Original Article

ROLE OF LOW LEVEL NITROGEN LASER THERAPY IN CHRONIC DRUG RESISTANT PULMONARY TUBERCULOSIS

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Summary

Aim: In this longitudinal study, the Role of Low Level Laser Therapy in Chronic Drug Resistant pulmonary tuberculosis has been studied for a period of 10 years from 1995 to 2004 and follow up was done for a period of 3 years.

Material and Methods: 61 patients in Nitrogen Laser Therapy group (LLLT Group) and 61 were kept as control group. The aim of study was to describe the efficacy and safety of low level nitrogen laser therapy in management of chronic drug resistant pulmonary tuberculosis. All the patients, included in this study, had already taken anti-tubercular drugs for more than one year and were still sputum smear and culture positive.

Results: Among LLLT group, 44 (72.13%) patients became sputum smear and culture negative for MTB (*Mycobacterium Tuberculosis*) as compared to 26 (42.62%) in control group. Of the 44 patients, 22(50%) converted within first month.

Conclusion: Low Level Nitrogen Laser Therapy may be used as an adjuvant to anti-tubercular drugs in cases of chronic drug resistant pulmonary tuberculosis. **[*Indian J Tuberc 2006; 53:135-140*]**

Key Words: Tuberculosis, Low Level Nitrogen, Laser.

INTRODUCTION

Tuberculosis affects more than 8 million people and has serious repercussion on economy, psychological and social status. Since the declaration as a global emergency in 1993 by the WHO, significant development in the treatment and control of tuberculosis has been the implementation of the short course directly observed treatment along with fixed dose combination of existing drugs. However, the available therapeutic regimens have inherent disadvantage of long treatment duration, results in patient's non-compliance, and yields the risk of having drug resistance. Hence new modalities of treatment that are potent, active resistant against strain and curtailment of treatment period are needed to combat this disease. In countries that are poor MDR cases, which cannot be treated with the standard medicine, can be a death sentence. MDR - PTB (Multi Drug Resistant Pulmonary Tuberculosis) is at least 50 times more expensive than CAT-1 regimen. Drugs available to treat MDR TB are weak, and have more adverse reactions.

Lungs of patients affected by TB, a single founder strain of *Mycobacterium Tuberculosis*, may undergo mutagenesis during treatment, leading to drug resistance independently in discrete physical locales, resulting in parallel evaluation of heterogeneous sub-population of drug resistant bacilli. Relying on drug susceptibility test of organisms isolated from patient sputa may not provide an accurate representation of the bacterial susceptibility in all sub-populations within the lung.

The growth of MTB is well known to occur in proportion to oxygen tension. Thus another factor contributing to the florid bacterial growth seen at the luminal surface of the cavity could be improved access to oxygen in the micro-environment.

The risk of spreading infection to the other sites in the same patient and to non-infected persons from an individual with cavitary tuberculosis is very high. There is difficulty in reaching adequate drug concentration because of lack of adequate circulation.

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In continuation of the pioneering work of Finsen on treatment of skin TB by UV[1] light and *in vitro* reports on bactericidal effect of UV light on tubercular bacilli[2], Eshanchanov *et al* reported the use of UVA radiation from nitrogen laser (337 mm) for the treatment of patients with PTB[3]. *In vitro* experiments have also been carried out to understand the therapeutic mechanism involved. It has been shown that nitrogen laser irradiation can inhibit growth of tubercular bacilli particularly at high intensities[4]. *In vitro* experiments have also provided some evidence as potential implements of nitrogen laser irradiation on the immune system, e.g nitrogen laser irradiation was seen to enhance the intra-cellular killing of internalized bacterial in human neutrophil[5]. Nitrogen laser irradiation leads to temporary inactivation of drug sensitive as well as drug resistant clinical isolates of MTB[6]. Laser therapy improves the blood circulation and essentially increases oxygen supply and so stimulates mycobacteria to reproduction, making infecting agents relatively easily available for anti-tubercular drugs. The present study has been carried out to describe the efficacy and safety of low level nitrogen laser therapy in management of Chronic Drug Resistant pulmonary tuberculosis.

MATERIAL AND METHODS

One hundred twenty two patients with drug resistance pulmonary tuberculosis admitted to single medical unit of Department of Medicine ,M.G.M. Medical College & M.Y.Hospital, Indore, over a 10 year period from 1995 to 2004 were included in a retrospective pattern.

The study was conducted with the consent of all patients. Their detailed medical history and physical examinations were taken from them and included in the study conducted between age-group 15-65 years with diagnosis of drug resistant tuberculosis. Drug resistance proven by (a) AFB culture and sensitivity; (b) received anti-tubercular treatment for more than 1 year showing no response and (c) presence of cavity in chest X-ray.

Baseline investigation included complete haemogram , blood sugar , sputum examination for presence of acid fast bacilli , AFB culture and sensitivity , screen test for human immunodeficiency virus, Australia - antigen for hepatitis - B virus, Skiagram chest and CT chest.

Intra-cavitary laser irradiation

Intra-cavitary nitrogen laser was given at the site of lesion or cavity. Cavities were localized topographically using percussion and auscultation , chest radiography and CT scan were done to localize the cavity. The anatomical site of entry was localized between the inter-costal space nearest to the chest wall and then the patient was positioned accordingly, either sitting or supine, depending on the site of puncture. The patient was given 0.6 mg of atropine intra-muscularly 20 minutes before the procedure. With all aseptic precaution, local anesthesia was given and a 10 ml syringe filled with normal saline and fitted with a 126 G 50 mm jelco cannula was introduced at the site, negative pressure was created by pulling back the piston while pushing the needle forward. Few bubbles of air entry into the syringe confirmed the entry of the jelco cannula into the cavity. The syringe with the guide needle was immediately withdrawn and the optical fibre was introduced and fixed at the site. Laser machine started. 2mW nitrogen laser was given for 780 sec, once weekly for total 10 sittings. The nitrogen laser used was pulse nitrogen (2 mw average power, at a wavelength of 337.1 nm, a repetition rate of 10 Hz, energy per pulse of 10-30 µJ and a pulse width of 7 nanoseconds) Nitrogen laser was coupled into a fibre optic with a diameter of 200 µm and an angle of divergence in the order of 20^{o} would imply an energy density of approx. 1.6 J/cm2 at the fibre tip and approx. 0.82 mJ/cm2 at a distance of 5 cm from the fibre tip assuming a spherical cavity. Therefore, 780 seconds exposure time results in dose of approx. 980 J/cm2 at the fibre tip and approx. 492 mJ/cm2 at the distance of 5 cm from the tip. Appropriate statistical test of significance was used in analysis of data (χ^2 test)

RESULTS

In the present study, 122 patients were taken, including 61 patients in nitrogen laser therapy

group and 61 were kept as control group. Male to female ratio was 1.71:1. Mean age of patient was 30.78 (Table 1), mean duration of illness before receiving therapy was 3.19 yrs. (Table 2). The most common drug resistance was found to be of Isoniazid , followed by Pyrazinamide, Streptomycin and Rifampicin. In our study least resistant was found to be of Quinolone group (Ciprofloxacin) (Figure-1).

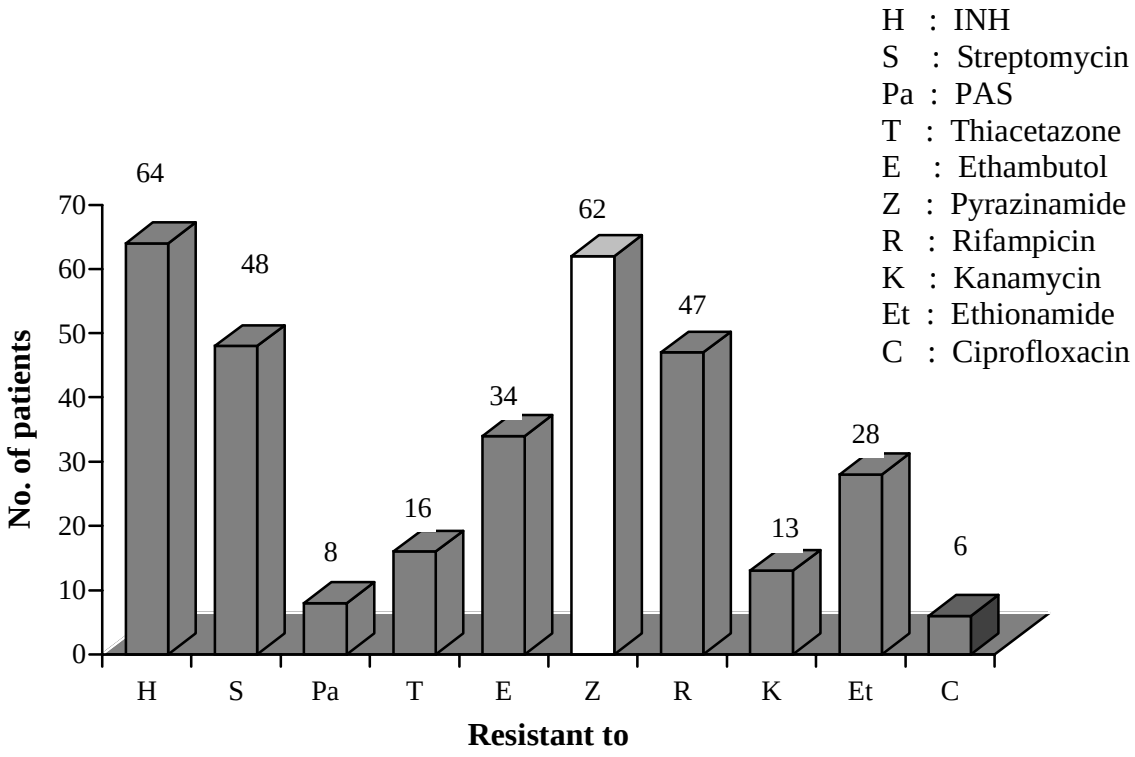

Fig: Pattern of drug resistance according to culture sensitivity report

Table 1: Age wise distribution of cases among LLLT Group and Control Group

Age (in yrs.)	LLT Group		Control Group	
	No.	%	No.	%
15-25	20	32.78	21	34.42
26-35	26	42.62	23	37.70
36-45	11	18.03	11	18.03
46-55	3	4.91	6	9.83
56-65	1	1.63	0	0
Total	**61**	**100**	**61**	**100**

(z test, z=0.09; p> 0.10; Insignificant)

Table 2: Duration of illness before receiving treatment among LLLT Group and Control Group

Duration (in months)	LLT Group		Control Group	
	No.	%	No.	%
12-24	29	47.54	37	60.65
25-36	15	24.59	7	11.47
37-48	3	4.91	6	9.83
49-60	5	8.19	5	8.19
> 5 yrs	9	14.75	6	9.83
Total	**61**	**100**	**61**	**100**

(z test, z=1.45; p> 0.05; Insignificant)

Table 3: Time taken for sputum conversion in LLLT Group and Control Group

	LLLT group		Control group	
Sputum Conversion Positives to negatives	No.	%	No.	%
1st month	22	50.00%	7	26.92%
2nd month	12	27.27%	9	34.61%
5th month	6	13.63%	2	7.69%
6th month	3	6.81%	5	19.24%
8th month	1	2.27%	3	11.53%
Total	**44**	**72.13%**	**26**	**42.62%**
Not Improved	17	27.86%	35	57.37%
Grand Total	**61**	**100%**	**61**	**100%**

Sensitivity is 72.13%, specificity 57.37%, χ^2 test; p value <0.05 significant.

Table 3 shows that out of 61 patients, 44 (72.13%) became sputum smear and culture negative for MTB among LLLT group as compared to 26(42.62%) in control group. Among LLLT group, 22 patients (50%) converted within 1st month as compared to 7 cases (26.92) in control group. Sputum conversion is faster and maximum during the first month of laser therapy (50%).

Improvement was observed according to drug resistance pattern (Table 4). Of the 61 patients, 44 (72.13%) among LLLT group as compared to 26(42.6%) in control group showed improvement. Improvement was maximum in patients of single drug resistance.

Table 4: Improvement according to Drug Resistance

	LLLT Group			CONTROL		
Drug Pattern	**Improved**	**Not improved**	**Total**	**Improved**	**Not improved**	**Total**
Single drug resistance	12(85.71%)	2(14..28%)	14	5(71.42%)	2(28.57%)	7
Two drugs resistance	7(70%)	3(30%)	10	5(50%)	5(50%)	10
Three drugs resistance	7(70%)	3(30%)	10	6(40.00%)	9(60.00%)	15
More than three	18(66.66%)	9(33.33%)	27	10(34.48%)	19(65.51%)	29
Total	**44(72.13%)**	**17(27.86%)**	**61**	**26(42.62%)**	**35(57.37%)**	**61**

Sensitivity is 72.13 %, specificity is 57.37 % , χ^2 test; p <0.05 significant.

Table 5: Improvement according to radiological findings

X-ray findings	LLLT GROUP			CONTROL GROUP		
	Improved	**Not improved**	**Total**	**Improved**	**Not improved**	**Total**
Single cavity	13(81.25%)	3(18.75%)	16	12(70.58%)	5(29.41%)	17
Two cavities	3(75%)	1(25%)	4	1(33.33%)	2(66.66%)	3
Multiple cavities with fibrosis	23(74.19%)	8(25.80%)	31	8(25%)	24(75%)	32
Unilateral destroyed lung with F/C lesion opposite lung	4(40%)	6(60%)	10	1(11.11%)	8(88.88%)	9
Total	**43(70.49%)**	**18(29.50%)**	**61**	**22(36.06%)**	**39(63.93%)**	**61**

Sensitivity is 70.5% , specificity is 63.9% , χ^2 test; p value is < 0.05 significant.

Out of 61 patients, 43 (70.41%) improved radiologically as compared to 22 (36.06%) in control group (Table 5). Maximum improvement was seen in single cavity. Radiological improvement was seen in terms of complete closure of cavity in 20% of improved patients and regression of cavity and thinning of the wall of cavity in 42.85% of improved patients. Rest of the patients' cavity size remained as such.

Five patients had slight Haemoptysis, 7 developed pneumothorax, all were managed conservatively.

All patients, who completed full course of treatment, were followed up for an average period of 3 years. Seven patients (11.47%) showed bacteriological relapse while 4 (6.55%) relapsed within 6 months and 3 (4.91%) relapsed after 12 months after completion of treatment.

DISCUSSION

Multi drug resistant pulmonary tuberculosis (MDR-PTB) is one entity which presently has no other modality of treatment except the second line drugs like Cycloserin, Kanamycin, Ethionamide, Prothionamide, PAS and so on, which in a developing country like India is a costly affair. Also these drugs are not freely available, therefore the patients' compliance becomes poor. The use of alternative modalities of treatment for tuberculosis like UV radiation, electrotherapy, and drugs like iodoform and formaldehyde have been recognized for over one hundred years. Before the advent of chemotherapeutic drugs, agents like iodoform and formaldehyde have been used in treatment of phthisis (tuberculosis) with some success. Radioactive agents such as radium thorium have also been used in treatment of tuberculosis as early as 1903 by Soddy et al. Hence it was proven that apart from chemotherapeutic drugs, alternative modalities of treatment have a role in treatment.

Although the exact mechanism by which beneficial effects of LLLT observed in tuberculosis is not known but it has been observed that nitrogen laser irradiation leads to temporary inactivation of drug sensitive as well as drug resistant clinical isolate of MTB6. UVA radiation has been reported to lead to alteration in cell membrane properties *via* damage to membrane lipid[7-9]. Nitrogen laser irradiation alters the fluidity of lipid region of the cell wall[6].

Another important aspect concerning Nitrogen laser irradiation (337nm)induced inactivation of MTB is that UV (320-400nm)irradiation of cell is known to lead to generation of oxygen radicals as singlet oxygen photosensitized reaction involving endogenous photochromophore[10].

Out of 61 patients, 44(72%) became sputum smear and culture negative for MTB in LLLT group. Among those who achieved Bacteriological conversion, 22 patients (50%) converted within first month as compared to 26.92 in control . Sputum conversion rate is higher and faster in LLLT group as compared to control group. Similar studies were also conducted in Tashkent by Eshankhanov[3] et al and in India by Bhagwanani et al [11],Puri M.M.[12], yielding similar results.

Maximum improvement was seen in younger age group with resistant to one drug and single cavity. Patients who completed treatment were followed up for 24 to 36 months. 7 patients showed bacteriological relapse because of poor drug compliance and multiple cavities.

Laser therapy for MDR-PTB is a newer modality of treatment which gives patients a ray of hope for better quality of life. Results are encouraging and LLLT is well tolerated by the patients. Further work is now required to evaluate the basic mechanism of action of laser and optimize the parameter as far as dose delivery and duration of laser irradiation is concerned.

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