



ST PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE
SCHOOL OF PUBLIC HEALTH

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Pattern Of Treatment Outcome And Safety Of Prednisolone In The Treatment
Of Leprosy Reactions Among Leprosy Patients In Alert Hospital, Addis Ababa,
Ethiopia.

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LIST OF ACRONYMS

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AHRI	Armauer Hansen Research Institute
ALERT	All Africa Leprosy and tuberculosis Rehabilitation and Training center
BB	Mid borderline
BL	Borderline Lepromatous
BT	Borderline Tuberculoid
DM	Diabetic Mellitus
EHF	Eye Hand Foot
ENL	Erythema Nodosum Leprosum
FMOH	Federal Ministry of Health
GLU	Global Leprosy Update
HIV	Human Immune Virus
ILEP	The International Federation of Anti-Leprosy Associations
LL	Lepromatous
MDT	Multi-Drug Therapy
NFI	Nerve Function Impairment
OR	Odds Ratio
PI	Principal Investigator
RR	Reversal Reaction
SAE	Severe Adverse Events
SPSS	Statistical Package for Social Sciences
T1R	Type 1 Reaction
T2R	Type 2 Reaction
TT	Tuberculoid
TB	Tuberculosis
WHO	World Health Organization

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ABSTRACT

Background: Leprosy reaction is inflammation caused by the body's immune system attacking the leprosy bacteria. If left untreated or improperly managed, may lead to irreversible nerve damage causing mortality, disability, and physical deformities. Oral prednisolone is a recommended and widely used drug to manage these reactions. Despite this, the treatment outcome and safety of prednisolone in treating leprosy reactions as well as factors associated with clinical practices were not studied well. Thus, this study is conducted to assess the treatment outcome and safety of prednisolone in the treatment of leprosy reactions, and to assess associated factors or predictors in ALERT hospital.

Methods: A Hospital based retrospective chart review was conducted. The sample size was calculated by using Open Epi StatCalc and the total sample size required becomes 249. Based on inclusion and exclusion criteria 262 charts were selected and all was included in the study. Data were collected using data abstract form from patient medical records and entered into Epi- data version 4.0. All data were exported to SPSS version 25 for further analysis. Descriptive statistics was computed to get summary results and binary and multinomial logistic regression analyses were used to predict factors that affect the treatment outcome and safety of prednisolone.

Results: In this study 262 patients' record files were reviewed. The median age of study subjects was 30 years, with an IQR of 25–42.5 years. Two-third of study participants (66.8%) were males. This study shows that improvement with prednisolone treatment in leprosy reaction (T1R&T2R) was 62.2%. The odds of improved outcome with treatment of prednisolone increases by 6.9 fold for patients who have grade 0 WHO grading as compared to those having WHO grade 2 grading at the start of treatment which is statistically significant. According to the finding of this study among 262 patients 79.4% of the patients experienced at least one adverse event.

Conclusion: This study showed two fifth of patients with no improvement with prednisolone for both in type one and two reactions. WHO disability grading at start of treatment has a statistically significant impact on treatment outcome of prednisolone for treatment of leprosy reaction. This study also showed the percentage of adverse event associated with prednisolone treatment is high and the percentage increases significantly with duration and dose of prednisolone treatment without benefit for outcome of treatment.

Key Words: Leprosy, Leprosy reaction, Prednisolone, Treatment outcome, Effectiveness Safety, Adverse drug events/reaction, and Side effects.

1. INTRODUCTION

1.1 Background

Leprosy is an infectious disease caused by bacteria called *Mycobacterium Leprae* and predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disability (1). The diagnosis of leprosy is essentially a clinical one, based on finding one or more of the cardinal signs of leprosy. It should be made positively, and not by exclusion or by therapeutic trial (2). Even though the leprosy case has decreased dramatically to less than 1 case per 10,000 inhabitants in 2000 globally, in 2015 a total of 210 000 new leprosy patients were diagnosed worldwide (3).

Ethiopia is among 14 countries with high leprosy endemic, reporting more than 1,000 new cases annually. A total of 3,970 new leprosy cases (with 85% Multi-Bacilli) were registered in 2015 (4). Multi-drug therapy (MDT) is highly effective in treating leprosy and the infection is curable. However, about 30–50% of patients with leprosy experienced reactions that results in further complications (5). In Ethiopia Leprosy reaction affected approximately 46.8% of patients with leprosy infection (6). Leprosy reaction is inflammation caused by the body's immune system attacking the leprosy bacteria and may cause permanent damage to nerves and can affect the skin and other organs as well. If left untreated or improperly managed, reactions may lead to irreversible damage. Most of the deformities and disabilities in patients are primarily caused by the damage that results from leprosy reactions (7).

The two main types of leprosy reactions are Type 1 reaction (T1R), also known as reversal reaction (RR) and Erythema Nodosum Leprosum (ENL) or Type 2 reactions (T2R). T1R is characterized by an increase in inflammation in skin lesions or nerves or both, pain and sensitivity in nerves (neuritis), progressive neurological failure (8,9). T2Rs (ENL) are acute inflammatory reactions with multisystem disorder and other organ involvement includes iritis, arthritis, lymphadenitis, orchitis, and neuritis in addition to the skin.

Corticosteroids have been used in the management of leprosy reactions for over several years and oral prednisolone is the most common treatment for severe reactions (2). Even though prednisolone is recommended standard treatment regimen, studies showed variable results on the effectiveness of prednisolone in treating leprosy reactions. Results of observational study showed prednisolone is not effective enough to restore nerve function in T1R. Findings from randomized controlled trial (RCT) reported better improvement with prednisolone (10–13).

The safety of prednisolone is a significant issue and should be given due consideration. The use of potent immune suppressants is a potential risk in areas endemic for severe infections. Prolonged and high dose of prednisolone in severe and frequent recurrence reactions in leprosy patients raises the issue of a safety concern as it is usually associated with serious adverse drug events (ADEs) (12,14,15).

In Ethiopia Prednisolone is the first-line drug in both types of reactions. Recurrence and flare-up are still challenging in clinical practices and to manage these, additional and high doses of prednisolone are usually prescribed (4). Even though the prevalence of reactions is high and steroid is widely used, the treatment outcome and safety of this drug are uncertain as it was not studied. Thus, this study is aimed to assess the treatment outcome and safety of prednisolone along with predictors associated with them in the treatment of leprosy reactions.

1.2 Statement of Problem

Leprosy reaction is an immunological response to the *Mycobacterium leprae*, it can occur before, during, or after treatment with MDT. T1Rs cause Nerve Function Impairment (NFI) in about 30% of patients with reaction (16). On other hand ENL affects up to 5% to 40% of patients with leprosy (17). Estimated mortality rate is 1.4% and 8.1% in T1R and T2R respectively (16). The reaction also leads to disability and deformity in leprosy patients that exposes them to many social problems like social stigma and discrimination. Thus, to manage the impacts of the reactions, prednisolone is recommended by WHO and is the commonest drug being used in many countries including Ethiopia. Despite prednisolone being widely used, Results of the observational study reported the limited effectiveness and safety of this drug that made the management of leprosy reactions remains challenging (10,11). Relatively findings from the randomized controlled trial (RCT) reported better improvement with prednisolone(13,19). Prednisolone is more effective in treating T1R in the skin than nerve, recovery rates in skin signs (88%) but improvements in nerve function; sensory (49%) and motor nerve (74%)(19). In T2R/ENL, prednisolone does not prevent recurrences and usually, an ENL flare-up occurs when doses are decreased to 20-30mg per day (20–22).

Oral prednisolone, the drug of choice, has frequent side effects and approximately 40% of individuals do not show clinical improvement (10). The adverse effects of corticosteroids are significant, the long-term beneficial effects are uncertain, and the optimal therapeutic regimen has not been established (23). To treat reactions long term and high dose of prednisolone is usually required, but its long-term use is a potential risk for severe infections

and other ADRs . (24)It was reported that long-term use of 30mg to 100mg prednisolone can cause severe side effects. (12,14,25).

In Ethiopia prevalence of leprosy reactions are high, T1R ranges from 28.7% to 47% while T2R accounted for 18.1% to 31.7% and managing these reactions remains challenging in clinical care (6). As observed from clinical practice, prednisolone is not sufficient enough to control reactions, and recurrence of reaction episodes is more common for an unknown reason. Thus, an additional and high dose of prednisolone is usually prescribed for the long term may increase the risk of steroid complication. Despite these, there is no recent study done on the treatment of leprosy reaction with prednisolone, thus, its treatment outcome and safety in clinical practices and factors or predictors associated is unknown.

1.3 Significance of the study

This study revealed the Treatment outcome and safety of prednisolone in the management of leprosy reactions. The findings of this study provides clinicians practicing in ALERT and several others clinicians working in Leprosy clinic with evidence of the outcome pattern and safety profile of prednisolone in the treatment of patients with leprosy reaction and their associated factors which will help them as a evidence for dealing with the challenge they are facing in patient care. It is also an input to health policymakers in Ministry of health and other non-governmental organization working on Leprosy program. Finally, it serves as an input to researchers in Armauer Hansen institute, ALERT hospital and other similar institute working in the area for future researches.

2. LITERATURE REVIEW

In this chapter, the literature related to leprosy reactions and their management is reviewed. To give brief background information, the literature started with a review of an overview of leprosy and leprosy reactions. Then types of leprosy reactions with their management were described, and lastly, treatment outcome and safety with associated factors were reviewed.

2.1 Overview of Leprosy Diseases

Leprosy, or Hansen's disease (HD), is an ancient bacterial disease that, although curable, continues to be a significant health problem in many parts of the world. Leprosy is an infectious disease caused by *Mycobacterium Leprae* and predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disability (26). Leprosy may also involve sites such as the eyes, mucous membranes, bones, and testes and produces a spectrum of clinical phenotypes(27). It also affects all age groups and both gender, depending upon the opportunities and levels of exposure, poor living condition, and inadequate nutrition (28)

The registered prevalence of leprosy (the number of cases on treatment at the end of 2020) was 129 192, with a rate of 16.6 per million population. (29). Globally, 127 396 new cases were reported, for a case detection rate of 16.4 per million population. Both figures were much lower than in previous years, with a 27.7% reduction in registered prevalence and a 37.1% reduction in new cases as compared with 2019. This change is probably due to less detection and reporting during the COVID-19 pandemic. Only 127 countries (of 221) provided data in 2020, as compared with 160 in 2019. Data from all 23 global priority countries⁴ were received for 2020 (29).

more than five skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions (1). Based on immunity, Ridley-Jopling (1966) categorized leprosy patients into a spectrum with polar tuberculoid (TT) and lepromatous (LL) forms and middle types of borderline tuberculoid (BT), mid borderline (BB), and borderline lepromatous (BL) leprosy. It assists the understanding of the disease and is usually used in research settings. Patients with different disease types exhibit different immunological responses to *M. leprae* that will result in many complications (30).

Globally, leprosy ranks as the top cause of permanent disability among infectious diseases. In Ethiopia Nationally, more than 30% of new cases present with grade 1 or 2 disability at the

time of diagnosis. Annually, around 3000-4000 new cases have been reported and registered in Ethiopia, with no decline in incidence in the past 20 years. The Prevalence of Leprosy has sharply declined from 19.8/10,000 in 1983 to 0.3 in 2016, following the introduction of Multi-Drug Therapy (MDT). Ethiopia is among 14 countries high leprosy endemic reporting more than 1,000 new cases annually(4).

2.2 Leprosy Reactions

Reactions are acute exacerbations of signs and symptoms of leprosy occurring during the natural history of the disease affecting skin, nerves, eyes, or limbs. Left untreated or improperly managed, reactions can lead to nerve function impairment (NFI) and subsequently to disabilities(7).

Leprosy reactions affect 30 to 50% of patients with leprosy; they are inflammatory conditions that often appear at the initiation of treatment. However, they may occur at any time during the course of the disease(31). According to WHO Reactions may cause permanent damage to nerves and can affect the skin and other organs as well. Inflammation in a skin patch can be uncomfortable, but it is rarely very serious. Inflammation in a nerve, on the other hand, can cause serious damage, with loss of function caused by swelling and pressure in the nerve (7)

As stated in ministry guideline the two main types of reaction are Type 1 (Reversal) Reaction and Erythema Nodosum Leprosum (ENL), also known as Type 2 Reaction. Both types of leprosy reactions can occur before the start of treatment, during treatment, and after release from treatment (39).

2.2.1 Type 1(Reversal) Reaction

Type 1 (Reversal) reactions (T1Rs) occur when the body's immune response suddenly starts to become more active in attacking the leprosy bacilli in the body. T1Rs may occur before or during multidrug treatment (MDT) or even after it has been completed, but the commonest time for its occurrence is during the first 3 to 6 months of treatment (7).

According to studies type 1 reaction is due to an increase in cell-mediated immunity and a delayed-type hypersensitivity reaction to *Mycobacterium leprae* antigens. It is characterized by an increase in inflammation in skin lesions or nerves or both, pain and sensitivity in nerves (neuritis), progressive neurological failure (8,9) T1Rs predominantly affect the borderline states of leprosy(32), but small numbers of patients with the polar forms of leprosy may also experience T1Rs (33). In Brazil, a study of multi-bacillary patients in T1Rs found that 59.5% were BL patients, 33.4% were BB, and 7.1% were LL (34).

T1R is characterized by skin lesions that become erythematous and/or edematous and may ulcerate, edema of the hands, feet, and face can also be a feature of a reaction but systemic symptoms are unusual. Even though inflammation of the skin in T1R is self-limiting, it is very often accompanied by neuritis, which can have serious consequences, including permanent nerve damage, impairment, and disability. A T1R in the skin may therefore be taken as a possible pointer of impending neuritis (8).

Studies has been done on epidemiology of T1R along with the risk factors, to promote early medical intervention or prevent their occurrence. A study in Bangladesh showed that T1Rs are a major cause of nerve function impairment (NFI) in leprosy and affect up to 30% of susceptible individuals (32). The recurrence of T1Rs becomes a clinical and therapeutic problem, especially when they happen after treatment. But T1Rs tend to recur less than type 2 reaction and it was confirmed that approximately 33% of patients experience recurrence of reaction episodes after chemotherapy(8).

Multi-countries literature review identified the prevalence of T1R in different countries. Accordingly, in Malawi (35.7%), Vietnam (29.1%), Thailand (19.9%), Bangladesh (17%) and Ethiopia (16.5%) T1Rs reported (15). But recent studies done in Ethiopia reported a higher prevalence of T1R; out of 312, about 47% of patients developed T1R, from which about 1.4% died of T1R ($p = 0.0168$) (18) and other studies revealed that T1R accounted for 28.7% from 513 leprosy cases (6)

2.2.2 Type 2 Reactions

Type 2 reactions (T2Rs) or also known as Erythema Nodosum Leprosum (ENL) are acute inflammatory reactions with systemic involvement, entailing the activation of pro-inflammatory cytokines. In recent years, studies have suggested that cellular immune response is also a factor in triggering ENL episodes. Type 2 reaction affects other organs, in addition to skin, and coexists with systemic symptoms (8). The reaction or ENL can involve neuritis and NFI. A retrospective study done in 94 patients who had attended a “neuritis clinic” at a leprosy referral center in Nepal showed that ENL resulted in enlarged or tender nerves (99%), new and/or old nerve function impairment (NFI) (88%) and fever (78%), (35).

The impacts of ENL are usually high. People who have ENL usually feel ill and many organs may be affected. Erythema nodosum leprosum is often a recurrent or chronic condition and requires treatment for a long period. Having repeated episodes causes many burdens (health, social and psychosocial impacts) on patients. It may affect male fertility due to inflammation

of the testis. Women are affected by having fewer treatment options in their childbearing years due to the side effects of drugs such as thalidomide (36). Visible disability and deformity from reactions or side-effects from treatment trigger discrimination and stigmatization (37).

The incidence of ENL varies in different cohorts, from 5% (17) to 40% (36). The incidence also varied between countries: 5% in Ethiopia; 19%-26% in India, Nepal, and Thailand; and 37% in Brazil (7). However, previous studies conducted in Ethiopia showed higher figure than the WHO report; T2R/ENL was 18.1% from 513 leprosy cases(6) and another study also reported that of 312, 31.7% patients developed ENL from which 8.1% died ($p = 0.0168$) (18) Type 2 typically occurs in BL and LL patients develop when treatment begins. As the study showed, the rate of ENL in LL patients ranged between 11.1% and 26%, and in BL patients between 2.7% and 5.1% (38).

2.3 Management of Leprosy reactions

The management of leprosy reaction is started with the identification of types of reaction. The treatment strategies differ based on the types of reactions. As both T1R and ENL are immunological processes, their treatment is based on an immunosuppression mechanism. Corticosteroids remain the mainstay of treatment of reactions and have been used in the management of leprosy reactions for several years. Oral prednisolone is the most common treatment for severe reactions (2).

2.3.1 Treatment of Type 1 Reactions (T1R)

The treatment of T1Rs or RR is aimed at controlling acute inflammation, easing pain, and reversing nerve damage. MDT should be initiated in those presenting with a T1R or continued in those who develop a reaction whilst on it (15).

As WHO recommended, RR/T1R should be treated with a course of steroids, usually for 3-6 months duration. The standard regimen for treating T1R is oral prednisolone with an initial dose of 40mg daily, then the dose gradually tapered by 5mg every 2-4 weeks after evidence of improvement, and usually given for 12 to 20 weeks in total. In severe T1R, the starting dose of prednisolone maybe 60mg and above (1).Our national guideline also recommends similar starting dose and duration of therapy(39).

If the reaction is mild and there is no evidence of neuritis, analgesics such as acetylsalicylic acid or paracetamol are usually sufficient. In the presence of nerve involvement, analgesics and oral prednisolone is used at a dose of 40-60 mg daily with gradual tapering for at least 3–

6 months(1)). Cyclosporin is another option when steroids are not usable (22). In one study in which Azothioprine was assessed, efficacy in type 1 reaction was not demonstrated (40)

2.3.2 Treatment of Type 2 Reactions (T2R)

The incidence of type 2 reaction has decreased after the addition of clofazimine to MDT with an anti-inflammatory effect (41). If there are no findings of neuritis, supportive treatment care with aspirin, indomethacin, and paracetamol may be administered. Prednisolone (0.5–1 mg/kg/day) is the first choice if neuritis is present. When the reaction is decreased, the dose should discontinue by reducing the dose in time. However, frequently the reactions relapse during dose reduction. In this case, thalidomide, clofazimine, and pentoxifylline can be used as adjuvants (1).

For treatment of ENL, steroids are advised during the acute phase. For cases that show recurrence or chronicity, the treatment needs to be fortified with clofazimine, which has known anti-inflammatory action. At start 100 mg of clofazimine three times a day; then the dosage is subsequently tapered over 36–48 weeks depending on the severity and chronicity of the reactions,' (1). The reaction can be rapidly controlled by using thalidomide 300–400 mg/day, however, due to its teratogenicity, attention should be given to using thalidomide in women who have childbearing potential (42). Pentoxifylline is used as 400 mg three times daily. Compared to clofazimine, a study showed that pentoxifylline effectively reduced the initial severity, while clofazimine showed a slow but sustained effect (43). Resistant erythema nodosum leprosum cases can be treated successfully with methotrexate, infliximab, and etanercept (44).

2.4 Treatment outcome of Prednisolone in treatment of Leprosy Reactions

Corticosteroids are widely used for the treatment of leprosy reactions and their complications. However, the data concerning the Treatment outcome of treatment with steroids show a range of outcomes. The treatment outcome of prednisolone in treating reactions also varies concerning types of reactions

2.4.1 Treatment outcome of Prednisolone in Type 1 Reactions

Regarding T1Rs, there is a range of evidence on the treatment outcome of prednisolone from observational and Randomized Clinical Trial (RCT) studies. As a finding of a retrospective study in India showed, of an outpatient treated with prednisolone, only 50% of patients with T1Rs were judged to have improved nerve function (11). Again, a prospective cohort study in Bangladesh identified even less improvement in the course of steroid treatment. Of those

treated with prednisolone, only 33% and 37% of patients got full recovery of motor and sensory nerves function respectively whereas 31% and 32% didn't respond to prednisolone (failed to improve). Moreover, 12% of the motor and 13% of the sensory nerves further deteriorated despite treatment (10). Another prospective cohort study found that a six-month course of prednisolone resulted in no improvement in 27% of patients (45).

Even though WHO recommends prednisolone for treatment of T1R, evidence from studies showed that in a significant number of patients there was no improvement in nerve function impairment (NFI) and have multiple episodes of T1R (RR). The result of Cochrane systematic review identified that "evidence for the efficacy of corticosteroids is lacking, and the optimal dose and duration of treatment is unclear for treating nerve damage in leprosy reactions"; and indicated a need for larger, well-controlled randomized studies (46)

In addition to observational studies, RCTs were conducted to assess the effectiveness of steroids in the management of T1Rs (RR). A multi-centered randomized controlled trial was conducted to evaluate the difference between the effectiveness of prednisolone at 20 or 32 weeks of treatment duration. Then the proportion of patients with restored or improved nerve function at week 78 was 78.1% and 77.5% respectively ($p = 0.821$) which showed an insignificant difference between the two courses of treatments. Thus the 20-week course is sufficient to improve nerve function in 78% of patients with recent NFI. Approximately 16% and 15% of patients required additional prednisolone in arm week 20 and 32 respectively to treat new or deteriorating NFI and reactions (13). In addition, small size RCT of ciclosporin versus Prednisolone in the management of new type 1 reaction, revealed that recovery rates with prednisolone, in skin signs (88%) and improvements in nerve function sensory (49%) and motor nerve (74%). In cyclosporine group recovery rates with cyclosporine, in skin signs (91%) and improvements in nerve function sensory (66%) and motor nerve (75%) but the difference is not significant (12).

Regarding duration and doses of prednisolone in treating T1R, multi-centered RCT conducted in India showed that; "in case of a low dose of prednisolone started at 30 mg/day and gradually tapered until 5 months (total 2310 mg), 31% patients needed extra prednisolone at end of 12 months compared to and 24% in case of high-dose prednisolone regimen (3500 mg). But 46% of participants in the short-regimen group (2940 mg over three months) needed additional prednisolone," (47).

The results of RCT showed that the effectiveness of prednisolone in treating NFI and T1R ranges from 60-70%. New NFI (less than six months duration) has better rates of recovery than old NFI, and courses of prednisolone of 20 weeks or longer are better than 12 weeks courses. Recurrence of NFI and T1R are common, occurring in 30-50% of patients, and extra prednisolone is often needed to control signs of T1R. These longer courses of prednisolone put patients at higher risk of adverse events (48).

2.4.2 Treatment outcome of Prednisolone in Type 2 Reaction

Type 2 reactions or Erythema Nodosum Leprosum (ENL) is a serious complication of leprosy. It is normally treated with high-dose steroids, but its recurrent nature leads to prolonged steroid usage and associated side effects. The evidence from the study showed that prednisolone does not prevent recurrences and usually, an ENL flare-up occurs when prednisolone doses are decreased to 20-30mg per day (20).

In addition, due to resistance to prednisolone, higher doses of prednisolone are needed to control ENL flare-ups. Resistance to prednisolone or under-treated ENL results in further complication by the occurrence of NFI. NFI in patients with ENL may be under-treated if the short ENL regimes are followed. Longer periods of steroid treatment for NFI are more effective (47)

Comparative efficacy of thalidomide and prednisolone in the treatment of moderate to severe ENL has done in India identified the recurrence rate of reaction is high with prednisolone compared to thalidomide. Only 6% (2/28) of patients had recurrence after ceasing thalidomide, after 6 and 9 weeks each, whereas 67% (22/30) patients had recurrences 6 to 9 weeks after ceasing prednisolone. Almost 77% (17/22) of patients in prednisolone arms had a recurrence of ENL within 6–8 weeks of stopping treatment. Approximately 23% (5/22) of patients had recurrence when the dose of prednisolone was tapered to 10 mg/day. The mean period of remission with thalidomide and prednisolone were 10.92 months and 2.23 months respectively, over a total study period of 1 year (21).

Although high dose prednisolone is efficient in controlling the signs and symptoms of ENL within a few days, it is not efficient in preventing frequent flare-ups (47). Another study measured the efficacy of prednisolone by the mean number of ENL recurrence (ENL flare-up episodes) and time to ENL recurrence. This study showed that chronic ENL experienced more episodes of ENL recurrence than new ENL. The mean number of recurrence of ENL was 2.4 recurrences per patient in new ENL and 2.0 in chronic ENL. Regarding time to

recurrence, for patients with acute ENL, the mean time to the first episode of ENL recurrence was 9.2 weeks while 11.25 weeks for chronic ENL cases. Thus at week 32, for new and chronic ENL, 36% and 35% more additional prednisolone to treat ENL recurrence was needed respectively (22).

2.5 Factors Affecting Treatment outcome of Prednisolone in Leprosy Reactions

A randomized study of three different prednisolone regimes conducted in India in six leprosy treatment centers suggested that duration of treatment, rather than the starting dose of prednisolone, maybe more important in controlling T1Rs. Prednisolone 30mg tapered slowly to zero over 20 weeks was superior to prednisolone 60 mg tapered over 12 weeks Treatment (dose and duration), patient and diseases characteristics were identified to be linked to outcomes of prednisolone treatment (47).

In the same study the risk of needing additional corticosteroids was significantly less with the high-dose (60mg/day) five-month course than with the three-month course. Additionally, the risk of needing extra corticosteroids was just significantly less with the low dose (30mg/day) five-month course than with the three-month course. It was estimated that about 46% of participants in the short regimen (three months) needed additional prednisolone. The study confirmed that a longer duration of prednisolone treatment requires fewer additional steroids to control type 1 reactions than a short course of prednisolone. Duration and doses of prednisolone were identified to be associated with effectiveness.(47)

The response to corticosteroid treatment seems to depend on the severity and duration of nerve function impairment (NFI) before the start of treatment. It also reported that for people with complete motor paralysis or moderate motor impairment, 11% and 55%, respectively, recovered to good function. In the treatment of mild sensory impairment, a significantly higher proportion of participants improved with the prednisolone after four months and the difference disappeared by the six-month follow-up (46). Another study revealed that 50% of patients with acute NFI (less than six months) would recover nerve function if steroids were used for a median time of 6.5 months, but the maximum time to nerve recovery could be as long as 45 months (45). There is also evidence that shows the effectiveness of prednisolone is also affected by types of the dosage form. The study conducted in Nepal revealed that individuals treated with methylprednisolone were less likely than those treated with prednisolone alone to experience deterioration in sensory function between day 29 and day 113 of the study (50).In contrast, some studies reported that there was no significant

difference in the effectiveness of prednisolone regarding the duration of treatment. The study done in four Asian countries identified that the difference in the effectiveness of prednisolone in 20 weeks and 32 weeks of a course of treatment was not significant(13).

In multicenter RCT done in Nepal, Bangladesh and Indonesia, several predictors associated with the effectiveness of prednisolone were identified. Weight, body mass index (BMI), gender, WHO disability grade, and Eye-Hand Foot (EHF) score demonstrated a significant correlation with improvement and restoration from NFI in patients treated with prednisolone. However, WHO classification, Ridley-Jopling classification, BI (skin smear), and the presence or absence of severe Type 1, Type 2 reaction and treatment arms (duration) were not significantly correlated with treatment effectiveness (13).

2.6 Safety of Prednisolone in Patients Undergone Treatment of Reaction

The use of potent immune-suppressants is potentially problematic in areas endemic for severe infections such as tuberculosis. The First European Workshop on Glucocorticoid Therapy designated doses of prednisone between 30 mg and 100 mg, as 'high doses' are associated with severe side effects over long-term use. This group also considers that side effects are considerable and dose-dependent at 'medium doses' of between 7.5mg and 30 mg (14).

Prolonged and high dose of prednisolone in severe and frequent recurrence reactions in leprosy patients raises the issue of safety concern. There is evidence concerning the long-term sequelae of corticosteroids used to treat patients with T1Rs. Corticosteroids cause bone demineralization leading to osteoporosis. This is a dose-dependent phenomenon and the rate of loss of bone mineral density is considerable in the first 6 months of steroid therapy (15)

Findings from a retrospective study showed that prednisolone is associated with different ADEs. As a study in the United Kingdom reported, out of patients treated with prednisolone for ENL, overall 35% of patients developed ADEs while on treatment; gained weight (27%), Cushingoid features (15%) and steroid-induced diabetes (11%) were reported. One patient developed listeria monocytogenes meningitis which was attributed to steroid use (51). Another study in India also found out that, of 581 patients with T1R, 2.2% developed diabetes requiring an oral hypoglycemic agent during the initial phase of treatment with corticosteroids (15).

Several RCT studies reported long-term steroid therapy in leprosy reaction resulted in the occurrence of adverse drug reactions or events (ADRs/ADEs). A study (RCT) done in Nepal

identified that, from patients treated with prednisolone, 54.5% of participants experienced at least one adverse event. Most identified ADEs were minors; moon face (9.1%), acne (22.73%), gastritis (22.7%), and weight gain (4.5%), while glaucoma (4.5%) was reported as serious ADE (50).

Another RCT conducted in Nepal and Bangladesh also reported the occurrence of ADRs with the use of prednisolone. According to the findings of this study, from 401 patients who have taken prednisolone, 20% and 2% experienced minor and major ADEs respectively. Common observed majors ADEs were; peptic ulcer (0.5%), Diabetes (0.7%), infections (0.5%) and infected ulcer (0.2%). Minor ADEs identified were moon face (3%), acne (2%), fungal infection (1%), and gastric pain (18%)(52).

Multi-centered RCT in India, Bangladesh, Nepal, and Indonesia assessed ADEs at 20 and 32-week courses of treatments and reported both severe and minor events. Severe adverse events (SAE) occurred in both groups but were more often reported in the 32-week arm: 12 cases (2.7%) in the 32-week arm and four cases (0.9%) in the 20-week arm. This difference was statistically significant ($p = 0.04$). The main reported SAE's were hypertension 6 (0.7%), diabetes 6 (0.7%), and peptic ulcer 2 (0.23%) from 868 patients: all commonly recognized side effects associated with prednisolone treatment. Minor side effects were reported in 66% in the 32-week arm and 68% in the 20-week arm. In addition to ADRs, seven deaths, 3 in the 20-week arm and 4 in the 32-week arm were reported (13). Another RCT showed that many patients had one or more adverse drug events (ADE) attributable to prednisolone. Accordingly, minor ADEs reported were moon face (33.3%), acne (42.4%), fungal skin infections (45.5%), and dyspepsia (57.6%). The major ADEs were elevated blood sugar/diabetes (12.12%), anxiety (3%), and infections (69.7%), (22).

Adverse events related to long-term use of corticosteroids were also studied in other cases than leprosy reactions. A prospective study conducted on 88 patients in a French center assessed the frequency and risk factors of clinical adverse events occurring during prednisone therapy ($\geq 20\text{mg}$) for at least 3 months. As reported by this study, 71% of patients developed at least one adverse event. Lipodystrophy [63.0% (51.0–73.1)], neuropsychiatric disorders [52.5% (41.0–63.8)], skin disorders [46.2% (35.0–57.7)], muscle cramp [32.5% (22.5–43.9)], proximal muscle weakness [15% (8.0–24.7)], newly developed hypertension [8.7% (2.9–20.3)] and menstrual disorders in premenopausal women [39% (19.7–61.4)] were reported (53).

Additionally, a cross-sectional study done on 820 participants in France, identified frequency of ADEs with use of prednisolone 20mg [10mg - 48mg] over 3 or more months were insomnia (58.2%), mood disturbances (50.1%), hyperphagia (49.0%), and lipodystrophy (47.2 %), (54).

In general, studies reported 35% to 71% of patients developed at least one adverse event when treated with prednisolone for 3 months or more.

2.7 Factors Associated with Safety of Prednisolone

Prednisolone is a potent corticosteroid which possesses about four times the anti-inflammatory activity of hydrocortisone while causing less salt and water retention. Close supervision is recommended for patients receiving the agent. Doses should be individualized according to the severity and prognosis of the disorder, patient response and the anticipated duration of therapy. Furthermore, the dosage should be minimized to balance control of specific symptoms with reduction of undesirable effects.

Several risk factors or predictors were identified to be associated with adverse effects that occurred during prednisolone therapy. As a study in France reported, sex (female), age (young and elder), dose, duration, and history of long-term prednisolone were associated with prednisolone-related ADRs/ADEs. Each factor linked to specific ADEs; lipodystrophy was higher in women, younger subjects and increased with the cumulative dosage of prednisone; cutaneous disorders were observed more frequently in women and tended to increase with age; muscle cramps decreased with age and tended to be high in women (53)

2.8 Conceptual framework

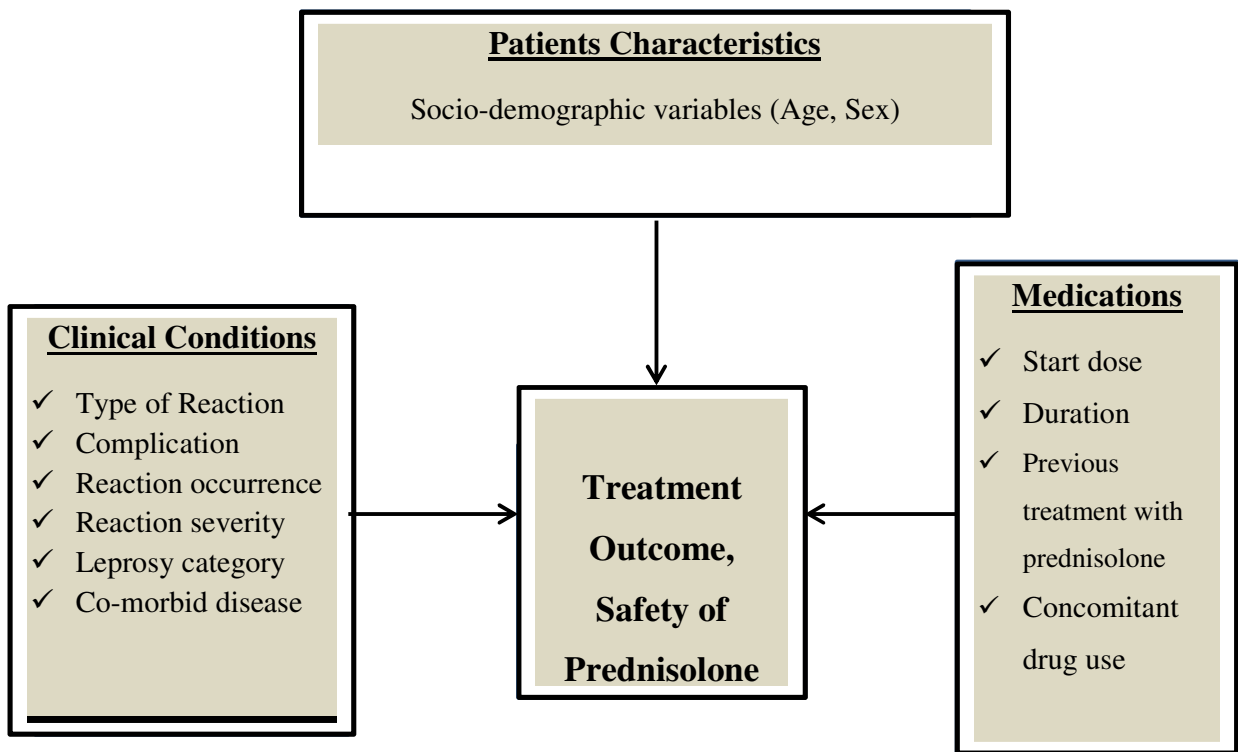


Figure2. 1 - Conceptual framework prepared by the PI after reviewing relevant literatures, showing the relationship of dependent and independent variables

3. OBJECTIVE OF THE STUDY

3.1 General Objective

To assess the Treatment outcome and safety of prednisolone with their associated risk factors in the treatment of Leprosy reaction among leprosy patients treated at ALERT hospital, Addis Ababa, Ethiopia.

3.2 Specific Objectives

- To assess the Treatment outcome of prednisolone in the treatment of leprosy reactions among patients treated in ALERT Hospital
- To assess the safety of prednisolone in patients treated for leprosy reactions in ALERT Hospital
- To identify factors associated with the Treatment outcome and Safety of prednisolone in the management of reactions in leprosy patients in ALERT Hospital

4. METHODS AND MATERIALS

4.1 Study Setting

The study was conducted in ALERT Centre, which is located 7km southwest of Addis Ababa, Kolfe Sub-city, on Jimma Road, around Zenebework. ALERT was established in 1934 and has been administrated by the Federal Democratic Republic of Ethiopia's MOH since 2002. ALERT Centre has Hospital, Training Centre for leprosy and tuberculosis (TB) and is associated with the Armauer Hansen Research Institute (AHRI), established in 1970, specializing in biomedical research related to TB, leprosy, leishmania, meningitis, HIV, and cholera. Currently, the center enrolls about one hundred (100) patients for treatment of leprosy per year according to annual report of the RED clinic/Leprosy clinic. In addition to the above the hospital provides specialized and all general health care services for 1.5 million estimated populations. ALERT hospital is the national referral center for leprosy-related complications and it is a large facility containing all leprosy-related specialties: Dermatology, Ophthalmology, Orthopedics, Orthotics, Plastic Surgery, Physiotherapy, Occupational Therapy, and a Rehabilitation Program including functioning laboratory and pharmacy.

4.2 Study design

A Hospital based retrospective chart review was conducted . The records of all leprosy patients who were treated for reactions with prednisolone from the calendar year of July 2017 to July 2022 were reviewed for evaluation of treatment outcome and safety.

4.3 Source population

All leprosy patients who were registered in the treatment logbook at ALERT Hospital

4.4 Study population

All leprosy patients who developed leprosy reactions and had been treated with prednisolone in the hospital from the calendar year of July 2017 to July 2022

4.5 Inclusion criteria

All patients who were treated with prednisolone for leprosy reactions in the hospital during the study period whose treatment outcomes were recorded were included.

4.6 Exclusion criteria

All patients with leprosy reactions who did not complete the treatment were transferred out to other health facilities and those whose treatment outcome was not evaluated/ recorded were excluded.

4.7 Sample size and sampling procedure

The sample size was calculated using OpenEpi StatCalc for this retrospective cohort study design. The calculated sample size for the cohort study was 249.

Figure 4.1 Sample size calculation

Sample Size for Frequency in a Population	
Population size(for finite population correction factor or fpc)(N):	700
Hypothesized % frequency of outcome factor in the population (p):	50%+/-5
Confidence limits as % of 100(absolute +/- %)(d):	5%
Design effect (for cluster surveys-DEFF):	1
Sample Size(n) for Various Confidence Levels	
ConfidenceLevel(%)	Sample Size
95%	249
80%	134
90%	196
97%	282
99%	341
99.9%	426
99.99%	479
Equation	
Sample size $n = [DEFF * Np(1-p)] / [(d^2 / Z^2_{1-\alpha/2} * (N-1) + p * (1-p))]$	

Based on inclusion and exclusion criteria, two hundred sixty-two (262) charts were selected, and all were included in the study.

4.8 Study Variables

4.8.1 Dependent Variable

- Treatment outcome
 - ✓ Improved
 - ✓ No Change/Same
 - ✓ Deteriorated
- Safety of treatment (Yes/No)

4.8.2 Independent Variable

- Socio-demographic variables (Age, Sex)
- Leprosy reactions type 1 and 2
- Occurrence of reaction New/Recurrence
- Reaction severity / WHO disability grade
- Leprosy Category – WHO Classification
- Leprosy Category - Ridley-Jopling classification (LL, BB, BL, TT, BT)
- Starting dose of prednisolone
- Duration of therapy
- Previous treatment with prednisolone
- Co-morbid disease (HIV, TB, DM)
- Concomitant drug use (Clofazimine, cyclosporine, thalidomide,)

4.8.3 Operational definition

Treatment Outcome - of prednisolone is measured with the improvement/restoration of nerve functions which can be defined as below (55).

Improved: - when the motor function improved by the VMT improving by one point in two or more muscles or by 2 points in one muscle and /or the sensory function improved by at least two out of 3 points per nerve on the hand and/or 3 or more points on the feet;

Unchanged: - the same number of nerves impaired

Deteriorated: - more deteriorated nerves than improved and/or restored nerves

Safety: - the extent of drug-free from hurt effect, evaluated in this study by adverse drug reaction/events. (12)

Adverse drug event (ADE): - Any untoward occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship to the treatment

Minor Adverse Event – Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities.

Major Adverse Event – Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment.

Serious adverse events: - Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening

4.9 Data collection

Data collection period was from August to October 2022, data was collected from patients' medical records using data abstract form which is prepared by the principal investigator in the English language. The content of the format includes socio-demographic information, Clinical information, Leprosy reaction treatment, Treatment outcome, adverse event associated with prednisolone use. Data collection was carried out by five trained nurses under supervisor principal investigator.

4.10 Data quality control

To assure the quality of data, the following measures were undertaken: - The data collectors were trained on the data collection format and techniques of data retrieval. A pretest was done to check the validity and reliability of the data collection format. Based on the findings, a necessary amendment was conducted. The information included in the data extraction format was also validated by cross-checking with individual patients' treatment charts. The principal investigator was strictly supervised data collectors daily to assure the reality, completeness, and consistency of filled formats.

4.11 Data analysis procedures

Each completed data collection tool was assigned unique code. The data were entered and cleaned in a template of variables prepared into Epi-data version 4.0 and exported to SPSS version 25 for further analysis. Different statistical analyses were used including frequencies of variables, descriptive statistics including mean and standard deviation. Descriptive statistics were computed to get summary results and binary and multinomial logistic regression analyses were used to predict factors that affect dependent variables. For each of the study variables, the association was estimated by the relative risk (RR) at a 95% confidence interval (95% CI). The association between outcome and safety of treatment (prednisolone) and explanatory variables were considered statistically significant if a p-value is less than 0.05 in regression analysis.

4.12 Ethical consideration

Before the study began, ethical clearance was obtained from St Paul's Hospital Millennium Medical College Ethics committee. Then official letter from St Paul's Hospital Millennium Medical college was written to the ALERT hospital and then permission was obtained from ALERT Hospital. All potential identifiers (names and mobile numbers) were removed from the format to ensure privacy and confidentiality.

4.13 Dissemination plan

The findings of this study will be submitted to and presented at St. Paul Hospital Millennium medical college. It will be also submitted to ALERT Hospital Leprosy center and the AHRI directorate of TB and Leprosy. Finally, efforts will be made to publish the findings in a peer-reviewed scientific journal to make them publicly available.

4.14 Definition of Concepts

4.14.1 Definition of key terms

Multi-Drug Therapy (MDT) – A combination of Dapsone, Rifampicin, and Clofazimine, a first-line drug regimen to treat leprosy(1)

Type 1 Reaction (T1R) - Typically occurs in TT and BT. It is due to an increase in cell-mediated immunity and a delayed-type hypersensitivity reaction to *M. leprae* antigens. It is characterized by an increase in inflammation in skin lesions or nerves or both (9)

Type 2 Reaction (T2R) - Typically, BL and LL patients develop when treatment begins. It is a reaction due to the formation of an immune complex with hyper humoral immunity represents cutaneous and systemic small vessel vasculitis, characterized by painful nodular lesions (erythema nodosum leprosum) that occur suddenly, severe swelling and pain in the joints, iridocyclitis, orchitis, sensitive lymphadenopathy, glomerulonephritis, and hepatosplenomegaly (9).

Tuberculoid (TT) - When cell-mediated immunity is well developed, the pattern of the disease is characterized by a single or few lesion which is localized to one or a few sites in the skin and a few peripheral nerves (30).

Borderline Tuberculoid (BT) - lesions are similar to those found in TT leprosy but are larger and more numerous, with less pronounced margins and less infiltration (30).

Mid Borderline (BB) - macular, papular, or plaque-like skin lesions including a combination of these can occur. Lesions may have a geographic appearance and some lesions have an ill-defined outer margin with a well-defined ("punched-out") inner margin (30).

Borderline Lepromatous (BL) - usually develop a few macular lesions which become more widespread and symmetrically distributed, Papular and nodular lesions may develop and are more defined than those seen in lepromatous leprosy (LL), (30).

Lepromatous (LL) - If cell-mediated immunity fails to develop the pattern of disease, heavy bacterial growth in both skin and nerves cause multiple lesions all over the body, which progress to nodules. It is a systemic disease with multiple organ involvement (30).

Nerve Function Impairment (NFI); - Sensory, motor, or autonomic neuropathy evidenced by a clinically detectable reduction in function in sensory, motor, and/or autonomic fibers(10).

Neuropathy (peripheral); - Functional impairment and/or structural damage to autonomic, sensory, and motor nerve fibers within the peripheral nervous system (46).

Leprosy reaction:- is inflammation caused by the body's immune system attacking the leprosy bacteria and its typical features are swelling, redness, heat, pain, tenderness of skin lesions, and loss of function (7)

Neuritis - reaction affecting the peripheral nerves, characterized by sudden pain or palpation of peripheral nerves, with or without thickening of nerve trunks (8).

Effectiveness - the extent to which a drug works under real-world circumstances, to achieves its intended effect in the usual clinical settings; it can be evaluated through observational studies of real practice (13)

Safety - the extent of drug-free from hurt effect, evaluated in this study by adverse drug reaction/events or major side effects (12)

Adverse drug reaction (ADR):- any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or the modification of physiological function (12)

Adverse drug event (ADE):- Any untoward occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship to the treatment(12).

Serious adverse events: - Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening (12)

Side effect: - an expected, well-known reaction resulting in little or no change in patient management or it an effect with a predictable frequency and an effect whose intensity and occurrence are related to the size of the dose (12).

T1R Recurrence or Flare-up: - an increase in skin severity score to 4 or more out of 9 AND/OR an increase in NFI defined as worsening of VMT by one point in two or more muscles, or by 2 points in one muscle and/or worsening of ST: decreased sensation in at least two out of 3 points per nerve on the hand and/or 3 or more points on the feet. NB: nerve tenderness was not part of the definition for T1R recurrence (12)

New ENL: - the occurrence of ENL for the first time in a patient with lepromatous or borderline lepromatous leprosy (36)

Recurrent ENL: - the appearance of specific ENL symptoms in a patient, who had had ENL previously treated with prednisolone and had been free of ENL symptoms for four weeks off prednisolone (36).

Chronic ENL: - an ENL episode lasting more than 6 months as the patient experienced a flare-up of ENL whilst on prednisolone treatment (36).

5. RESULTS

5.1. Socio demographic characteristic of study participants

A total of two hundred sixty-two cases were reviewed in this study. The median age of study subjects was 30 years, with an IQR of 25–42.5 years. Two-third of study participants (66.8%) were males. Majority (94.7%) of patients are adults.

Table 1: Socio demographic characteristic of patients on leprosy reaction treatment at ALERT center

Variables	Category	Frequency	Percent
Age group	Children	6	2.3
	Adult	248	94.7
	Old	8	3.1
	Median (IQR:Q1-Q3)	30(25-42.5)	
Sex	Male	175	66.8
	Female	87	33.2

5.1.2 Clinical information of patient on leprosy reaction treatment at ALERT Center

As illustrated in Table 2, among the study subjects, significant majority (90.4%) of case are Multi-bacillary (MB) according to WHO classification. Out of 236 subjects classified by Ridley-jopling classification; borderline leprosy (BL) and lepromatous leprosy (LL) takes the majority of cases 55.9% and 40.7% respectively.

Table 2: Category of leprosy by WHO and Ridley-jopling classification at ALERT center

Classification	Sub Category	Percent
WHO classification	MB	236(90.1)
	PB	25(9.5)
Ridley-jopling classification	LL	96(40.7)
	BB	2(0.8)
	BL	132(55.9)
	BT	6(2.5)

As indicated in Table 3, more than one third (38.3%) of bacillary index has 0 score and the remaining has one to six plus bacillary index among 240 patients with available data on the index. There is a limitation of recorded data on morphological index among the eight

recorded cases 50% has 0 morphological index and one case had 50% morphological index at start of treatment.

Table 3: Bacillary index and morphological index of patients on leprosy reaction treatment at ALERT center

Category	Classification	Frequency (%)
Bacillary index	0	92(38.3)
	1	15(44.6)
	2	20(8.3)
	3	40(16.8)
	4	30(12.5)
	5	25(10.4)
	6	18(7.5)
Morphological index	0	4(50)
	3%	1(12.5)
	6.3%	1(12.5)
	30%	1(12.5)
	50%	1(12.5)

Depending on type of reaction as depicted in table 4 below, type one reaction accounts for 58.8 percent of the cases whereas type two reaction accounts for 41.2 percent of the cases. Based on occurrence of reaction, recurrence reaction account for majority of the cases (67.9%) and new reaction account for (32.1) percent.

Table 4. Type of leprosy reaction and reaction occurrence of patients on leprosy reaction treatment at ALERT center.

Classification	Sub Category	Frequency (%)
Type of reaction	T1R	154(58.8)
	T2R	108(41.2)
Reaction occurrence	New	84(32.1)
	Recurrence	178(67.9)

Complication associated with reaction is depicted in table 5, majority of the case have both motor and sensory impairment (41.1 %) followed isolated sensory impairment which account for 28.4 percent of the cases and isolated motor impairment accounts only 1.1 percent of the

cases. Half of the cases had WHO grade 0 disability score followed by grade 1 and 2 accounting 30.5 percent and 19.5 percent respectively.

Table 5 WHO disability grading and complication subcategory of patients on leprosy reaction treatment at ALERT center

Classification	Sub Category	Frequency(%)
WHO disability grading	Grade 0	131(50.0)
	Grade 1	80(30.5)
	Grade 2	51(19.5)
Complication	Motor impairment	3(1.1)
	Sensory impairment	65(24.8)
	Both motor and sensory impairment	108(41.2)

As shown in Table 6 Almost all patient has no comorbid condition except very small minority of cases (5.7%) which constitutes DM, HIV, HTN, cardiac illness and others like Epilepsy.

Table 6 Comorbid condition in patients on leprosy reaction treatment in ALERT center

Variable	Disease category	Frequency
Comorbid condition	HTN	6(2.3%)
	DM	5(1.9%)
	HIV	2(0.8%)
	Cardiac illness	1(0.4%)
	Others	1(0.4%)

Table 7 History of prednisolone treatment, Adherence and concomitant drug in patients on treatment of leprosy reaction in ALERT center

Variable	Category	Frequency(%)
History of non-adherence	Yes	103(39.3%)
	No	159(60.7%)
Previous Rx with prednisolone	Yes	80(30.5%)
	No	182(69.5%)
Concomitant drug use	Yes	85(32.4%)
	No	177(67.6)

5.1.4 Treatment Outcome of leprosy reaction patient’s treated with prednisolone

Out of 262 patients 62.2 percent has improvement with prednisolone; 28.6 percent has no change with the treatment and 9.2 percent of patients had deteriorated with treatment as indicated below in figure 5.1

Figure 5.1 Treatment outcome of prednisolone in leprosy reaction patients of ALERT center

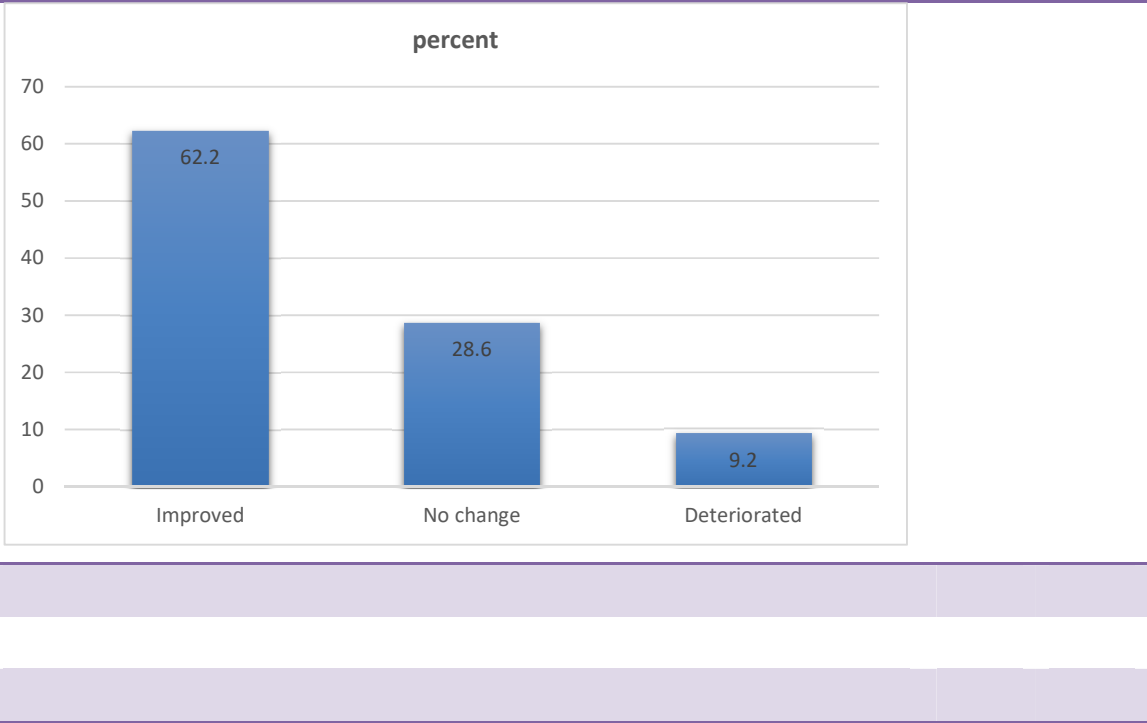


Table 8 below illustrates as compared to females among 175 males in the study, 64.4 percent has improvement, 69.3 percent has no change and 75 percent has deteriorated outcome in respective category. Of the 236 patients categorized as multi- bacillary leprosy by WHO classification, as compared to pauci- bacillary 90.2 percent has improved, 90.7 percent has no change in treatment, 87.7 percent has deteriorated outcome result in their respective category. Outcome pattern by Redley - jopling classification shows as compared to others, LL has 39.7, 50.8 and 20.8 percent improvement, no change and deteriorated outcome respectively in respective category. There are 154 Type one reaction; of these, as compared to Type two reaction 59.5 percent has improvement, 56 percent has no change in treatment and 62.5

percent has deteriorated outcome in respective category. New reaction is 84 in number; out of these, as compared to recurrence 35 percent has improved outcome, 25.3 percent has no change in treatment and 33.3 has deteriorated outcome in respective category. There is a wide range of complication associated with Leprosy Reaction; in this study 108 patients had both sensory and motor impairment; out of these, when compared to other type of complication 30.5 percent has improved outcome, 60 percent has no change in treatment and 54.2 percent has deteriorated outcome in respective category. In this study 132 patients have grade 0 WHO disability score; when compared to Grade 1 and grade 2 disability, 64.4 percent has improved outcome 22.7 percent has no change in treatment and 37.5 percent has deteriorated outcome in respective category.

Of the 182 patients who have no previous treatment of prednisolone, 72.4 percent has improvement, 65.3 percent has no change with treatment and 62.5 percent has deteriorated outcome when compared to those who had previous history of treatment in respective category.

Table 8 cross tabulation of Outcome pattern of leprosy reaction treatment

Variables	Category	End Outcome			Total, n(%)
		Same/No Change, n(%)	Improved, n(%)	Deteriorated, n(%)	
Sex	Male	52(69.3)	105(64.4)	18(75.0)	175(66.8)
	Female	23(30.7)	58(35.6)	6(25.0)	87(33.2)
Leprosy category- WHO classification	MB	68(90.7)	147(90.2)	21(87.5)	236(90.1)
	PB	7(9.3)	16(9.8)	3(12.5)	26(9.9)
Ridley-Jopling classification	LL	31(50.80)	60(39.7)	5(20.80)	96(40.7)
	BB	-	1(0.7)	1(4.2)	2(0.80)
	BL	30(49.20)	86(57.0)	16(66.7)	132(55.9)
	BT	-	4(2.6)	2(8.3)	6(2.5)
Type of reaction	T1R	42(56.0)	97(59.5)	15(62.5)	154(58.8)
	T2R	33(44.0)	66(40.50)	9(37.5)	108(41.5)
Reaction occurrence	New	19(25.3)	57(35.0)	8(33.3)	84(32.1)
	Recurrence	56(74.7)	106(65.0)	16(66.7)	178(67.9)
Complication associated with reaction	Motor impairment	-	3(1.8)	-	3(1.1)
	Sensory impairment	17(22.7)	43(26.4)	5(20.80)	65(24.8)
	Sensory and Motor impairment	45(60.0)	50(30.7)	13(54.2)	108(41.2)
	No	13(17.3)	67(41.1)	6(25.0)	86(32.8)
WHO disability grade	Grade 0	17(22.70)	105(64.4)	9(37.5)	131(50.0)
	Grade 1	33(44.0)	39(23.9)	8(33.3)	80(30.50)
	Grade 2	25(33.3)	19(11.70)	7(29.2)	51(19.50)
Previous treatment with prednisolone	Yes	26(34.7)	45(27.6)	9(37.5)	80(30.5)
	No	49(65.3)	118(72.4)	15(62.5)	182(69.5)

5.4 Adverse drug event occurred with prednisolone treatment in patients with leprosy reaction.

Adverse event occurred in 79.4 percent of the patients out of the 262 patients; the rest 20.6 percent of patients had no adverse event reported. Among minor adverse event reported dyspepsia is the commonest one occurring in 74.8% of the cases and among the major adverse events reported infection occurs in 6.5 percent. Hospitalization is the severe adverse event identified occurring in 35.1 percent of the patients as indicated in Table 9.

Table 9 Adverse events occurred in leprosy reaction patients treated with prednisolone in ALERT center

Item	category	Frequency	Percent
Moon face	Yes	3	1.1
	No	259	98.9
Weight gain	Yes	1	0.4
	No	261	99.6
Acne	Yes	8	3.1
	No	254	96.9
Hyperphagia	Yes	1	0.4
	No	261	99.6
Dypepsia	Yes	196	74.8
	No	66	25.2
Muscle cramp	No	262	100.0
Menstrual disorder	Yes	1	0.4
	No	261	99.6
Fungal skin infection	Yes	14	5.3
	No	248	94.7
Lipodystrophy	No	262	100.0
Infections	Yes	17	6.5
	No	245	93.5
Osteoporosis	Yes	9	3.4
	No	253	96.6
Neuropsychiatric	Yes	7	2.7
	No	255	97.3
Insomnia	Yes	1	0.4
	No	261	99.6
Mood disorders	Yes	5	1.9
	No	257	98.1
Peptic ulcer	Yes	5	1.9
	No	257	98.1
Diabetes	Yes	7	2.7
	No	255	97.3
Hypertension	Yes	13	5.0
	No	249	95.0
Hospitalization	Yes	92	35.1
	No	170	64.9
Death	No	262	100.0

5.5 Factors affecting the outcome of prednisolone treatment in leprosy reaction in ALERT Hospital

The data fulfills Assumptions for multinomial regression (no multicollinearity, observation are independent, no outliers). The model fitness was assessed using chi-square statistics. The Chi-square value is 60.517 and the p value is less than 0.05(p 0.001) indicating that there is significant relationship between the dependent variable and the independent variable in the final model. The Pearson (445.826) and deviance (343.574) statistics test shows that the model is fit. Since the test are not statistically significant, that is the p value is greater than 0.05.

The pseudo R- Square measures are Cox and Snell (0.226), Nagelkerke's (0.275) and McFadden (0.148). As shown in table 10 below the model accounts for 14.8% to 27.5% of the variance and represents relatively medium-sized effect.

Table 10 Pseudo R square test for multinomial logistic regression analysis of outcome

	.226
	.275
	.148

A multinomial logistic regression analysis was done to identify predictor variables. Variables like age, Sex, Leprosy reactions type 1 and 2, Occurrence of reaction New/Recurrence, Reaction severity / WHO disability grade, Leprosy Category – WHO Classification, Leprosy Category - Ridley-Jopling classification (LL, BB, BL, TT, BT), Starting dose of prednisolone, Duration of therapy, Previous treatment with prednisolone, were selected for the A multinomial logistic regression model. Then, in A multinomial logistic regression analysis, it was found that only Reaction severity / WHO disability grade ($P < 0.05$) is statistically significant.

Reaction severity by WHO disability grading at start of treatment has a statistically significant impact on treatment outcome of prednisolone for treatment of leprosy reaction in patients with improved outcome as compared to patient with no change in outcome of treatment as depicted in table 11. The odds of improved outcome with treatment of prednisolone increases by 6.9 fold for patients who have grade 0 WHO grading as compared to those having WHO grade 2 grading at the start of treatment which is statistically

significant (Exp (B) 6.96, p 0.001). Other Variable or predictors has no statistically significant impact on improved outcome of leprosy reaction treatment by prednisolone.

Table 11 Multinomial logistic regression analysis of Outcome and independent predictors

End Outcome ^a		B	SE	Wald	df	Sig.	AOR	95% C.I. for AOR	
								Lower	Upper
Improved	Intercept	15.774	1615.891	0.000	1	0.992			
	Age	0.011	0.014	0.646	1	0.422	1.011	0.984	1.038
	Starting dose of prednisolone	-0.005	0.020	0.055	1	0.815	0.995	0.956	1.036
	Duration of therapy	-0.002	0.003	0.785	1	0.376	0.998	0.993	1.003
	Sex								
	Male	-0.184	0.388	0.224	1	0.636	0.832	0.389	1.780
	Female	0 ^b			0				
	Leprosy Category – WHO Classification								
	MB	0.735	0.634	1.345	1	0.246	2.086	0.602	7.227
	PB	0 ^b			0				
	Leprosy Category - Ridley-Jopling classification								
	LL	-16.596	1615.891	0.000	1	0.992	6.201E-08	0.000	. ^c
	BB	1.916	2.090	0.841	1	0.359	6.794	0.113	408.108
	BL	-15.836	1615.891	0.000	1	0.992	1.326E-07	0.000	. ^c
	TT	0 ^b			0				
	Leprosy reactions								
	T1R	0.175	0.473	0.136	1	0.712	1.191	0.471	3.012
	T2R	0 ^b			0				
	Reaction occurrence								

New	0.008	0.435	0.000	1	0.986	1.008	0.430	2.362
Recurrence	0 ^b			0				
Complication associated with reaction								
Motor impairment	14.594	1482.398	0.000	1	0.992	2178404.030	0.000	. ^c
Sensory impairment	-0.298	0.546	0.299	1	0.585	0.742	0.254	2.164
Motor & sensory impairment	-0.675	0.532	1.608	1	0.205	0.509	0.179	1.445
No complication	0 ^b			0				
WHO disability grade								
WHO disability grade 0	1.941	0.579	11.228	1	0.001*	6.966	2.238	21.681
WHO disability grade 1	0.566	0.496	1.301	1	0.254	1.761	0.666	4.655
WHO disability grade 2	0 ^b			0				
Previous treatment with prednisolone								
Yes	-0.608	0.461	1.744	1	0.187	0.544	0.221	1.342
No	0 ^b			0				
History of non-adherence								
Yes	0.459	0.423	1.177	1	0.278	1.583	0.690	3.628
No	0 ^b			0				

Deteriorated	Intercept	15.934	1615.892	0.000	1	0.992			
	Age	0.006	0.020	0.082	1	0.775	1.006	0.967	1.047
	Starting dose of prednisolone	-0.003	0.031	0.010	1	0.919	0.997	0.939	1.059
	Duration of therapy	0.000	0.004	0.005	1	0.944	1.000	0.992	1.007
	Sex								
	Male	-0.020	0.602	0.001	1	0.973	0.980	0.301	3.187
	Female	0 ^b			0				
	Leprosy category- WHO classification								
	MB	0.712	0.903	0.622	1	0.430	2.039	0.347	11.973
	PB	0 ^b			0				
	Leprosy category- Ridley-Jopling classification								
	LL	-18.733	1615.891	0.000	1	0.991	7.320E-09	0.000	. ^c
	BB	2.160	0.000		1		8.670	8.670	8.670
	BL	-16.769	1615.891	0.000	1	0.992	5.218E-08	0.000	. ^c
	TT	0 ^b			0				
	Type of reaction								
	T1R	-0.625	0.714	0.766	1	0.381	0.535	0.132	2.169
	T2R	0 ^b			0				
	Reaction occurrence								
	New	-0.058	0.666	0.008	1	0.931	0.944	0.256	3.483
	Recurrence	0 ^b			0				
	Complication associated with reaction								
	Motor impairment	-0.750	2582.314	0.000	1	1.000	0.472	0.000	. ^c

Sensory impairment	-0.349	0.854	0.166	1	0.683	0.706	0.132	3.765
Motor & sensory impairment	-0.321	0.794	0.163	1	0.686	0.726	0.153	3.441
No complication	0 ^b			0				
WHO disability grade								
WHO disability grade 0	0.890	0.860	1.070	1	0.301	2.435	0.451	13.140
WHO disability grade 1	0.222	0.701	0.101	1	0.751	1.249	0.316	4.939
WHO disability grade 2	0 ^b			0				
Previous treatment with prednisolone								
Yes	0.080	0.692	0.013	1	0.908	1.083	0.279	4.208
No	0 ^b			0				
History of non-adherence								
Yes	0.169	0.625	0.073	1	0.787	1.184	0.348	4.035
No	0 ^b			0				

5.6 Factors affecting the Safety of prednisolone treatment in leprosy reaction in ALERT Hospital

The data fulfills Assumptions for binomial regression (no multicollinearity, observations are independent, no outliers). Model fitness was assessed using chi-square statistics. The Chi-square value is 25.498 and the p value is less than 0.05 ($p = 0.000$) indicating that there is a significant relationship between the dependent variable and the independent variable in the model. The Hosmer and Lemeshow test statistics test proves that the model is fit. Since the test are not statistically significant, that is the p value is greater than 0.05. The classification table shows that the model predicts 99 percent of those who develop safety issue as contrary to those with no report of safety which only predicted 5.6 percent of the cases. The overall classification accuracy is 79.8 percent of the samples are correctly predicted to fall into their respective group.

The pseudo R-Square measures are The Cox and Snell (0.093) and Nagelkerke's (0.145). Table 12 shows the model accounts for 9.3% to 14.55% of the variance and represents relatively medium-sized effect.

Table 12 Pseudo R square test of binary logistic regression analysis safety of prednisolone

Model Summary			
Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	241.088 ^a	.093	.145
a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.			

Table 13: Binary logistic regression analysis of factor affecting safety of prednisolone

Variables	AOR	95% C.I. for AOR		P-value
		Lower	Upper	
Age	1.014	0.989	1.039	0.272
Sex				
Male	0.631	0.308	1.292	0.208
Female	1			
Starting dose of prednisolone	1.049	1.006	1.094	0.026
Duration of therapy	1.02	1.01	1.03	<0.001
History of non-adherence				
Yes	0.568	0.282	1.142	0.112
No	1			

The above binary logistic regression Table 13 shows as duration of treatment with prednisolone increases the odds of developing adverse event increase by a factor of 1.02 which is statistically significant (AOR: 1.019, p 0.000). Also the odd of developing adverse event increases by 5.2 percent as a dose of prednisolone increases which is statistically significant (AOR: 1.052, p 0.021). The data shows Sex, Age and previous treatment with prednisolone has no statistically significant effect on Safety report of the drug.

5.2 Discussion

Treatment outcome of steroids show a range of outcomes. This study shows that improvement with prednisolone treatment in leprosy reaction (T1R&T2R) is 62.2%. Separately proportion of improvement for T1R is 63% and for T2R is 61.1% This is consistent with finding a systematic review which showed that the effectiveness of prednisolone in treating NFI and T1R ranges from 60-70%(48). The figure is more than retrospective study in India which showed, of an outpatient treated with prednisolone, only 50% of patients with T1Rs were judged to have improved nerve function (11). The reported improvement in this study is less than prospective study done in India which reported 27% of patients with no improvement (45) and a multi-centered randomized controlled trial conducted in four countries which shows improved nerve function in 78% of patients with recent NFI (13). This difference might be due to the design of the study used.

This study shows that recurrence case accounts 54.5% in T1R is and 45.5% in T2R this is consistent with a systematic review done on effectiveness of prednisolone in T1R which states recurrence of NFI in T1R are common, occurring in 30-50% of patients. Pattern of treatment outcome in new reaction and recurrent reaction is 67.9% and 59.6% respectively this is also consistent with the finding of systematic review which concluded New NFI has better rates of recovery than old NFI.

The finding in this study shows that there is no statistically significant impact of duration of treatment in leprosy reaction for improvement which is not consistent to a multicenter RCT done on three steroid regimens for treatment of T1R which concluded NFI in patients with ENL may be under-treated if the short ENL regimes are followed. Longer periods of steroid treatment for NFI are more effective (47).

The response to prednisolone treatment seems to depend on WHO disability grading at start of treatment. This study shows that WHO disability grading at start of treatment has a statistically significant impact on treatment outcome of prednisolone for treatment of leprosy reaction. WHO grade 0 patients has 80.2% improvement, WHO grade 1 disable patients has 48.8% improvement and patients with WHO grade 2 disability has 37.2% improvement. This finding is in agreement with the study by Cochrane systematic review which reported that for people with complete motor paralysis or moderate motor impairment, 11% and 55%, respectively, recovered to good function(46). It is also consistent with multicenter RCT done in three countries (Nepal, Bangladesh and Indonesia) where WHO disability grade

demonstrated a significant correlation with improvement and restoration from NFI in patients treated with prednisolone (13). WHO disability grading is statistically significant association across all design of study which shows it is independent predictor of outcome.

According to the finding of this study among 262 patients 79.4% of the patients experienced at least one adverse event. This is comparable with A prospective study conducted on 88 patients in a French center which reported 71% of patients developed at least one adverse event(53). The figure is more than a study done in Nepal which identified 54.5% of participants experienced at least one adverse event(50).

In this study among the minor adverse event develop dyspepsia occur in (78.4%) patients followed by fungal skin infection (5.1%) patients , from Major ADE, infection occurs in (6.5%) patients followed by hypertension(5%) of patients. From severe adverse event hospitalization occurs(35.1%) of patients. This figure is different from a study done in Nepal with most identified ADEs was minors; moon face (9.1%), acne (22.73%), gastritis (22.7), and weight gain (4.5%), while glaucoma (4.5%) was reported as serious ADE (50). It is also different from another RCT showed that reported minor ADEs reported were moon face (33.3%), acne (42.4%), fungal skin infections (45.5%), and dyspepsia (57.6%). The major ADEs were elevated blood sugar/diabetes (12.12%), anxiety (3%), and infections (69.7%), (22). Our study finding of common ADE is different Form prospective study done on 88 patients in French center which shows Lipodystrophy 63%, neuropsychiatric disorders 52.5%, skin disorders 46.2%, muscle cramp 32.5%, proximal muscle weakness 15%, newly developed hypertension 8.7% and menstrual disorders in premenopausal women 39% were reported (53).The reason for this difference is probably due to late presentation of the patients to health setting after their condition is in advanced stage as compared to other developed and middle income countries where patients present to health setting in early phase of their condition.

The finding in this study showed that increment of prednisolone treatment duration increases the odds of developing adverse event by 2.1 fold which is statistically significant. Also the odd of developing adverse event increases by 5.2% with increment of starting dose of prednisolone which is statistically significant. Age, gender and previous history of treatment with steroid have no statistically significant value. This finding is similar with a study in French center which reported dose, duration, and history of long-term prednisolone were associated with prednisolone-related ADRs/ADEs(53).

6. CONCLUSION

Treatment outcome of prednisolone in ALERT Hospital shows a range of outcomes. The finding of the study showed that two fifth of the cases has no improvement with prednisolone treatment in leprosy reaction (T1R&T2R). Among patients who have no improvement, two third had no change and one third has deteriorated outcome. WHO disability grading at start of treatment has a statistically significant impact on treatment outcome of prednisolone for treatment of leprosy reaction. Only twenty three and eleven percent of Grade one and Grade two patient has improved outcome respectively. Other Variable or predictors including duration of prednisolone treatment as well as dose of prednisolone has no statistically significant impact on improved outcome of leprosy reaction treatment by prednisolone.

In This study, more than two third of the patients experienced at least one adverse event, among the adverse event reported significant proportion of patients reported minor adverse event and serious adverse event. Most identified ADE is dyspepsia. The study showed that increment of prednisolone treatment duration increases the odds of developing adverse event. Also the odd of developing adverse event increases with increment of starting dose of prednisolone.

7. RECOMEDATION

After thorough assessment and considering the foregoing finding and discussion of the study the following recommendation are presented.

The study finding showed for both in type one and two reactions there are a significant proportion of patients with no improvement with prednisolone. Moreover it shows that there is no impact of treatment duration as well as prednisolone dose on outcome of treatment. Thus this study recommend an RCT to be conducted to entertain other option of therapy for those patients without improvement by prednisolone in the hospital especially for those patients with WHO grade 1 and WHO Grade 2 disability in which more than two third of the patient has no improvement with prednisolone.

As this study showed the percentage of adverse event associated with prednisolone treatment is high and the odds increases significantly with increased duration of treatment without benefit for outcome of treatment. Based on this finding it is not recommended to use of prednisolone for long duration. In addition this study also provided evidence increased dose is associated to increased adverse event without benefit for outcome of treatment. Thus using low dose prednisolone is recommended. In order to practice the above recommendation the finding should be supported by RCT.

Strength and Limitation of the study

This study incorporate the outcome pattern, the safety and factor associated with the outcome and safety of predenisolone which make it unique among other studies conducted in the area. Limitation of this study is associated with the design of the study which is affected by incomplete documentation of predictor variables of interest ,Safety report of patients due to recall problem and outcome variable which led to exclusion of medical records.

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Annex

Data Collection Form for Study Protocol

Card No. _____

A. Demographic Information;					
S.N.	Questions	Response	S.N.	Questions	Response
1	Age	_____ years			
2	Sex	1. M 2. F			
					Specify: _____
B. Clinical information					
S.N	Questions	Responses		Remarks	
1	I. Leprosy category- WHO classification II. Ridley-Jopling classification	I. MB, PB II. LL, BB, BL, TT, BT			
2	Bacterial Index(BI)/Morphological index(MI)	BI_____ MI_____			
3	Type of reaction	(A) .T1R/RR (B). T2R/ ENL			
4	Reaction occurrence	A. New B. Recurrence			
5	Complication associated with reaction	A. Motor impairment B. Sensory impairment C. Both			
6	WHO disability grade	A. 0 B. 1 C. 2			
7	Co-morbid disease (HIV, TB, DM...)	Specify: _____			
C. Leprosy Reaction Treatment					
1	Starting dose of prednisolone	_____mg			
2	Duration of therapy	_____ weeks			
3	History of non-adherence	1. Yes 2. No			
4	Previous treatment with prednisolone	1. Yes 2. No			
5	Concomitant drug use (Clofazimine, cyclosporine, thalidomide,)	1. Yes 2. No If yes, Specify _____			

D. Treatment outcome			
End Outcome 1. Improved 2. Same/No change 3. Deteriorated			
E. ADE/ADR/SAE/ associated with Prednisolone			
S.N	Any ADRs or ADEs or SAEs	Did it occurred	Type of drug reaction/events
			Minor ADR/ADE Major ADR/ADE SAE
1	<i>Moon face</i>	Y/N	
2	<i>Weight gain</i>	Y/N	
3	<i>Acne</i>	Y/N	
4	<i>Hyperphagia</i>	Y/N	
5	<i>Gastric pain/dypepsia</i>	Y/N	
6	<i>Muscle cramp</i>		
7	<i>Menstrual disorder</i>	Y/N	
8	<i>Fungal skin infection</i>	Y/N	
10	<i>Lipodystrophy</i>	Y/N	
11	Infections (specify as; viral or bacterial)	Y/N	
12	Osteoporosis /Bone problem	Y/N	
13	Neuropsychiatric disorders	Y/N	
14	Insomnia	Y/N	
15	Mood disorders	Y/N	
16	Peptic ulcer	Y/N	
17	Glaucoma	Y/N	
18	Diabetes		
19	Hypertension	Y/N	
20	<i>Hospitalization</i>	Y/N	
21	<i>Death</i>	Y/N	



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FEDERAL MINISTRY OF HEALTH
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School of Public Health



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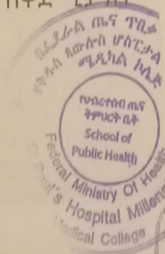
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ጉዳዩ:- ድጋፍ እንዲደረግላቸው መጠየቅን ይመለከታል፤

በቅዱስ ጳውሎስ ሆስፒታል ሚሊኒየም ሜዲካል ኮሌጅ በ MPH Weekend program የ 2ተኛ ዓመት ተማሪ የሆነው ገመቸስ ሚካኤል ዳታ ለመ፡ሰብሰብ ወደ እናንተ ተቋም የላከነው ስለሆነ ለጥናቱ አስፈላጊውን መረጃ እና እገዛ እንዲደረግለት በትህትና እየጠየቅን፤ ለመደረግልን ቀና ትብብር በቅድሚያ እናመሰግናለን፡፡



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የዶክተር ገመቸስ ሚካኤል
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