Original Research Article

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Addition of immunotherapy to chemotherapy in pediatric borderline leprosy: a clinical evaluation

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ABSTRACT

Background: Immunotherapy with BCG, BCG + M. leprae, ICRC, MIP has been observed to be effective in improving the treatment in adulthood leprosy. Clinical improvement with accelerated bacterial clearance and histological up grading using MIP vaccine as an immunotherapeutic with standard WHO-MDT has been reported in adult cases with high bacillary load. However, there is lack of information in borderline pediatric leprosy which is characterized by a state of shifting immunity and would therefore be ideally suited to such observations. This pilot study is originated from involvement of our Institute in a trial aimed for improving the therapy of pediatric borderline leprosy by using combined immunotherapy and chemotherapy. The study was aimed to assess the clinical improvement by adding immunotherapy (MIP vaccine) with chemotherapy (WHO -MDT) in pediatric borderline leprosy.

Methods: A total of 98 new pediatric borderline leprosy cases were included, after formal written consent, detailed clinical examination. A non-randomized trial was conducted. In this study, patients attending the OPD were serially recruited in two treatment groups. In group-1 (Mw vaccine plus WHO- MDT) 50 pediatric cases and in Group-2 (MDT only), 48 pediatric borderline cases were recruited. The therapeutic regimens containing MIP vaccine was injected intra-dermally at the start of therapy and every six months in addition to chemotherapy (WHO- MDT) in group 1 pediatric patient and chemotherapy only (WHO- MDT) were given in group-2 pediatric cases and effect was observed on clinical parameters (size of lesions, erythema, infiltration, sensory improvement) and bacillary clearance. **Results:** Addition of immunotherapy resulted in faster clinical recovery from disease, faster bacillary clearance in pediatric borderline leprosy cases.

Conclusions: This study shows the usefulness of adding immunotherapy (MIP vaccine) to chemotherapy (WHO-MDT) in pediatric borderline leprosy for faster clinical improvement.

Keywords: Chemotherapy, Immunotherapy, Leprosy, MIP vaccine, WHO-MDT, Pediatric borderline

INTRODUCTION

Immunotherapy with BCG, BCG+ M, leprae, MIP, ICRC has been observed to be effective in improving the treatment in adulthood leprosy. ¹⁻⁴ Clinical improvement with accelerated bacterial clearance and histological up grading using MIP vaccine has been reported in adult

cases with high bacillary load.⁵⁻⁷ However, there is lack of information in borderline pediatric leprosy which is characterized by a state of shifting immunity and would therefore be ideally suited to such observations. MIP in general shows a good response in adulthood leprosy but its role as adjuvant with chemotherapy on clinical recovery of pediatric leprosy has not been reported so far.

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Hence it is important to study these changes in children because they reflect the continued transmission of the diseases in the socity. So the present study planned to assess the additive effect of immunotherapy (MIP vaccine) with standard MDT on clinical parameters (like size and no. of lesions, erythema, infiltration, sensory improvement) and on bacillary clearance in the immunological labile borderline leprosy of children.

METHODS

A non-randomized trial was conducted. In this study, total of 98 untreated pediatric borderline cases (BT-53, BB-30, BL-15) attending the OPD were serially recruited in two treatment groups. Group-1 (Mw vaccine plus MDT) and in group-2 (MDT only) 50 borderline cases (BT-28, BB-17, BL-5) in trial group and 48 borderline cases (BT-25, BB-15, BL-8) in control group were recruited after written informed consent from their parents .

Inclusion criteria

Only borderline untreated pediatric cases of up to 15 year of age were included in this study. Patients were diagnosed according to clinical criteria and smear positivity and classified in to three groups according to Ridley and jopling classification.⁸

- Borderline tuberculoid (BT)
- Borderline borderline (BB)
- Borderline lepromatous (BL).

Exclusion criteria

- Patients who did not have conclusive evidence for the diagnosis of borderline leprosy and more than 15 year of age
- Patients with HIV infection, other additional immunosuppressive illness such as diabetes mellitus, hematological and reticuloendothelial malignencies.

Recruitment

In this study, total of 98 untreated pediatrics borderline leprosy cases attending OPD were serially recruited; 50 borderline cases in trial group and 48 borderline cases in control group were recruited in the study. After the formal written consent, detailed clinical examination and charting of the clinical parameters like size and number of lesion was done on transparent hypergrid charts, slit skins smear examination of all patients was done, Slit skin smears were taken from four sites and results were recorded on the riedley scale. In group 1 cases, MIP vaccine was injected 0.1 ml (0.5 x 10 bacilli) intradermally at the start of therapy and every six months in addition to chemotherapy (WHO-MDT) to all the patients and in group 2 cases, only standard WHO-MDT were given to all the pediatric cases. BT cases were followed up after 6 doses of MDT and 2 doses of MIP vaccine and BB/BL cases were followed up after 12 doses of MDT plus 3 doses of MIP vaccine.

Diagnosis of borderline leprosy

Borderline leprosy cases were classified into three groups according to Ridley and jopling classification based on immunohistological scale

Borderline tuberculoid (BT)

Skin lesions are single or few in number, variable in size and dry, impaired touch, pain and temperature sensation. Lepromin response is positive and usually skin smears are negative. Histopathology shows narrow clear sub epidermal zone above the granulomas, Lymphocyte are plentiful but less well focalized. Nerves swollen but recognizable. B.I. = 0-2+(AFB).

Borderline borderline (BB)

Skin lesions are numerous, variable in size and shiny. Sensation is impaired. Smear is moderately positive and Lepromin test is negative. Histopathology shows sheets of epitheliod cells with no giant cells. Lymphocytes are rather sparse and diffusely infiltrating nerves show structural disorganization but no granulomas. B.I.=3-4+ have few lymphocytes.

Borderline lepromatous (BL)

Large no. of lesions, variable in size, shiny surface, and sensation slightly diminished. Skin smears are strongly positive, but lepromin response is negative. Histopathologically seen histiocytic granulomas with cells of slightly epitheliod appearance, heavily laden with bacilli, few lymphocytes. There is infiltration with foamy cells but no golbi. Numerous diffuse lymphocytes are seen, more than in BB or BT. B.I= 4-5 +.

Clinical scoring

Each patient was assessed at recruitment, at 6th, 12th, 24th and 36th month of follow up period. For each lesion maximum possible score at intake was 12 and the minimum score at follow up was zero. Each patient was clinically assessed and scores given as shown in the Table 1.

Follow up during therapy

Clinical progress of lesions

- Number and size of lesions
- Erythema
- Infiltration
- Sensation.

Reduction in bacillary index (B.I)

Evaluation and statistical analysis

Data were analyzed using tabular and graphic presentation and statistical procedures viz. summary statistics, t-test is used compare means and X^2 for proportion.

RESULTS

As described, 50 borderline cases in trial group and 48 borderline cases in control group were recruited in the study. They were further distributed according to sex, age and type of diseases.

Table 1: Clinical scoring.

Clinical navametors	Score awarded						
Clinical parameters	3	2	1	0			
Size of lesion	clearly visible	Faintly visible	Doubtful	none			
Erythema	Entire region erythmetous	Dusky erythema	Partial/marginal	no			
Infiltration	Markdly raised elevated lesion	Flattening of infiltration	Minimal infiltration	no			
Anesthesia	Complete loss on pin prick	Less sensation but not completely loss	Not consistent or doubtful	no			

Size (area of lesion = length x breadth): initial score: 3 (for every up to 20% increase or decrease, subtract 0.5, lesion disappeared -0)

Out of 50 children in trial group, there were 28 (56.7%) males and 22 (43.3%) females. In the control group, out of 48 children, there were 25 (53.3%) were males and 23 (46.7%) were females (Table 2). The age distribution of children in both the treatment groups is comparable in 0 to 5, 6 to 10 and in 11 to 15 age groups (Table 3).

Table 2: Distribution of the borderline paediatrics patients according to sex.

Sex	Group-1 (MDT+MIP)	Group-2 (MDT only)
Male	28 (56.66%)	25 (53.33%)
Female	22 (43.33%)	23 (46.66%)
Total	50 (100%)	48 (100%)

Table 3: Distribution of the borderline paediatrics patients according to age.

Age (years)	Group-1 (MDT+MIP)	Group-2 (MDT only)
0 to 5	8 (16%)	7 (14.7%)
06 to 10	18 (36%)	20 (41.6%)
11 to 15	24 (48%)	21 (43.7%)
Total	50 (100%)	48 (100%)

Table 4: Distribution of the borderline pediatrics patients according to type of disease.

Type of disease	Group-1 (MDT+Mw)	AFB positive	Group- 2 (MDT only)	AFB positive
BT	28	05	25	04
BB	15	14	15	13
BL	07	07	08	08
Total	50	26	48	25

Table 4 provides distribution of subjects by the type of disease, borderline tuberculoid (BT), borderline borderline (BB) and borderline lepromatous (BL) in both the treatment groups. In group 1, out of 50 subjects, 28 were BT with 5 cases as AFB+, 15 were BB with 14 AFB+ and rest 7 were BL with 7 AFB+. In Group 2, 25 cases were BT with 4 as AFB+, 15 were BB with 13 as AFB+ and 8 were BL with 8 as AFB+.

Effect of immunotherapy and standard MDT on mean total score at each assessment

The mean clinical score of BT cases treated with MIP + chemotherapy showed significant decline in mean clinical score from 11.00 to 3.85 (65%) at 6 months further declined to 1.64 (85%) at 12 months. and further reduced to 0.03(99.7%) at 36th month as compare to control group (MDT only) where declined was from 11.12 to 7.2(35.2%) at 6 month and further declined to 5.36 (51.8%) at 12 months and last to 2.8 (74.8%). The difference of decline in mean clinical score compared in both groups (interventional vs. control) at 6 months (65% vs. 35.2%, p <0.005) at 12 months (85% vs. 51.8%, p < 0.001) and at 36th months (99.7% vs.74.8%, p < 0.001). Difference in reduction in mean clinical score in interventional group was 29.8% more at 6 months, 33.2% more at 12 months and 24.9% more at 36th months.

The mean clinical score in patients of BB/BL groups also decreased substantially from 11.91 to 4.77 (60%) at 6 months, further declined to 2.45(79.4%) by 12 months and further reduced to 0.09 (99.2%) by 36^{th} month in group 1 (MIP+MDT) as compare to control group (MDT only) where declined was from 11.78 to 7.61 (35.3%) at 6 month and further declined to 6.39 (45.7%) at 12 months and last to 3.47 (70.5%). The difference of decline in mean clinical score compared in both groups (Interventional vs. Control) at 6 months (60% vs. 35.3%, p < 0.005) at 12 months (79.4% vs.45.7%, p < 0.001) and at 36^{th} months (99.2% vs.70.5%, p < 0.001). Difference in reduction in mean clinical score in interventional group

was 24.7% more at 6 months, 33.7% more at 12 months and 28.7% more at 36th months (Table 9).

Effect of immunotherapy and standard MDT on mean bacillary index of BT, BB, and BL cases

The fall in BI was much faster in cases group-1 (MDT + immunotherapy groups) as compared to group-2 (MDT alone). As a result of a faster fall in the BI, the patients in (MDT + immunotherapy group) became negative much earlier than the patients in (MDT alone) in BT, BB and BL sub groups of all the borderline patients. Table 10 showing greater and earlier decrease in mean bacillary

index in BT, BB, BL cases of interventional group (MIP+MDT) from 2.88, 2.5, 2.1, 0.6 and last to 0.038 on 6,12,24 and 36 months respectively as compare to control group (MDT Only) where the mean bacillary index in BT,BB,BL cases decreases from 3.05, 2.8, 2.7, 1.7 and last to 0.72 on 6,12,24 and 36 months respectively. The difference at different time intervals was much earlier and statistically significant in interventional group. The reduction in mean bacillary index was faster and higher by 5%, 15.3%, 33.1% and 21.6% at 6, 12, 24 and 36 months respectively in Interventional group than in MDT group (Table 10).

Table 5: Effect of immunotherapy and standard MDT on total clinical score at each assessment of BT and BB/BL patients.

Assessment time	Statistical parameters	Group-1(BT) (n = 28)	Group-2(BT) (n = 25)	t- values p-value	Group-1 (BB/BL) (n = 22)	Group-2 (BB/BL) (n = 23)	t values p value
At Intake	Mean score	11.00	11.12	t-0.53	11.91	11.78	t-0.61
	S.D	0.82	0.83	P < 0.05	0.29	0.42	P < 0.005
At 6 months	Mean score	3.85(65%)	7.2(35.3%)	t-15.67	4.77(60%)	7.61(35.3%)	t-15
	S.D.	1	0.5	P > 0.001	0.61	0.66	P>0.001
At 12 months	Mean score	1.64(85%)	5.36(51.8%)	t-17.62 P >0.001	2.45(79.4%)	6.39(45.7%)	t-17.22 P >0.001
	S.D.	0.49	0.95	P >0.001	0.96	0.49	P >0.001
At 24 months	Mean score	0.07(99.3%)	3.92(64.8%)	t-25.96 P >0.001	1.18(90%)	4.04(65.7%)	t-16.74 P >0.001
	S.D.	0.26	0.7	F >0.001	0.5	0.64	F >0.001
At 36 months	Mean score	0.03(99.7%)	2.8(74.8%)	t-20.98 P >0.001	0.09(99.2%)	3.47(70.5%)	t-26.02 P >0.001
	S.D.	0.18	0.64	r >0.001	0.29	0.51	r >0.001

Table 6: Effect of immunotherapy on mean bacillary index of BT, BB, BL cases in both groups.

Type of diseases	Mean bacillary index	At intake	At 6 M	At 12 M	At 24 M	At 36 M
Group-1(MIP+MDT) BT,BB, BL $(N = 26)$	Mean	2.88	2.5 (13.2%)	2.1(27.1%)	0.65(77.4%)	0.038 (97.9%)
	S.D.	0.43	0.58	0.73	0.56	0.19
Group-2(MDT only) BT, BB, BL (N = 25)	Mean	3.05	2.8 (8.2%)	2.7(11.47%)	1.7 (44.3%)	0.72 (76.3%)
	S.D.	0.40	0.38	0.46	0.43	0.54
	t value, P value	1.54, P > 0.05	2.36, P < 0.02	3.5, P < 0.01	7.96, P < 0.001	5.96, P < 0.002

Local reaction to MIP vaccine

Mycobacterium indicus pranii (MIP) was well tolerated by the patients and did not lead to any systemic side effects. There was a local reaction develops at the immunization site after 1 month, in the form of a circular area with scaling, crusting and occasional bruising in all the patients. 2 Borderline patients showed a shallow ulcer at site of injection of Mw vaccine after 2 month of I/D injection. On subsequent vaccination the reaction did not produce any ulceration.

DISCUSSION

As the nation is passing through the eradication phase of leprosy, reports are suggesting a change in epidemiology and symptomatology of the disease. More patients of borderline leprosy as compared to highly bacillated forms of the diseases are now prevailing, and in our earlier studies it was recommended to consider the addition of immunotherapy (MIP) to chemotherapy to achieve faster bacteriological and histological responses in adulthood leprosy. Present study planned to see the observation on clinical status in pediatric leprosy ,it aims to assess the additive effect of immunotherapy (MIP vaccine) with standard MDT (WHO) on clinical profile of untreated borderline patients of pediatric leprosy (BT, BB, BL) till completion of therapy and follow up .

The mean clinical score of cases treated with MIP with chemotherapy showed significant and rapid reduction of clinical score at 6, 12, 24 and 36 months of assessment period as compared to only chemotherapy group where we observed slower and lesser reduction. In BT patients in both the regimens mean clinical score decreased substantially over to 36 months, The difference of decline in mean clinical score compared in both groups (interventional vs. control) at 6 months (65% vs. 35.2%, p < 0.05) at 12 months (85% vs 51.8%, p < 0.001) and at 36th months (99.7% vs.74.8%, p < 0.001). Difference in reduction in mean clinical score in interventional group was 29.8% more at 6 months, 33.2% more at 12 months and 24.9% more at 36th months.

In BB/BL patients in both the regimens mean clinical score decreased substantially over to 36 months, The difference of decline in mean clinical score compared in both groups (interventional vs. control) at 6 months (60% vs. 35.3%, p < 0.005) at 12 months (79.4% vs. 45.7%, p < 0.001) and at 36th months (99.2% vs.70.5%, p < 0.001). Difference in reduction in mean clinical score in interventional group was 24.7% more at 6 months, 33.7% more at 12 months and 28.7% more at 36th months. By addition of immunomodulators to MDT in BT/BB/BL has also been reported in our earlier study but not in pediatric leprosy. Narang et al also reported that using MIP and BCG vaccines, the mean reduction in clinical scores was significantly more as compare to only MDT in adult hood leprosy. ¹⁰

Although the initial BI was comparable with both groups, the fall in BI during the course of treatment was different. BI is a semi-quantitative measure of the total load and includes both the live as well as the dead bacilli. The fall much faster in cases (MDT+immunotherapy groups) as compared to group-2 (MDT alone). As a result of a faster fall in the BI, the patients in (MDT + immunotherapy group) became negative much earlier than the patients in (MDT alone). In BT,BB,BL cases of interventional group (MIP+MDT) the BI decreased from 2.88, 2.5, 2.1, 0.6 and last to 0.038 on 6, 12, 24 and 36 months respectively as compare to control group (MDT only) where the mean bacillary index in BT,BB,BL cases decreases from 3.05, 2.8, 2.7, 1.7 and last to 0.72 on 6, 12, 24 and 36 months respectively. The difference at different time intervals

was much earlier and statistically significant in interventional group. The reduction in mean bacillary index was faster and higher by 5%, 15.3%, 33.1% and 21.6% at 6, 12, 24 and 36 months respectively in Interventional group than in MDT group. This rapid attainment of smear negativity by the addition of MIP vaccine as a immunomodulator to MDT has also been reported .The average fall in BI with the standard MDT is reported about 1 log per year. 11 Zaheer at al reported a statistically significant fall of 1-84±0.18 in LL per year who received MDT+ MIP as compare to fall 0.98±0.11 in patients on MDT alone. 12 Sharma et al reported that 63% of cases of BL and LL on MDT+MIP became skin smear negative compared to 25% of MDT group in the same period.⁶ Sarkar et al reported a fall in BI 2.05 per vear in patients who received MDT+MIP as compared to BI fall of 1.05 per year in patients who received MDT alone.¹³ But all these studies conducted in adults not in children, The present study do so that the addition of immunotherapy to MDT does help in a greater and more rapid fall in a BI and achievement of early smear negativity status in pediatric leprosy.

CONCLUSION

This trial shows the potential usefulness of this approach of addition of immunotherapy to standard chemotherapy in borderline pediatric leprosy cases. Addition of immunotherapy resulted in faster clinical recovery from disease and faster bacillary clearance. Such information are expected to be useful in improving the immunotherapeutic approaches for treating granulomatous conditions in general and in leprosy in particular.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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