NITROGEN AND HELLIUM-NEON LASER THERAPY IN THE TREATMENT OF DRUG-RESISTANT PULMONARY TUBERCULOSIS.

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The failure of drugs in the treatment of tuberculosis is very frustrating for the physician. In recent years scientists in Russia (the former USSR) have reported on and developed a method of endocavitary nitrogen laser irradiation of patients having the cavitary form of pulmonary tuberculosis. The nitrogen laser acts by emitting ultra violet light which is bacteriocidal for tuberculosis bacilli. The present study reports on ten patients with pulmonary tuberculosis which was sputum positive for acid fast bacilli. The patients included drug-resistant cases. The nitrogen laser probe was introduced directly into the tuberculous cavity percutaneously. In order to improve the immune mechanisms of these patients, helium-neon laser was also given intravenously. Three out of ten patients became sputum negative for *M. tuberculosis*. However, further extensive studies and research work is required to evaluate this new modality of therapy in the treatment of pulmonary tuberculosis.

Introduction

Even today, tuberculosis remains an important world wide problem with an estimated 3 million persons per year having newly identified pulmonary tuberculosis with positive sputum smears.⁽¹⁾ Although the currently available antituberculous drug regimens are highly effective, inappropriate use of medication over the past forty years has resulted in an increased prevalence of patients discharging drug resistant organisms.⁽²⁾ The treatment of these patients with costly, less effective, and more toxic second line drugs (such as kanamycin, cycloserine, ethionamide, PAS - para-amino-salicylic acid) is frankly unaffordable in a developing country. Moreover, failure of second line treatment is even more frustrating. Thus, there exists a need for new drugs and new modalities in the treatment of drug-resistant tuberculosis.

The use of immunomodulating agents or substances is an exciting new area of investigation in the treatment of tuberculosis. Acquired immunity of *Mycobacteria tuberculosis* is mediated by T-cell lymphocytes.⁽³⁾

The role of the macrophage as a host defence cell to kill or phagocytose tubercle bacilli is well established.⁽⁴⁾ In treatment of tuberculosis preference should be given to a laser which emits ultraviolet radiation which is also fatal to *M. tuberculosis*. Scientists in the former USSR have developed a method of endocavitary laser irradiation of patients having cavitary form of pulmonary tuberculosis using an ultraviolet laser, the "Therapeutic Laser Device "Alice" (a nitrogen laser with wave length of 337 nm.) At the same time, helium-neon laser irradiation exerts an activating influence upon the immune response of the mononuclear macrophage system⁽⁵⁾ and produces changes in human lymphocytes.⁽⁶⁾ A clinical trial has also shown this laser-activated immunostimulation effect.⁽⁷⁾ Experimental studies involving the irradiation of *Mycobacterium tuberculosis* bacilli with HeNe laser energy have shown a decrease in the growth properties and virulence of *M. tuberculosis*.⁽⁸⁾ The present study was aimed at studying laser therapy in patients with totally drug-resistant pulmonary tuberculosis.

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Materials and Methods

Patients

Ten patients with pulmonary tuberculosis admitted in L.R.S. Institute of Tuberculosis and Allied Diseases were enrolled for study if they met the following criteria (i) Sputum smear and culture positive for *Mycobacterium tuberculosis* bacilli in spite of having received adequate antitubercular drugs (ii) A cavity not less than 3 cm in diameter detectable in chest x-ray; and (iii) the ability to provide informed consent.

Methods

A day before laser therapy a base line chest x-ray and sputum examination for acid fast bacilli by microscopy was carried out using the Ziehl Meelsen method. Sputum culture for *Mycobacterium tuberculosis* bacilli was performed on Lowenstein Jensen medium.

Intracavitary nitrogen laser irradiation was given using the 'Medical Therapeutical laser Device "Alice"', a nitrogen laser with a wavelength of 337 nm and output power of 1.5 mW. The patients were carefully instructed regarding details of the procedure and its overall safety, accuracy, and possible complications (pneumothorax and haemoptysis). Written consent was obtained. Before the procedure the exact position of the cavity was ascertained from the most recent chest x-ray, tomograms or fluoroscopy. 2% lignocaine was infiltrated into the skin and soft tissue down to the estimated depth of the pleura over the cavity. A long sterile needle No.15, attached to a 20 ml syringe containing 5 ml of normal physiological saline, was inserted into the appropriate intercostal space. The needle was directed towards the cavity on as straight a perpendicular

axis as possible. The puncture of the cavity was marked with the appearance of air bubbles in the syringe. After this syringe was detached from the needle, the laser operational probe was inserted through the needle into the cavity and the cavity wall was irradiated for 15 minutes at the first session. The aspiration needle was withdrawn and the puncture site was sealed. An X-ray of the chest was performed to confirm there were no overt problems. The second irradiation session (10 minutes) was performed after 48 hours.

Endovascular HeNe laser irradiation was carried out with a medical therapeutical laser device "SHIFO-2B" at a wavelength of 632.8nm and an output power of 1.5mW. After selecting a suitable venepuncture site on the lower arm, a 20 g intravenous cannula was inserted under totally sterile conditions. A pre-sterilized HeNe pipe probe was introduced into the vein through the intravenous cannula. To prevent the process of thrombosis on the probe surface, an intravascular injection of 1-2 ml of diluted heparin (5000 units in 400 ml of normal saline) was given before endovascular laser therapy. Three sessions of 20 minutes each were given at 24 hours intervals. The patency of the cannula was maintained by using heparinized saline. After the third sitting the cannula was removed. The laser probe was cleaned with hydrogen peroxide and dipped in ethyl alcohol for 10 minutes before each sitting.

Evaluation of efficacy

Clinical, radiological and sputum examination for acid fast bacilli were done to assess the efficacy of the laser therapy. Patients were evaluated daily for relief in cough, amount of expectoration, fever, chest pain and

Table 1: Drugs taken by each patient in the current study, and the duration of the pharmacotherapy

Patient No.	Drugs Taken	Duration of Treatment
1	S H R E	19 months
2	S H R Z E	9 months
3	S H R Z E T	5 months
4	S H T R Z	18 months
5	S H R	12 months
6	S H R Z E K C En H P	7 years
7	S H R Z T	3 years
8	S H R Z E P T	8 years
9	E H R Z	13 months
10	S H R Z K En C P T	3 years
S= Streptomycin E= Ethambutol Z= Pyrazinamide H= Isoniazid P= Para-amino-salicylic acid C= Cycloserine T= Thioacetazone R= Rifampicin En= Ethionamide K= Kanamycin		

Table 2: Relief from symptoms following laser therapy.

Symptom	No. of Patients	Patients with Relief
Fever	6	4*
Cough	8	6*
Sputum production	10	3*
Chest Pain	5	2*

*Relief was short-lived for 2 weeks.

general well being for a week and then once a week for one month. Chest X-ray was carried out at the end of the second week and fourth week following laser irradiation to ascertain any decrease in the size of the cavity. Sputum was examined for acid fast bacilli by microscopy with Ziehl Neelsen method. Culturing for *Mycobacterium tuberculosis* bacilli was performed on Lowenstein Jensen medium.

Evaluation of adverse effect

Patients were monitored throughout the procedure for pulse, blood pressure, and respiration. They were especially examined for any signs of pneumothorax. A test chest x-ray was performed after each session of nitrogen intracavitary laser irradiation. Haemography was carried out every week for 2 weeks.

Results

Ten patients with drug-resistant pulmonary tuberculosis were given intracavitary nitrogen laser therapy and endovascular HeNe laser therapy combined with the patients' previous antitubercular regime. Two patients of the ten were female. The mean age was 33.2 years (range 24-49 years). All these patients were sputum positive for *M. tuberculosis* by direct microscopy and culture in spite of treatment with antitubercular drugs for at least nine months. (Table. 1)

Clinical improvement in relief of cough, fever, amount of expectoration and chest pain was observed in all patients after laser therapy, but the relief was, however, short-lived.

In the first two weeks of laser therapy there was decrease in the count of acid fast bacilli in the sputum of five patients, but only three were smear negative for A.F.B. at the end of 4 weeks (Table 3). Two of these three patients were followed for five months by sputum smear examination for A.F.B. and culture of their sputum for *M. tuberculosis*. All three patients remained smear negative in the follow up period and sputum culture was negative for *M. tuberculosis* after two months. (Table 4). There was no radiological change in the chest x-ray of these patients.

The complications observed with the intracavitary nitrogen laser therapy were surgical emphysema (one patient); haemoptysis (one patient); and pneumothorax

Table 3: Sputum examination by the Ziehl Neelsen method in the first four weeks following laser therapy.

Patient No.	Sputum Smear for A.F.B											
	Before Laser therapy	After Laser Therapy									3rd week (Once)	4th week (Once)
		First two week - Microscopic examination on alternate day.										
1	+++	+	+	+	+++	+	+	+	+++	Pos.	Pos.	
2	+++	+	+	+	+	+	+	+	+++	Pos.	Pos.	
3	+	0	0	0	0	0	+	0	Pos.	Pos.		
4	+	0	0	0	0	0	0	0	0	Neg.	Neg.	
5	+	0	+	+++	0	0	0	+	0	Pos.	Pos.	
6	+	0	0	0	0	0	0	0	0	Neg.	Neg.	
7	+	+	0	0	0	0	0	0	0	Neg.	Neg.	
8	+	+++	+	+	+	+	+	+	+++	Pos.	Pos.	
9	+	+++	+++	+++	+	+	+	+	+	Pos.	Pos.	
10	+++	+	+	+	+	+	+	+	+	Pos.	Pos.	

Key: 0= No bacilli seen; += 1-9/100 field; ++ = 1-9/10 field; +++ = 1-9/field; Neg = Negative; Pos. = Positive.

Table 4: Sputum examination by Ziehl Neelson method and culture on Lowenstein Jensen media in three patients with drug-resistant pulmonary tuberculosis following laser therapy.

Patient No. 4			Patient No. 6			Patient No. 7		
TaLT	Sa/AFB	C-Mt	TaLT	Sa/AFB	C-Mt	TaLT	Sa/AFB	C-Mt
2 days	Negative	Positive	2 days	Negative	Negative	2 days	Negative	Positive
13 days	Negative	Positive	13 days	Negative	Contam.	13 days	Negative	contaminated
19 days	Negative	Positive	19 days	Negative	Negative	19 days	Negative	Negative
2 months	Negative	Positive	1 month	Negative	Negative	2 months	Negative	Negative
3 months	Negative	negative	2 months	Negative	Negative	5 months	Negative	Negative
5 months	Negative	Negative	5 months	Negative	Negative			
6 months	Negative	Negative	7 months	Negative	Negative			
7 months	Negative	Negative						

Key: TaLT = Duration after laser therapy; Sa/AFB = Smear examination for acid fast bacilli; C-Mt = Culture for *M. tuberculosis*; Contam. = contaminated

(two patients). No side effects or complications were observed with the intravenous HeNe laser irradiation. The complications with intracavitary nitrogen laser therapy were managed conservatively in all patients except in one patient in whom an intercostal drainage tube was inserted for pneumothorax.

Discussion

The accepted treatment regimes for drug-resistant pulmonary tuberculosis is frankly unaffordable in developing countries. In addition second line drugs have a low response rate.⁽²⁾ Treatment of cases who fail to respond to second line therapy is very frustrating. Therefore, new drugs and modalities for treatment of drug-resistant cases are desperately needed, particularly in developing countries where the incidence of T.B. is highest. In this series of ten patients of drug-resistant pulmonary tuberculosis, administration of laser therapy in combination with the patient's previous antitubercular regimen was associated with sputum conversion for *Mycobacterium tuberculosis* bacilli in 3 out of 10 patients. Certain points strongly suggest the likelihood of response to laser therapy: (i) sputum conversion for acid fast bacilli by direct microscopy in the first week of laser therapy in 2 out of 3 responders; and (ii) the sputum in 2 out of 3 responders became culture negative for acid fast bacilli within 2 weeks of laser therapy (Table 4). All these patients were sputum positive for *M. tuberculosis* prior to laser therapy in spite of a long duration of treatment with anti tubercular drugs. Finally, (iii) no

new drug was added, and the patient's previous antitubercular regimen was continued.

Conclusion

The role of intracavitary nitrogen Laser and endovascular HeNe laser as an adjunctive treatment for drug-resistant cases of pulmonary tuberculosis is not fully defined, but it appears promising as an adjunctive therapy combined with antitubercular drugs in a preliminary study of ten patients with drug-resistant pulmonary tuberculosis. The symptomatic relief seen in cough, fever, expectoration and chest pain after initiation of laser therapy was short lived: it is very possible that three sessions of HeNe endovascular irradiation were not sufficient. Three out of ten patients became sputum negative for *M. tuberculosis* bacilli. Comparative clinical trials of laser therapy are needed to define more fully the role of intracavitary nitrogen laser therapy in the treatment of drug-resistant pulmonary tuberculosis. The possible risk of pneumothorax and haemoptysis with intracavitary nitrogen laser irradiation has to be balanced against the risks to the patients and to the community if the disease were to be left untreated or were treated in the previous conventional way.

To formulate the guidelines for laser therapy in drug failure pulmonary tuberculosis, further studies should address the issue of optimal laser energy, duration and frequency of irradiation. There is also an immense need of research to study the impact of laser therapy on immune system of the body and *Mycobacterium tuberculosis*.

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