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Original Article

Efficacy of intralesional injection of platlet rich plasma in combination with methoterexate in chronic plaque psoriasis

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Abstract

Objective To determine the efficacy of intradermal injection of platelet rich plasma in combination with methotrexate in patients of chronic plaque psoriasis.

Methods It was a descriptive case series performed in department of dermatology, FJMU/SGRH Lahore from April 4, 2018 till Oct 4, 2018. A total number of 73 patients enrolled from outpatient department, after acceptance from ethical review board and written informed consent, patients fulfilling the inclusion and exclusion criteria. The demographic information like age, gender, address was collected and recorded as per proforma. All cases were treated under supervision of consultant dermatologist having more than 5 years of clinical experience to avoid bias. The study was conducted for 16 weeks, in which patients were treated for a period of 15 weeks and results were calculated by the end of 16th week. All cases were treated with PRP and MTX both. Autologous PRP was prepared from patient's peripheral blood through 2-stage centrifugation process as per established protocol. Each patient was given intra-lesional PRP in psoriatic plaques on 1st week, 0.1 ml of PRP was given at each point with 2cm spacing followed by 15mg of intralesional MTX weekly for 4 weeks i.e. 2nd, 3rd, 4th and 5th week` after 1 week of PRP injection, 15 mg of MTX were divided among the plaques so that 1.25mg was given at each point with a space of 2cm between two points. Second administration of intralesional PRP was done in the psoriatic plaques on 6th week followed by similar administration of intra-lesional MTX on 7th, 8th, 9th and 10th week. Third intralesional PRP was given on 11th week and then intra-lesional MTX was given again on 12th, 13th, 14th and 15th week. Both PRP and MTX were given through intra-lesional route to avoid toxicity associated with systemic administration. All cases were observed for the effect of treatment by the end of 16th week and PASI was calculated. Efficacy was labeled as per operational definition.

Results The mean age of cases was 39.60 ±12.15 years in range of 18 and 60 years. There were 24 (32.88%) male and 49 (67.12%) female cases, with higher female cases. According to operational definition 60 (82.19%) had efficacy while 13 (17.81%) cases did not meet the criteria of efficacy.

Conclusion The efficacy of intradermal injection of platelet rich plasma in combination with methotrexate in patients of chronic plaque psoriasis is highly effective. This combination can be utilized for substantial improvement in term of improvement of PASI score.

Key words
Psoriasis, anti-inflammatory, PASI, PRP, combination therapy.

Introduction

Psoriasis is a chronic, inflammatory and proliferative skin disease , associated with systemic manifestations in many organ systems.[1] It makes the patient prone to various cardio-metabolic diseases and psychological disorders like depression.[2-4] It affects 2-3% of general population. Psoriasis affects adult women and men equally, however age of onset is earlier in

girls. It has different clinical variants but plaque psoriasis is a typical morphological presentation of psoriasis. Lesions in psoriasis predominantly involve extensor surfaces and are characterized by red, scaly, sharply demarcated, indurated plaques.[1]

Initially psoriasis was thought to be a T-lymphocyte mediated disorder.[5] Newer researches reveal that NF-kB play a key role in immune and inflammatory responses in the pathogenesis of psoriasis. NF-kB is a complex protein that controls transcription of DNA, cytokine production and cell survival.[5] Active phosphorylated NF-kB is elevated in psoriatic lesions which poorly regulates the interaction between epidermal keratinocytes and immune cells resulting in epidermal hyperplasia.[6] Several treatment modalities including topical, systemic and biologic agents are being used for the control and cure of psoriasis. Methotrexate (MTX) is one of the systemic agents which inhibits DNA synthesis by folate antagonism and subsequently inhibits proliferation of lymphocytes. Though widely used in clinical settings, MTX therapy causes a multitude of systemic side effects like bone marrow suppression, mucositis, hepatotoxicity, liver and pulmonary fibrosis.[1]

Advance treatment modalities of psoriasis like tumor necrosis factor (TNF)-alpha blockers, glucocorticoids and interleukin-17 inhibitors target and suppress the NF-kB signalling mechanisms. However, prolonged down regulation of Nuclear factor-kappa B (NF-kB) results in immune-deficiencies. So there is an urgent need for newer treatment therapies.[7]

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The researchers now have used the idea of selective inhibition of NF-kB signalling pathway by devising local procedures with combinational therapies, involving regenerative medicine to overcome the harmful effects of chronic NF-KB inhibition and diminish the potential toxicity attributed to conventional therapy.[8] Platelet rich plasma (PRP) has been a recent advancement in this respect, it is an autologous preparation of platelets in concentrated plasma, the alpha-granules of concentrated platelet release a cocktail of growth factors that stimulate and accelerate soft tissue healing through NF-kB suppression.[9,10]

With this background, PRP could be devised as an adjuvant therapy to help decrease the inflammation in psoriasis. A study reported combined effect of intralesional PRP and MTX injection in chronic plaque psoriatic patients, in which 12 (75%) out 16 cases achieved PASI $\geq$75% at 16th week of treatment.[11]

The current study is designed to assess the efficacy of intradermal injection of platelet rich plasma plus methotrexate in patients of chronic plaque psoriasis. No such local study is done so far on the subject so data on local population is lacking. We found a study that reported high efficacy of PRP and MTX.[11] The current study can add data for the local population and the results can be applied in future to treat chronic plaque psoriasis thus reducing its impact on quality of life and gaining more patients' satisfaction.

Methods

It was a Descriptive case series conducted in department of dermatology, FJMU/ SGRH Lahore (April 4, 2018 till Oct 4, 2018) on a sample of 73 patients selected through non probability consecutive sampling, estimated using percentage of efficacy as 75%[11] using 10%

margin of error and 95% confidence level. Patients of either gender with age range of 18-60 years were diagnosed cases of chronic plaque psoriasis as per operational definition having stable disease for 6 months, not on any specified systemic treatment for the disease for last 3 months, not using any topical medication for last 1 month were included to participate in the study.

Chronic Plaque Psoriasis A person suffering from sharply demarcated, erythematous, indurated plaques with silvery white scales present predominantly over the extensor surfaces, for last 6 months involving less than 20% of the body surface area, sparing the scalp, palms and soles. All cases with PASI <50% score were inducted in this study.

Efficacy It was considered if PASI score is ≥75% at 16th week of treatment.

Patients having any other concomitant chronic inflammatory dermatoses e.g. Lichen Planus, vitiligo or suffering from any bleeding, clotting disorder, hepatitis B or hepatitis C, pregnant and lactating females were excluded. After written informed consent and approval from ethical review board patients who satisfied the inclusion and exclusion criteria were enrolled from OPD of Dermatology department, FJMU/ SGRH Lahore. The demographic information like age, gender, address was collected and recorded as per proforma. All cases were treated under supervision of consultant dermatologist having more than 5 years of experience to avoid bias. The study was conducted for 16 weeks, in which patients were treated for a period of 15 weeks and results were calculated by the end of 16th week. All cases were treated with PRP and MTX both. According to standard protocol autologous PRP was prepared from patient's peripheral blood through 2-stage centrifugation process. Each patient was given intra-lesional PRP in psoriatic plaques on 1st week, 0.1 ml of PRP was given at each point with 2cm spacing followed by 15mg of intralesional MTX weekly for 4 weeks i.e. 2nd, 3rd, 4th and 5th week` after 1 week of PRP injection, 15mg of MTX were divided among the plaques so that 1.25mg was given at each point with a space of 2cm between two points. Second administration of intralesional PRP was done in the psoriatic plaques on 6th week followed by similar administration of intra-lesional MTX on 7th, 8th, 9th and 10th week. Third intralesional PRP was given on 11th week and then intra-lesional MTX was given again on 12th, 13th, 14th and 15th week. Both PRP and MTX were given through intra-lesional route to avoid toxicity associated with systemic administration. All cases were observed for the effect of treatment by the end of 16th week and PASI was calculated. Efficacy was labelled as per operational definition. Data was recorded by researcher herself on a given proforma. Data was entered, tabulated and analysed using statistical package for social science (SPSS) 22. For quantitative data like age and baseline PASI score, the mean and standard deviation were calculated. For qualitative data like gender and efficacy was presented using frequency (%). Qualitative variables like age, gender, duration of disease were stratified along with baseline PASI score to address effect modifiers. Post stratified Chi-square test was applied taking p value ≤0.05 as significant.

Results

The mean age of cases was 39.60±2.15 years with minimum and maximum ages as 18 and 60 years (**Table 1**). A total of 35 (47.9%) cases

Table 1 Descriptive statistics of age (years).

	Age (years)
Mean	39.60
S.D	12.15
Range	18-60
Minimum	18.00
Maximum	60.00

Table 2 Descriptive statistics of PASI baseline

PASI baseline	
Mean	23.04
S.D	12.56
Range	4 – 48
Minimum	4.00
Maximum	48.00

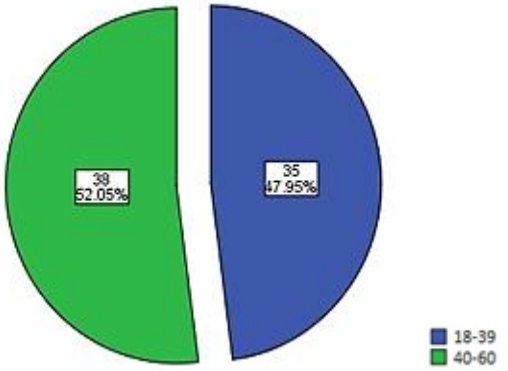

Figure 1 Frequency distribution of age groups.

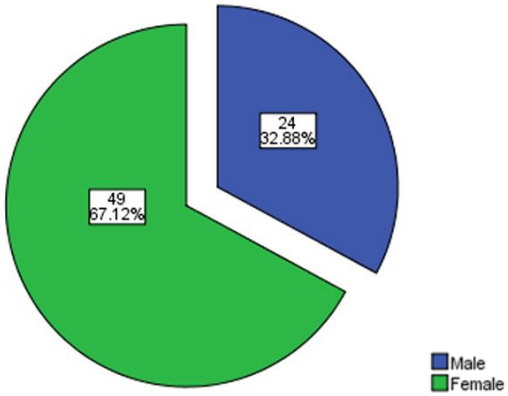

Figure 2 Distribution of gender.

were 18-39 years old and 38 (52.1%) cases were 40-60 years old **(Figure 1**). There were 24 (32.88%) male and 49 (67.12%) female cases, with higher female cases (**Figure 2**). The mean PASI score at baseline was 23.04±2.56 with minimum and maximum score as 4 and 48 (**Table 2**). A total of 41 (56.2%) cases had PASI score 4-24 and 32 (43.8%) cases had 25-48 at baseline (**Figure 3**). There were 33 (45.2%) cases who had duration of disease as 6-12 months and 40 (54.8%) cases had duration as >12 months **(Figure 4)**. According to operational definition 60 (82.19%) had efficacy while 13 (17.81%) cases did not meet the criteria of efficacy (**Figure 5**). In cases who had

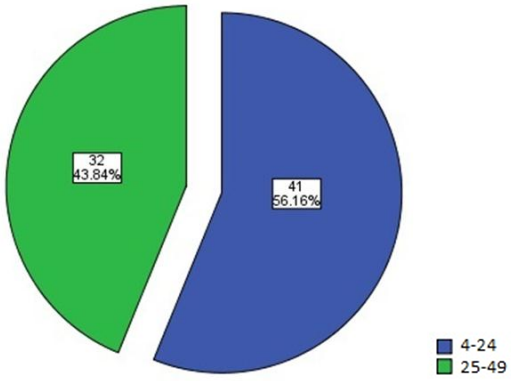

Figure 3 Distribution of PASI at baseline.

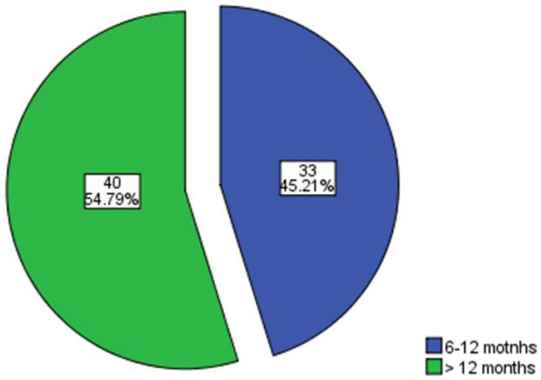

Figure 4 Distribution of duration of disease.

efficacy, 27 (45%) cases were of age 18-39 years and 33 (55%) cases were 40-60 years of age while in cases who do not had efficacy, 8 (61.5%) cases were 18-39 years old and 5 (38.5%) cases were 40-60 years of age, the frequency of efficacy was statistically same in both age group, p-value >0.05 (**Table 3**). In cases who had efficacy, 17 (28.3%) cases were male and 43 (71.7%) were female cases while in cases who do not had efficacy, 7 (53.8%) were male and 6 (46.2%) were females; the frequency of efficacy was statistically same in both male and female cases, p-value >0.05 (**Table 4)**. In

Table 3 Comparison of Efficacy with respect to age groups (years).

Age groups (years)	*Efficacy*		*Total*
	Yes	*No*	
18-39	27(45.0%)	8(61.5%)	35(47.9%)
40-60	33(55.0%)	5(38.5%)	38(52.1%)
Total	60(100)	13 (100.)	73 (100%)

Chi-square=1.171; P-value=0.279

Table 4 Comparison of efficacy with respect to age groups (years).

Gender	*Efficacy*		*Total*
	Yes	*No*	
Male	17(28.3%)	7(53.8%)	24(32.9%)
Female	43(71.7%)	6(46.2%)	49(67.1%)
Total	60(100.0%)	13(100.0%)	73(100.0%)

Chi-square=3.152; P-value=0.076

Table 5 Comparison of efficacy with respect to PASI baseline.

PASI baseline	*Efficacy*		*Total*
	Yes	*No*	
4-24	35(58.3%)	6(46.2%)	41(56.2%)
25-49	25(41.7%)	7(53.8%)	32(43.8%)
Total	60(100.0%)	13(100.0%)	73(100.0%)

Chi-square=0.644; P-value=0.422

Table 6 Comparison of efficacy with respect to duration (months).

Duration (months)	*Efficacy*		*Total*
	Yes	*No*	
6-12 months	26(43.3%)	7(53.8%)	33(45.2%)
> 12 months	34(56.7%)	6(46.2%)	40(54.8%)
Total	60(100%)	13(100%)	73(100%)

Chi-square=0.47; P-value=0.549

cases who had efficacy, 35 (58.3%) cases had 4-24 base line PASI score and 25 (41.7%) of the cases had 25-49 baseline PASI score while in cases who do not had efficacy, 6 (46.2%) cases had baseline PASI as 4-24 and 7 (53.8%) cases had 25-49 baseline PASI score, the frequency of efficacy was statistically same in both age of PASI at base line, p-value >0.05 (**Table 5**). In cases who had efficacy, 26 (43.3%) cases had duration of disease as 6-12 months and 34 (56.7%) of the case had duration of disease as >12 months while in cases who do not had efficacy, 7 (53.8%) cases had duration as 6-12 months and 6 (46.2%) cases had >12 months, the frequency of efficacy was statistically same in both groups of duration, p-value >0.05 (**Table 6**).

Discussion

Psoriasis is a chronic skin condition affecting 2-3% of population. It is an immune-mediated disease which significantly disturbs patient's psychosocial life and pre disposes to conditions such as metabolic syndrome, depression and so on.[12] There is always a room for newer treatment strategies because 50% of patients remain dissatisfied with the current therapies. Although exact pathogenesis is still not understood, nuclear factor kappa B (NF-kB) that mediates inflammation plays the key role in the pathogenesis of psoriasis.[13]

Tsuruta have proposed that it is an abnormal interaction between epidermal keratinocytes and T lymphocytes due to NF-kB which causes epidermal hyperplasia. Newer antipsoriatic drugs such as TNF-alpha blocker, glucocorticoids and interleukin-17 blockers specifically suppress NF-kB signalling. Aim of treatment is to achieve maximum benefits by maintaining an equilibrium with the side effects. Chronic NF-kB inhibition results in immunodeficiency. This is preventable through newer options such as localized therapy.[14] Combined treatment is a better option for recalcitrant disease since it enhances desired outcomes due to synergistic effect. The response is absolute with less systemic side effects which is associated with conventional therapy.[8] Platelet Rich Plasma (PRP) accelerates soft tissue healing. Many researches utilised PRP as an option for various conditions with promising results. Platelets contain many growth factors, which when released mimic physiological healing process through NF-kB suppression.[15]

In this study the mean age of cases was 39.60±12.15 years with minimum and maximum ages as 18 and 60 years. There were 24 (32.88%) male and 49 (67.12%) female cases, with higher female cases. Moreover another retrospective study was done on 85 patients (44 male; 41 female; age range 14-78 years, mean 44 years; 79 Caucasian, 6 Asian) with chronic plaque psoriasis were identified.[16] In our study the mean was lesser and we had higher female ratio. In current study according to operational definition 60 (82.19%) had efficacy while 13 (17.81%) cases did not meet the criteria of efficacy. A study reported combined effect of intralesional PRP and MTX injection in

chronic plaque psoriatic patients, in which 12 (75%) out 16 cases achieved PASI ≥75% at 16th week of treatment.[11] In current study efficacy was higher than that previous study.[11] Another study suggested that SC MTX is an effective option in patients with chronic plaque psoriasis who did not respond to oral MTX.[17] Subcutaneous MTX could be considered prior before planning biological therapy. Moreover, the SC route may be preferable as first choice of MTX administration. A randomised controlled trial comparing oral and SC MTX is required to validate these findings. However, there are further areas of research in which individual roles of S/C MTX and PRP should be researched for treating recalcitrant plaques of chronic plaque psoriasis and then be compared with a combination therapy of S/C MTX and PRP.

Conclusion

The efficacy of intradermal injection of platelet rich plasma in combination with methotrexate in patients of chronic plaque psoriasis is highly effective. This combination can be utilized for substantial improvement in term of improvement of PASI score.

References

1. Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. *Autoimmun Rev*. 2014;**13(4-5)**:490-5.
2. Mattei P, Corey K, Kimball A. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *J Europ Acad Dermatol Venereol*. 2014;**28(3)**:333-7.
3. Olivier C, Robert PD, Daihung D, Urba G, Catalin MP, Hywel W, *et al*. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol*. 2010;**146(8)**:891-5.
4. Geale k,Henriksson M,Jokinen J,Egenolf MS.Association of skin psoriasis and somatic comorbidity with the development of psychiatric illness in a nationwide Swedish study. *JAMA Dermatol*. 2020;**156(7)**:795-804
5. Sanchez APG, Nunes DCB, Swiczar BCC (2020) Immunopathogenesis of Psoriasis. *J Dermatolog Clin Res*. 2020;**8(2)**:1131-5
6. Goldstein J.D., Bassoy E.Y., Caruso A., Palomo J., Rodriguez E., Lemeille S., Gabay C. IL-36 signaling in keratinocytes controls early IL-23 production in psoriasis-like dermatitis. *Life Sci Alliance*. 2020;**3**:e202000688.
7. Christophers E, Griffiths C, Gaitanis G, Van De Kerkhof P. The unmet treatment need for moderate to severe psoriasis: results of a survey and chart review. *J Eur Acad Dermatol Venereol*. 2006;**20(8)**:921-5.
8. Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. *Am J Clin Dermatol*. 2014;**15(6)**:467-78.
9. Zhang J, Middleton KK, Fu FH, Im H-J, Wang JH. HGF mediates the anti-inflammatory effects of PRP on injured tendons. *PlOS One*. 2013;**8(6)**:1-12.
10. Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, *et al*. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: Mechanisms of NF-κB inhibition via HGF. *J Cellul Physiol*. 2010;**225(3)**:757-66.
11. Chakravdhanula U, Anbarasu K, Verma VK, Beevi SS. Clinical efficacy of platelet rich plasma in combination with methotrexate in chronic plaque psoriatic patients. *Dermatol Therap*. 2016;**29(6)**:446-50.
12. Goldminz A, Au S, Kim N, Gottlieb A, Lizzul P. NF-κB: an essential transcription factor in psoriasis. *J Dermatol Sci. 2013*;**69(2)**:89-94.
13. Tsuruta D. NF-κB links keratinocytes and lymphocytes in the pathogenesis of psoriasis. *Recent Pat Inflamm Allergy Drug Discov*. 2009;**3(1)**:40-8.
14. Zhang J, Middleton KK, Fu FH, Im H-J, Wang JH. HGF mediates the anti-inflammatory effects of PRP on injured tendons. *PLoS One*. 2013;**8(6)**:e67303.
15. Yesudian PD, Leman J, Balasubramaniam P, Macfarlane A, Al-Niaimi F, Griffiths C, *et al*. Effectiveness of Subcutaneous Methotrexate in Chronic Plaque Psoriasis. *J Drugs Dermatol*. 2016;**15(3)**:345-9.
16. Reich K, Sorbe C, Griese L, Reich JLK, Augustin M. The value of subcutaneous vs. oral méthotrexate: real-world data from the German psoriasis registry PsoBest. *Br J Dermatol*. 2020;**184(4)**:765-7.
17. Lukmanji, A., Basmadjian, R. B., Vallerand, I. A., Patten, S. B. & Tang, K. Risk of depression in patients with psoriatic disease: a systematic review and meta-analysis. *J Cutan Med Surg*. 20202;**25(3)**:257–70.