INTRODUCTION

Lithium has been used as an active prophylactic agent in bipolar affective disorders (BPADs) for several decades. Systematic use leads to the improvement of the disease course. Lithium has been the focus of numerous investigations of its side effects. Most of the studies have been concerned with the effects of lithium on the heart, kidneys, and thyroid gland. Although lithium is notorious to cause cutaneous lesions, the literature on skin disorders secondary to lithium therapy is limited. Acneiform eruptions, psoriasis, maculopapular eruptions, and follicular eruptions are the most common cutaneous reactions to lithium. Lithium tends to increase the incidence of multiple cutaneous lesions among BPAD patients on lithium therapy. Incidence of cutaneous side effects directly correlates with the dose of lithium and therapeutic range of serum lithium level. Altering the dose of lithium does not statistically influence the cutaneous lesion.

Key words: Bipolar affective disorder, cutaneous lesion, dosage of lithium, duration of lithium, Indian studies, isotretinoin, lithium therapy, serum lithium level

Aim: To assess the incidence of cutaneous lesion in bipolar affective disorder (BPAD) patients on lithium therapy. To evaluate the relationship between duration of lithium therapy, dosage of lithium, serum lithium level, and cutaneous lesions. To assess whether reduction/stoppage of dose of lithium has any change in the course of cutaneous side effects. To look for a relationship between addition of isotretinoin and the course of mood disorder.

Methodology: We retrospectively collected hospital case records of 125 consecutive BPAD patients initiated lithium therapy, assessed with inclusion and exclusion criteria. We follow up them for 2½ years for the assessment of above said aims.

Results: The prevalence of skin reaction in BPAD patients with lithium therapy was 19.8%. Among patients on lithium therapy, cutaneous lesion emerged in initial 6 months and later after 1 year of treatment. Nearly 55% of patients on higher doses of lithium (1200 mg) had a cutaneous lesion. Patient on therapeutic serum level of lithium had a higher incidence of skin lesion. Out of six patients in whom dosage of lithium was reduced, three of them had reduced lesions \( (P = 0.6) \), in two patients, skin lesion increased, and one patient had no change. Among 11 patients treated with isotretinoin, only two patients had emergence of depressive symptoms.

Conclusion: Lithium continues to increase the incidence of multiple cutaneous lesions among BPAD patients on lithium therapy. Incidence of cutaneous side effects directly correlates with the dose of lithium and therapeutic range of serum lithium level. Altering the dose of lithium does not statistically influence the cutaneous lesion.

Key words: Bipolar affective disorder, cutaneous lesion, dosage of lithium, duration of lithium, Indian studies, isotretinoin, lithium therapy, serum lithium level

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to aggravate cutaneous conditions that are associated with the pathological findings of neutrophilic infiltration.[3]

The prevalence of lithium-induced skin reactions ranges between 3% and 34%.[3] Literature reveals that longer the duration of lithium therapy, more is the development of side effects.[4] However, occurrence of skin reaction may be seen as early as few days from the start of lithium therapy. Few studies highlight that most of lithium-induced side effects occurred when dosage of lithium was within 800/mg/200/mg.[4] However, there is no study on the relationship between cutaneous side effects and dosage of lithium. In previous studies, lithium-induced side effects occurred mostly within therapeutic range and a few above therapeutic range of serum lithium level.[5] However, in our clinical practice, we see skin reactions occurring within the therapeutic serum lithium level.

Literature shows that decrease in dosage of lithium results in reduced cutaneous side effects.[6] In our clinical practice, once skin disease occurs even reduction in lithium dosage does not reduce the cutaneous side effects. Controversial views have been seen in the use of isotretinoin for cutaneous lesion and the development of mood symptoms. Some studies show that mood symptoms and isotretinoin have no correlation.[6] On the contrary, many studies show worsening of mood symptoms and development of suicidal ideation with the use of isotretinoin, even with undercover psychiatric medications.[7,8]

With the available conflicting conclusions from the available literature, we proposed to do this study with the primary aim of assessing the incidence of cutaneous lesions in BPAD patients on lithium therapy. The secondary aims were to evaluate the relationship between duration of lithium therapy, dosage of lithium, serum lithium level, and cutaneous lesions. To assess whether reduction/stoppage of dose of lithium has any change in the course of cutaneous side effects. To look for relationship between addition of isotretinoin and the course of mood disorder. To the best of our Knowledge, this is the first study of this kind studying various parameters of association between lithium therapy and cutaneous lesion.

METHODOLOGY

Eligibility criteria
Our study participants were patients with diagnosis of BPAD who were on lithium therapy and patients who were newly started on lithium.

Inclusion criteria
All patients who were diagnosed as BPAD based on the International Classification of Diseases 10 criteria between the age group of 18–65 years who were on lithium were included in our study.

Exclusion criteria
Patients who had skin disease before starting on lithium, patients who were on medications known to cause skin disease, patients on other mood stabilizers (Divalproex sodium and Carbamazepine), and patient who did not come for follow-up (for a period of 2½ years) were excluded from our study.

Data collection process
We consequently selected 125 patients according to the date of registration with diagnosis of BPAD who were already on lithium therapy and who were newly initiated on lithium. We took their hospital records from medical record department and followed them for 2½ year. The following data for every patient were obtained - age, sex, socioeconomic status, duration of treatment with lithium, dosage of lithium, presence of cutaneous lesion including nature of the condition, serum level of lithium during the onset of cutaneous lesion, and response to lithium dose reduction.

We arbitrarily divided the dose of lithium into <800 mg, 800–1200 mg, and >1200 mg. We divided serum lithium level into three groups <0.8, 0.8–1.2, and >1.2 mEq/L in accordance with NICE guidelines. In patients receiving isotretinoin for skin disorder, we looked for the development of mood symptoms after initiating this therapy.

RESULTS

In the present study, out of 125 patients, 24 were excluded according to exclusion criteria (16 - no follow-up, 3 - were on multiple mood stabilizers, 4 - past history of skin disease, and 1 - patient on drug known to cause skin lesion). The remaining 101 patients were included in the study, among them twenty patients developed cutaneous lesions secondary to lithium therapy. Table 1 sets out the sociodemographic profile of these patients. Among these, twenty patients 60% were females and 40% were males. The mean age of participants was 37.4 (standard deviation - 11.17). The subjects belonged to different socioeconomic status.

In this study, a cutaneous lesion was considered as possibly secondary to lithium medication due to temporal correlation

| Variables                  | Mean (SD)/number of patients (n) |
|---------------------------|----------------------------------|
| Age (years)               | 37.4 (11.17)                     |
| Gender                    |                                  |
| Male                      | 8 (40)                           |
| Female                    | 12 (60)                          |
| Socioeconomic status      |                                  |
| Upper                     | 6 (30)                           |
| Middle                    | 7 (35)                           |
| Lower                     | 7 (35)                           |

SD – Standard deviation
between initiation of lithium and onset of skin lesion. The diagnosis of skin disease was based on a diagnostic examination by a dermatologist. Of the 101 lithium-treated patients, twenty (19.8%) were diagnosed with skin disorder secondary to lithium administration. Majority of the patients had acne or acneiform eruptions \((n = 11)\), three patient had psoriasis, and the remaining were diagnosed with other disorders which is listed in Table 2. One patient had both acne and alopecia.

Patients diagnosed with cutaneous lesions had been on lithium for a mean of 8.55 months, 11 (55%) developed skin reaction within 6 months duration, 1 (5%) developed skin reaction between 6- and 12-month duration, and 8 (40%) developed skin reaction after 12-month duration [Table 3]. Among patients who developed skin reaction \((n = 20)\), ten patients \((50\%)\) received >1200 mg of lithium [Table 4]. This shows that as the dose of lithium increases the frequency of skin lesion increases. Serum lithium levels taken during the onset of cutaneous lesion showed eight patients \((40\%)\) with low lithium level, ten patients \((50\%)\) were within therapeutic level, and 5% with high lithium levels (for one patient, serum lithium level was not available) which is shown in Table 5.

Out of twenty patients who developed skin lesion, in only 6 patients, the lithium dosage was reduced. Among which one patient had no change in skin lesion, in three patients (were on dermatological intervention), skin lesion reduced \((P = 0.6)\), and in two patients, skin lesion increased. Isotretinoin was given to 11 patients among them, nine of them remained euthymic and only two patients had depression (undercover of medications).

**DISCUSSION**

From various literatures, it is evident that lithium can exacerbate the existing skin lesion,\[^9\] so in our study, we excluded patients who were already having skin disease \((n = 4)\). Although we were able to exclude past history of skin disease, family history of skin disease was not available since it was a retrospective study. The overall incidence of cutaneous reactions secondary to lithium therapy in the study sample was 19.8% percent \((n = 20)\), which is less compared to 31% incidence in the previous study.\[^10\] This low incidence in the present study may be due to underestimation of skin reaction prevalence due to the fact that it was a retrospective study and only details entered in the case records were noted. Among the lithium-treated patients, females were found to be significantly more likely to report a secondary cutaneous condition. Studies have reported contrary prevalence among different sexes.\[^10\] Incidence of acne or acneiform eruptions was high when compared with other skin reactions in the present study which was comparable which previous review article.\[^11\] Psoriasis was the second most common of the skin lesion, which is in accordance with certain Indian studies.\[^12\]

In our study, most of the skin manifestations (55%) occurred within 6 months of start of lithium therapy. In contrary, a similar analysis in the comparison group revealed no statistically significant differences between the secondary cutaneous condition and the cutaneous condition-negative patients in terms of length of treatment.\[^10\] At this point, it is important to note that early emergence of skin reaction may result in noncompliance of lithium which in turn results in relapse and recurrence of mood disorder. Increase in a dosage of lithium had more prevalence of skin manifestations which was evident in our study (55% of patients with skin lesion were on lithium dose >1200 mg). Although reduction in skin lesion was noticed in three patients after reduction of lithium dosage, the \(P\) value was 0.6, meaning change in lithium dose and course in skin reaction once it has occurred and has no statistical significance. Hence, continuing the same dosage of lithium or reducing it to the lowest therapeutic serum lithium level after the onset of skin lesion may be advisable. Most of the patients receiving isotretinoin remained euthymic, similar results were seen in the previous study.\[^7\] Although there are contrary studies showing the use of isotretinoin resulting in depressive symptoms.\[^8\]
The major shortcomings of this study are that it is a retrospective study. Our sample size was small; hence, results should be interpreted with caution. Patients who were diagnosed with skin diseases were followed up by different dermatologist. It would have been better if same dermatologist examined the patients to study the improvement in skin lesion after reducing the dosage of lithium. Compliance of patient was exclusively analyzed only with records. A prospective study of cutaneous disorders associated with long-term therapy is warranted.

CONCLUSION

Lithium can increase the incidence of multiple cutaneous lesions among BPAD patients on lithium therapy. Incidence of cutaneous side effects directly correlates with the dose of lithium and therapeutic range of serum lithium level. It is an important clinical concept that clinician should be aware about skin reaction secondary to Lithium treatment and educate the patient about Skin reaction before starting treatment to improve the attrition rate. If the cutaneous side effect is mild, it should be treated topically. If the dermatoses under lithium treatment are severe, a reduction in the lithium dosage should be considered to the lowest therapeutic serum lithium level.

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Conflicts of interest
There are no conflicts of interest.

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