen in these patients.

Similarly a study by Christian et al enrolled three cases of recalcitrant morphea and attained good results after using IVIG in treatment of morphea.

There is just one case report by Yamazaki et al that used subcutaneous immunoglobulin for treatment of deep morphea in a child and showed successful response.

In the present study, it's one of kind and for now the largest number of patients being enrolled for this innovative treatment approach.

The study showed improvement of severity of disease was significant after the initiation of treatment at different time interval ($p<0.0001$). One-way analysis of variance showed that there was significant difference in mean mLoSSI at different time interval ($p=0.002$). Also, Tukeys post hoc test confirmed that mean mLoSSI deceased significantly at different time interval after the imitation of treatment with intralesional IVIG ($p<0.01$).

No adverse affects were seen after the treatment initiation or none of the cases have yet shown any relapse after treatment discontinuation,proving it to be a safe and effective option.

CONCLUSION

Disease activity of morphea is based on assessment of current validated clinical scores which is a crucial step in the initial evaluation of patients with morphea. Late diagnosis or an incorrect severity assessment may cause to a delay of appropriate treatment which may lead to physical and functional disabilities as well as decreased quality of life. For pediatricmorphea, the linear and deep types initiation of adequate systemic therapy is pivotal for achieving disease control and reducing subsequent damage. Again, childhood morphea is mainly associated with a more severe disease course and higher risk of relapse even after years of remission. Moreover, certain cases do not respond to current therapeutics, i.e., methotrexate, systemic corticosteroids and mycophenolatemofetil.

Intravenous immunoglobulin (IVIG) is a pooled antibody which is a biological agent used to manage various immunodeficiency states including autoimmune, infectious, and inflammatory states. The ultimate goal of IVIG therapy is to normalize a compromised immune system. The result of this study revealed that IVIG therapy was found to be effective to treat morphea. Thus, IVIG therapy may be useful for the treatment of morphea.

Recommendation:

Importance may be given for early diagnosis and correct severity assessment of morphea. In case of failure of standard protocol of treatment IVIG therapy may be recommended for the treatment of morphea. Community based awareness programme about the sign and symptoms of morphea may be introduced for early diagnosis.

REFERENCES

1. Sapra A, Dix R, Bhandari P, Mohammed A, Ranjit E. A Case of Extensive Debilitating Generalized Morphea. Cureus. 2020;12(5):e8117.
2. Leitenberger JJ, Cayce RL, Haley RW, Adams-Huet B, Bergstresser PR, Jacobe HT. Distinct autoimmune syndromes in Morphea. Arch Dermatol. 200;.145:545–50. doi: 10.1001/archdermatol.2009.79
3. Peterson LS, Nelson AM, Su WP, Mason T, O'Fallon WM, Gabriel SE. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-1993. J Rheumatol. 1997;24:73–80.
4. Weibel L, Laguda B, Atherton D, Harper JI. Misdiagnosis and delay in referral of children with localized scleroderma. Br J Dermatol. 2011;165:1308–13.
5. Herrick AL, Ennis H, Bhushan M, Silman AJ, Baildam EM. Incidence of childhood linear scleroderma and systemic sclerosis in the UK and Ireland. Arthritis Care Res (Hoboken). 2010; 62:213–8.
6. Finlay GA, Russell KJ, McMahon KJ, D'Arcy EM, Masterson JB, FitzGerald MX, O'Connor CM. Elevated levels of matrix metalloproteinases in bronchoalveolar lavage fluid of emphysematous patients. Thorax. 1997; 52: 502–506.
7. Fukuda Y, Ishizaki M, Kudoh S, Kitaichi M, Yamanaka N. Localization of matrix metalloproteinases-1, -2, and -9 and tissue inhibitor of metalloproteinase-2 in interstitial lung diseases. Lab Invest.1998.78: 687–698.
8. Kroft EB, Groeneveld TJ, Seyger MM, de Jong EM. Efficacy of topical tacrolimus 0.1% in active plaque morphea: randomized, double-blind, emollient-controlled pilot study. Am J ClinDermatol. 2009;10(3):181-7.
9. Kreuter A, Hyun J, Stücker M, Sommer A, Altmeyer P, Gambichler T. A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. J Am AcadDermatol. 2006;54(3):440-7.
10. Poojary S, Jaiswal S, Bhalala KB, Bagadia J, Shah KS, Arora S, et al. A cross sectional observational study of pediatricdermatophytosis: Changing clinico mycological patterns in Western India. Indian J PaediatrDermatol. 2021;22:236–40.
11. Güngörer V, Çelikel E, Tekin ZE, Tekgöz, Sezer NM, Karagöl C, et al. Juvenile Localized Scleroderma from a Pediatric Rheumatology Perspective: A Single-Center Experience. Chron Precis Med Res. 2023; 4(1): 15-2.
12. Jindal AK, Handa S, Loganathan SK, Sudhakar M, Kaushik A, Suri D, et al. Juvenile localized scleroderma: A single-centre experience from India. J EurAcadDermatolVenereol. 2023;37(3):598-604.

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13. Chiu YE, Shmuylovich L, Kiguradze T, Anderson K, Sibbald C, Tollefson M, et al. Body site distribution of pediatric-onset morphea and association with extracutaneous manifestations. JAAD;2021:38-45.
14. Chan ES, Cronstein BN. Methotrexate-how does it really work? Nat Rev Rheumatol. 2010;6(3):175-8.
15. Martini G, Fadanelli G, Agazzi A, Vittadello F, Meneghel A, Zulian F. Disease course and long-term outcome of juvenile localized scleroderma: Experience from a single pediatric rheumatology Centre and literature review. Autoimmun Rev. 2018;17:727–34.
16. Lisa NG, OluwadamilolaOke, Shaw KS, LaChance AH, Vleugels RH. Intravenous immunoglobulin for the treatment of morphea: A retrospective review of 2 academic medical centers. Penn Medicine.
17. Kromer C, Mitterlechner L, Langer N, Schön MP, Mössner R. Response of recalcitrant generalized morphea to intravenous immunoglobulins (IVIg): three cases and a review of the literature. Eur J Dermatol. 2021;31(6):822-829. doi: 10.1684/ejd.2021.4173. PMID: 35107073.
18. Yamazaki-Nakashimada MA, Saez-de-Ocariz M, Maldonado-Colin G, García-Romero MT. Subcutaneous immunoglobulin for the treatment of deep morphoea in a child. ClinExpDermatol. 2018;43(3):303-305.

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