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Efficacy and safety of isotretinoin in comparison to methotrexate in the patients suffering from moderate-to-severe plaque psoriasis: A prospective cohort study

Suhrita Paul[1], Abhijit Das[2], Chitrita Ghosh[3]

[1]Vice Chancellor, West Bengal University of Health Sciences, Kolkata, [2]Professor and Head, [3]Senior Resident, Department of Pharmacology, Burdwan Medical College, Burdwan, West Bengal, India

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ABSTRACT

Background: Psoriasis is a common dermatological disorder with both inflammatory and genetic etiology. In India, the incidence of psoriasis is on the verge of rise. Very less data is available on the efficacy of isotretinoin versus methotrexate in patients suffering from plaque psoriasis. **Aims and Objective:** In this prospective cohort study, we aimed at comparing the efficacy and safety of systemic isotretinoin with systemic methothotrexate in patients suffering from moderate to severe plaque psoriasis in a tertiary care medical college hospital in eastern India. **Materials and Methods:** It was a prospective cohort study conducted in the dermatology and pharmacology department of Burdwan Medical College between December 1, 2020, and August 31, 2021, on 60 patients suffering from moderate to severe plaque psoriasis. Patients receiving methotrexate and isotretinoin as systemic therapy of psoriasis from the dermatology outpatient department at the time of the study constituted the methotrexate and isotretinoin group, respectively. Each group had 30 patients. Psoriasis area severity index (PASI) score and dermatology life quality index (DLQI) score were utilized for evaluation of improvement in disease severity and quality of life, respectively. Different laboratory parameters and patients reported side effects were noted for evaluation of safety. **Results:** Fifty-eight patients completed the study (28 patients from methotrexate group and 30 patients from isotretinoin group). Both drugs were effective in managing psoriasis. 100% patients in the methotrexate group and 89.28% patients in the isotretinoin group had reached the threshold for a minimal response (25% reduction from baseline PASI score after 12 weeks of treatment). The mean percentage reduction in PASI score was 70.23 ± 6.78 and 52.78 ± 7.34 in methotrexate and isotretinoin group respectively at the end of 12 weeks therapy. This difference was statistically significant. Methotrexate was more effective in improving quality of life. The mean percentage reduction in DLQI score were 60.02 ± 5.04 and 28.49 ± 4.84 in methotrexate and isotretinoin group respectively at the end of 12 weeks therapy. This difference was statistically significant. Isotretinoin group showed fewer patient-reported side effects and lower fluctuation of laboratory parameters. **Conclusions:** Methotrexate is more efficacious than isotretinoin in disease remission and improving quality of life in patients suffering from mild to moderate plaque psoriasis. Isotretinoin is safer than methotrexate.

Key words: Dermatology life quality index score; Isotretinoin; Methotrexate; Psoriasis area severity index score; Psoriasis

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INTRODUCTION

Psoriasis is a chronic, inflammatory and proliferative skin disorder in which both genetic and environmental factors have a critical role.[1] It is frequently associated with numerous underlying comorbidities including cardiovascular disease and diabetes.[2-5] Due to the chronic path of the disease and need for lifelong treatment, psoriasis results in substantial

Address for Correspondence:
Dr. Chitrita Ghosh, Senior Resident, Department of Pharmacology, Burdwan Medical College, Burdwan - 713 104, West Bengal, India.
Mobile: +91-8145157647. **E-mail:** chitritaghosh@gmail.com

disease burden and significant deterioration of a person's quality of life.[6]

The incidence of psoriasis is on the verge of rise with approximately 125 million people affected worldwide.[7] Its prevalence varies from 0% to 11.8% in different populations. In India, the incidence of psoriasis among dermatology patients ranges between 0.44% and 2.2%, with an overall incidence of 1.02%.[8] Psoriasis occurs in both genders at all ages with a slight male predominance.[9]

The most common morphological form, plaque psoriasis, characterized by sharp demarcated, erythematous, scaly, indurated plaques, accounts for about 90% of all cases.[10] It affects preferably the extensor surface and the scalp.

Based on disease severity, therapeutic efficacy, adverse effects, patient preference, and individual patient response, psoriasis can be managed with topical and/or systemic therapies. The treatment objectives include initial rapid control of disease progression, maintenance of long-term remission, and improvement in the quality of life.

The first-line treatment of mild-to-moderate plaque psoriasis consists of topical emollient, corticosteroids, topical Vitamin D analog therapies.[11,12] Systemic therapy is required in treating severe form of psoriasis unresponsive to topical therapy. This includes conventional systemic agents (methotrexate, oral retinoids, and cyclosporine) and the more recently developed biologics.[13]

In spite of the revolutionary progress in the field of the pharmacotherapy of psoriasis in the last decade by the introduction of biologics, methotrexate, an antifolate antimetabolite, remains the most commonly used systemic antipsoriatic agent for the treatment of moderate to severe types of plaque psoriasis, psoriatic arthritis and nail psoriasis unresponsive to topical treatment owing to its effectiveness, availability, and affordability.[14] Although efficacious, methotrexate has its own share of adverse effects which include nausea, vomiting, abdominal discomfort, pancytopenia, hepatotoxicity, nephrotoxicity, and rarely, lung fibrosis.[15] Methotrexate is contraindicated in pregnancy due to its teratogenicity. A rapid and effective response have been seen with retinoids in the management of pustular psoriasis and erythrodermic psoriasis. Etretinate, the first retinoid, carried a potential risk of teratogenicity due to its long half-life and was withdrawn.

Acitretin is the active metabolite of etretinate, having a shorter half-life. It can be taken for long duration if not planning pregnancy for 3 years after stoppage of its use.[16] However, high cost of acitretin remains inhibitory.

Isotretinoin, in comparison, is a cheaper option. Besides, it has shorter half-life which reduces the duration of required contraception after cessation of therapy.[17,18] Only 1 month of contraception is needed once the patient stops using the medication. Isotretinoin is considered more effective in pustular psoriasis.[17-19] Only very few literatures regarding the efficacy of isotretinoin in chronic plaque psoriasis can be found. Moy et al., found acitretin effective in 18/19 of chronic plaque psoriasis and also achieved complete to moderate response with isotretinoin in their 4/10 patients suffering from chronic plaque psoriasis.[19] However, there is overall paucity of data on the efficacy of isotretinoin in patients having moderate-to-severe chronic plaque psoriasis. In this prospective cohort study, we compared the efficacy and safety of oral isotretinoin and oral methotrexate for the management of moderate-to-severe chronic plaque psoriasis in subjects aged 18 years and above.

Aims and objectives

Primary objectives

- To assess and compare the effectiveness of systemic isotretinoin in comparison to systemic methotrexate in disease remission.
- To assess and compare the improvements in the quality of life by both drugs.
- To compare the adverse events occurring in both drug groups.

Secondary objectives

- To find out the drug causing faster disease remission.
- To find out the drug causing faster improvement in quality of life.

MATERIALS AND METHODS

This was a prospective cohort study conducted between December 1, 2020, and August 31, 2021, on 60 patients suffering from moderate to severe plaque psoriasis in the department of pharmacology and department of dermatology of the Burdwan Medical College and Hospital, a tertiary care multispecialty academic government institution. The study proposal, informed consent form and case record form were pre-approved by the Institutional Ethics Committee of Burdwan Medical College.

Consent

Documented consent was obtained from all the participants before getting enrolled in the study. The study was explained to all the potential subjects verbally so that they had all the pertinent information regarding the study before giving consent. Every participant was then provided with the informed consent form written in his/her vernacular language. In case of illiterate subject the informed consent form was explained to them by reading it loud. All questions

were answered and all doubt was cleared. Once they agreed to take part in the study, consent was documented by signature of the potential participants along with date. In case of illiterate participant left thumb impression was taken instead of signature.

Inclusion criteria

- Age-18–70 years
- Either gender
- Normal cognition
- Suffering from moderate to severe plaque psoriasis (Psoriasis area severity index [PASI] score more than 10)
- Treatment plan-either systemic methotrexate or systemic isotretinoin along with equivalent topical therapy.

Exclusion criteria

- Pregnant women, lactating women, or women unwilling to use any contraceptive method.
- Patients suffering from psychiatric illness.
- Patients suffering from any severe systemic illness (hepatic, renal, or hematological impairment, deranged lipid profile, uncontrolled hypertension or diabetes mellitus, neoplasia).
- Acute infection requiring antimicrobial therapy.
- Patients who had received any systemic antipsoriatic in preceding 6 months.

During the period of the study, those patients who received tablet methotrexate 5 mg thrice weekly (One tablet each after breakfast and dinner on Saturdays and one tablet after breakfast on Sundays**)** along with tablet folic acid 5 mg once daily constituted the methotrexate group. Similarly, the isotretinoin group was comprised of the patients who were prescribed tablet isotretinoin at a dose of 30 mg twice daily from the dermatology Out-Patients Department (OPD) during the study period. Patients from both groups were receiving similar topical steroid ointments as adjuvant treatment as per prescription.

The consenting and eligible patients were thus included in two groups by serial inclusion from the Dermatology OPD of Burdwan medical college and hospital during the study period.

For evaluation of efficacy of both drugs in managing psoriasis, the reduction in the PASI score has been utilized. The PASI score is used to measure the severity of psoriasis. It is a validated tool used popularly in the therapeutic efficacy study of psoriasis.

The dermatology life quality index (DLQI) questionnaire, a widely used validated questionnaire to assess the quality of life associated with dermatological disorders, has been utilized in the current study for evaluation of the efficacy of both drugs in improving quality of life.

Data regarding each patient were recorded in the case record form during three visits after getting recruited in the study. The day on which the patients were assigned the treatment was considered the first visit. The visits taking place 4 weeks and 12 weeks after the treatment assignment was considered the second visit/first follow-up and third visit/second follow up respectively. Data related to all demographic variables and inclusion criteria were noted at the time of recruitment at the first visit. PASI score, DLQI score, all hematological data, data regarding lipid profile, renal profile, liver function test, random blood sugar, uric acid, serum electrolyte were noted in all three visits in the case record forms. Patient-reported adverse events of all the recruited patients in their second and third visits were also collected. All these data were later analyzed using statistical tools for drawing inference.

Sample size calculation

Statistically, calculated sample size went far beyond the availability of participants in dermatology outpatient department of the Burdwan Medical College and Hospital within predefined timeline. Hence, sample size was calculated according to the availability of participants. Annual psoriasis patient pool in dermatology OPD in Burdwan Medical College and Hospital is around 500. As plaque psoriasis comprises about 90% of all psoriasis and the proportion of moderate–to-severe plaque psoriasis is 20–30%, the availability of moderate to severe plaque psoriasis patients in 9 months in Burdwan medical college is 66–100. Taking the unwillingness to give consent, failure to meet inclusion criteria and 10% attrition rate into consideration, we had to exclude another 25% from the median of the aforesaid range. Hence, the sample size of our study was 60 patients suffering from mild-to-moderate plaque psoriasis.

Statistical analysis

Chi-square test or Fisher exact test was used to compare the baseline demography**.** Independent sample t-test or Mann-Whitney U test was used to compare the baseline PASI score and baseline DLQI score between the two groups**.** For comparison of efficacy in reducing disease severity and improvement in quality of life, independent sample t-test or Mann-Whitney U test was done comparing the mean percent reduction of PASI and DLQI score from base line to final follow-up case, respectively. Repeated measure ANOVA or Friedman test was used to compare the change in PASI score and DLQI score from baseline in each group from baseline to each follow-up. The choice of parametric and non-parametric tests was done according to the results of assumption tests using the obtained data. $P<0.05$ was considered statistically significant.

RESULTS

Out of 60 patients enrolled in the study, 58 patients completed the study. One patient in the methotrexate group stopped taking medication due to severe gastroenteritis. Another patient in methotrexate group was lost to follow up.

Baseline demography, disease severity score (PASI score), and quality of life score (DLQI score) of 58 patients completing the study are shown in Table 1. These variables were statistically similar in both the groups.

Both methotrexate and isotretinoin were effective in managing psoriasis (Figures 1 and 2). 100% patients in the methotrexate group and 89.28% patients in the isotretinoin group had reached the threshold for a minimal response which is determined by a 25% reduction from baseline PASI score after 12 weeks of treatment (Figure 3).

The mean percentage reduction in PASI scores from respective baseline value to week 4 and week 12 were significantly different in both groups. (P=0.03, and P=0.04, respectively in methotrexate group and isotretinoin group) and it showed progressive improvement (Table 2).

Methotrexate was more effective than isotretinoin in managing the disease severity as the mean percentage reduction in PASI score at both follow-ups as compared to the baseline PASI score were higher in the methotrexate recipients. These differences were statistically significant (P<0.05) at both follow-ups (Figure 1).

Both drugs showed significant improvement in the quality of life which was evident by the significant reduction in the mean DLQI score from baseline in both follow-up visits in both groups. Methotrexate was more effective than isotretinoin in improving quality of life as the difference in mean percentage reduction in DLQI score of both groups was statistically significant (P<0.05) at both follow-up visits (Figure 2).

It was found that methotrexate caused a faster disease remission in comparison to isotretinoin as methotrexate was capable of causing a faster reduction in the mean PASI score as compared to isotretinoin (Figure 4). In a similar way methotrexate also caused a faster improvement in the quality of life in comparison to isotretinoin (Figure 5).

Spontaneously reported adverse events were more in patients receiving methotrexate[18] compared to patients receiving isotretinoin.[14] Nausea and vomiting were the major patients who reported adverse events in the methotrexate group. One patient in the methotrexate group discontinued treatment due to gastroenteritis which subsided after discontinuation of stoppage of methotrexate therapy. Mucocutaneous adverse effects such as cheilitis, dryness of skin, and mouth were the major adverse event in patients receiving isotretinoin.

Values of different Laboratory parameters of the participants shown changes through the final follow-up from the baseline. The percentage increase in the values of many of the laboratory parameters was significantly more in the methotrexate recipients than in the isotretinoin recipients. There were two patients in the methotrexate group, in whom the hepatic transaminase enzyme reached more than threefold of the upper normal limit at the time of final follow-up. Other four patients in the methotrexate group developed altered lipid profile. Whereas two patients in the isotretinoin group experienced altered lipid profile.

DISCUSSION

Psoriasis affects both the genders with a male preponderance to some extent. Many studies exclude

Table 1: Baseline demography, disease severity score (PASI score) and quality of life score (DLQI score) of study participants

Demographic Variable	All participant (n=58)	Methotrexate (n=28)	Isotretinoin (n=30)	P value
Gender				
Male	34	16	18	0.062
Female	24	12	12	
Age (Years)				
Range	22-68	22–68	24–67	0.23
Mean	44.23±5.02	43.38±6.08	45.13±5.12	
Duration of disease (Years)				
Range	0.75–28	0.75–26	1.25–28	0.65
Mean	7.83±5.12	8.12±5.33	7.58±6.02	
PASI Score				
Range	11–25	11–23	11–25	0.09
Mean	15.18±5.23	14.29±5.23	15.78±5.93	
DLQI Score				
Range	6–14	6–13	6–14	0.13
Mean	9.19±4.23	9.24±4.02	9.16±3.41	

PASI: Psoriasis area severity index, DLQI: Dermatology life quality index

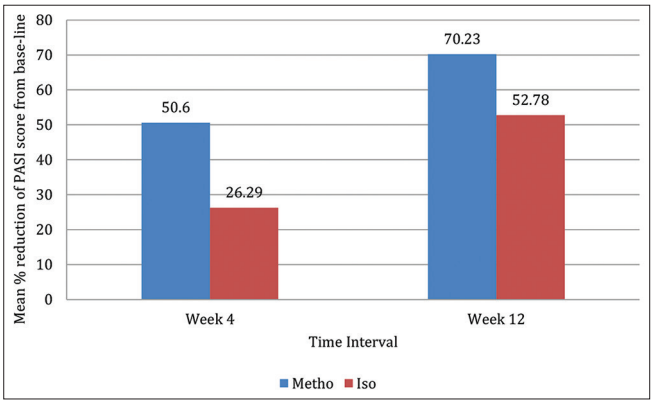

Figure 1: Mean percentage reduction in PASI score at both follow ups as compared to the baseline PASI score. PASI: Psoriasis area severity index

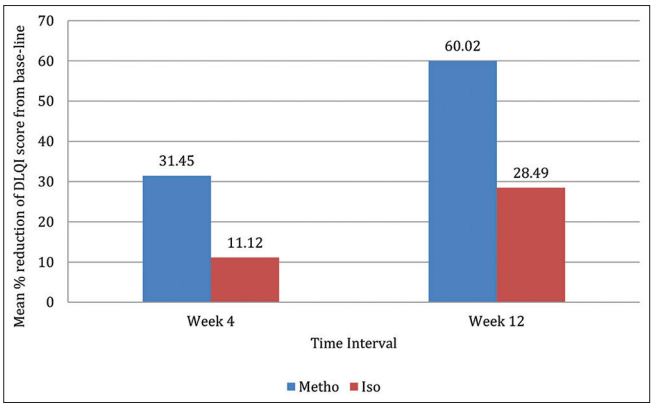

Figure 2: Mean percentage reduction in DLQI score at both follow ups as compared to the baseline DLQI score. DLQI: Dermatology life quality index

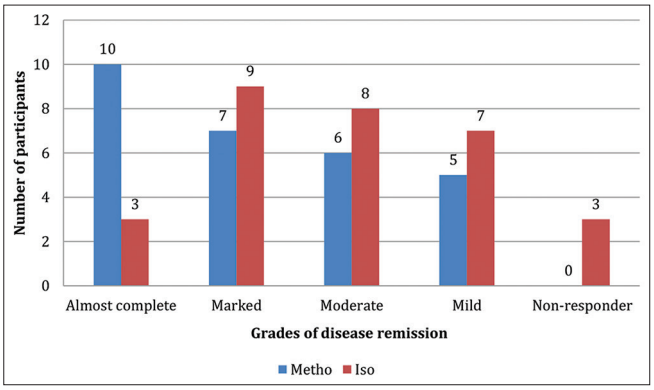

Figure 3: Number of participants having different grades of disease remission in both group at final follow up

females.[20-22] Fifty eight patients who completed this study comprised 20 females and 38 male patients aged between 22 years and 68 years (mean 44.23±5.02). The demographic profile in both the group was statistically comparable between them and with the previous studies reported.[22-26]

For the past 50 years, methotrexate has remained the gold standard of systemic care in psoriasis in spite of hepatotoxicity and hematological derangement. Many literatures proving its superior efficacy in psoriasis can be cited.[20-32] In a retrospective study conducted over 26 years on 157 patients suffering from extensive plaque or erythodermic psoriasis, Haustein and Rytter found long term, low-dose methotrexate to be sufficiently effective in 76% patients, moderately effective in 18% patients, and poorly effective in rest 6% patients.[15] Weinstein and Frost demonstrated more than 75% reduction in the PASI score at the end of 12 week's treatment in patients suffering from moderate to severe plaque psoriasis.[20] Kumar et al., studied 244 psoriatic patients treated with weekly oral methotrexate from 1981 to 2000 and found more than 75% improvement in 88% patients in 8.5±5.1 weeks.[31] Griffiths et al., found methotrexate to reduce the severity of psoriasis by at least 50% in at least 75% of patients.

The mean baseline PASI score in methotrexate group in our study was 14.29±5.23 and at the time of final follow-up after 12 weeks of treatment 35.71% of patients achieved almost complete remission, 60.71% patients achieved PASI 75, and 82.14% patients achieved PASI 50. This finding was in line with previous studies.[22,24,26]

Isotretinoin is considered more effective in pustular psoriasis than plaque psoriasis.[18,19,33,34] Anecdotal reports on its use in chronic plaque psoriasis suggest its effect suggest its efficacy on plaque psoriasis. Moy et al., compared isotretinoin with etretinate in moderate to severe psoriasis and observed moderate to complete response in 4 out of 10 patients treated with isotretinoin.[19] However, when combined with PUVA, Isotretinoin has shown equal efficacy to other retinoids.[35]

Very few studies comparing its efficacy with methotrexate is there. Abhinav et al., found it less efficacious than methotrexate at the end of 12 weeks in patients suffering from moderate to severe plaque psoriasis.[36]

The mean baseline PASI in isotretinoin group in our study was 14.29±5.23 and at the time of final follow-up after 12 weeks of treatment the mean percentage reduction in mean PASI score from baseline was 61.28%. 7 patients achieved marked to complete remission.

Finally, the mean percentage reduction of PASI score in the current study was higher in methotrexate group than in isotretinoin in both follow-up and the difference was statistically significant. This finding was similar with previous finding done by Abhinav et al.[36]

Gastrointestinal, thrombocytopenia, altered liver enzyme are well known adverse reaction of methotrexate which were observed in 18 patients receiving methotrexate. One

Table 2 : Grades of disease remission by PASI Score reduction

Grades of Improvement	% Reduction in PASI score
Almost complete remission	≥90
Marked improvement	≥75–90
Moderate improvement	≥50–75
Mild improvement	≥25–50
Non responder	<25

PASI: Psoriasis area severity index

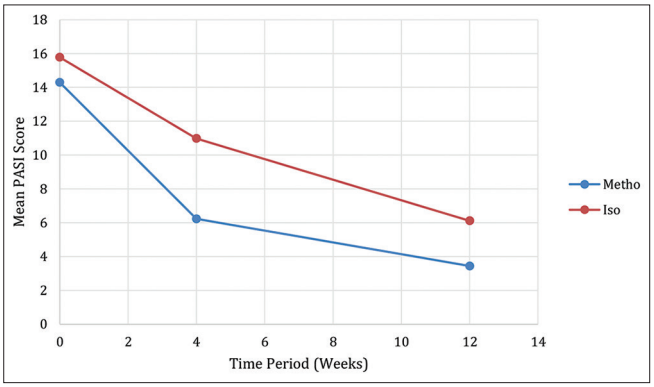

Figure 4: Drug causing faster reduction in mean PASI score. PASI: Psoriasis area severity index

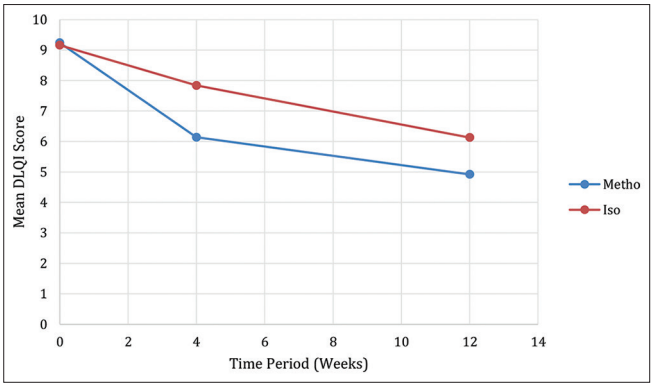

Figure 5: Drug causing faster reduction in mean DLQI score. DLQI: Dermatology life quality index

patient discontinued treatment for severe gastroenteritis. van Doore-Greebe et al., reported methotrexate-related side effects in their 73% patients among which 44% patients had altered liver enzyme and 43% experienced nausea.[21] Heydendael et al., also reported gastrointestinal adverse side effects in their 67% of participants receiving methotrexate among whom 65.52% had nausea.[23] Similarly, Akhyani et al., observed nausea (80%) and altered liver function test (33.3%) in majority of their subjects.[26]

Cheilitis (4), altered lipid profile (3), and dry skin/mouth (9), the well-reported adverse effect of isotretinoin was evident in 14 patients receiving isotretinoin in this study. No other serious adverse drug reaction warranting discontinuation of treatment was observed.

Two patients in our study were lost to follow-up in methotrexate arm. One patient stopped taking methotrexate due to severe vomiting reason related to methotrexate therapy. Another one patient in the same group was lost to follow-up.

CONCLUSIONS

From our study, we can conclude that isotretinoin is effective in managing patients suffering from moderate to severe plaque psoriasis and improving quality of life to some extent. Methotrexate is more effective in managing moderate-to-severe plaque psoriasis as well as improving quality of life. Methotrexate leads to a faster disease remission and faster quality of life improvement as compared to isotretinoin. Both the drugs are generally tolerated well though isotretinoin has fewer adverse effects than methotrexate. Further studies involving a larger sample size and extended follow-up duration are recommended before generalizing the finding to the general population.

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Authors Contribution:
SP- Concept and design of the study, manuscript preparation and revision; **AD-** Concept and design of the study, manuscript preparation and revision; **CG-** Concept, design, coordination, statistical analysis and interpretation, manuscript preparation and revision.

Work attributed to:
Department of Pharmacology, Department of Dermatology, Burdwan Medical College, Burdwan, Baburbag, Burdwan - 713 104, West Bengal, India.

Orcid ID:
Dr. Suhrita Paul - https://orcid.org/0000-0001-9942-4548
Dr. Abhijit Das - https://orcid.org/0000-0003-4045-697X
Dr. Chitrita Ghosh - https://orcid.org/0000-0003-2825-7273

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