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THE METHOD OF INDIVIDUALIZED REGIONAL LYMPHOTROPIC THERAPY WITH PHOTOPHORESIS IN PATIENTS WITH MULTIDRUG – RESISTANT PULMONARY TUBERCULOSIS

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We propose a method of individualized regional lymphotropic therapy (RLTT) with photophoresis, as part of multimodality treatment for newly identified destructive multidrug-resistant pulmonary tuberculosis (MDR-TB). The method was developed to meet local specifics of the causative agent, M.tuberculosis (MTB), and metabolic characteristics of the indigenous population of the north, which had been elucidated in earlier studies: low level of drug resistance to isoniazid, predominance of slow isoniazid acetylation rate irrespective of administration routes, leading to accumulation of high bactericidal concentrations of isoniazid in blood. The treatment method is suited for patients with low MTB resistance to isoniazid (1 mcg/mL), and slow or medium acetylation rate. Indications and contraindications are specified, as well. The method is protected by patent RU2650633 'Method for treating infiltrative pulmonary tuberculosis with multiple drug resistance' [12]. The proposed method requires administration of anti-tuberculosis drugs standardly recommended for chemotherapy of MDR-TB, market-authorized medical device for laser therapy, and standard equipment for procedure room and laser therapy room. The article describes administration sites, dosages, routes of administration and laser irradiation (photophoresis), drug regimens, and timings for x-ray check-ups. Use of the proposed method resulted in improved treatment efficiency per 6-month period: time to eradication of clinical manifestations shortened by a factor 1.3 (OR 6.31; 95% CI 1.31-30.37); time to culture conversion shortened by a factor of 1.4 (OR 5.1; 95% CI 1.85-14.09); time to cavity healing reduced by a factor of 1.6 (OR 3.42; 95% CI 1.51-7.72); duration of hospitalization needed for intensive phase shortened by a factor 1.2 ($p<0.01$).

Keywords: tuberculosis, levels of drug resistance to isoniazid, isoniazid inactivation, regional lymphotropic therapy, photophoresis, efficiency.

Introduction. The idea of personalized or individualized approach to patient treatment has been existing since the early days of medicine.

Key to treatment efficiency in tuberculosis (TB) are drug circulation lifetime, and concentrations of medications in blood and in the TB lesions. As a rule, treatment is prescribed based on local bacteriological specifics of the causative agent (MTB), and taking into account metabolic characteristics of the indigenous population of the north [2, 5, 11]. According to findings reported by Vinokurova M.K. (2010), multidrug-resistant MTB in the Sakha Republic (Yakutia) showed minor level of resistance to isoniazid (1 mcg/mL) in 92.4% of cases, minor and high levels of resistance to rifampicin (40 and 80 mcg/mL, respectively), while high levels of resistance to isoniazid (10 mcg/mL) and rifampicin (80 mcg/mL) were observed in 7.6% of cases [11].

As is known, one of the biological properties of MTB is its lymphotropism [2, 3, 15]. As far back as the 30s of the 20th century, Shtefko V.G. established bactericidal action of the lymph on the MTB as it enters the lymphatic bed. Later, evidence has been obtained supporting the view, that the lymphatic system of the lungs is not merely the route of infection spread, but also the area of the lungs where healing starts [3, 13]. Prof Y.M. Levin developed the method of regional lymphotropic therapy (RLTT), a method of drug delivery to the lymphatic system, and patients have been treated with it for more than 30 years in all sorts of health facilities. As certain parts of the lymphatic system have been shown to be interconnected with certain organs/tissues, drug administration to lymphatic vessels and nodes at certain, specified body regions enables preservation of optimal drug concentration in the target lesion for 24 hours, allowing achievement of high therapeutic efficacy [4, 9].

Gavriliev S.S. and colleagues have established that the majority of the population of Yakutia were weak isoniazid acetylators irrespective of administration route, and because of it, accumulated high bactericidal isoniazid concentrations in their blood [5]. Lower therapeutic effect in rapid acetylators, and respectively, higher therapeutic effect in weak acetylators, was observed by number of researchers [16]. The method of photophoresis (low-level laser therapy) has been successfully used to accelerate healing process, as it was shown to have beneficial effect on biochemical reactions, metabolism, microcirculation, and antioxidant activity [10, 6, 7, 8]. Further studies by Gavriljev S.S. and colleagues (2004) demonstrated that intercostal intramuscular administration of isoniazid followed by local photophoresis resulted in increased diffusion of isoniazid in the abnormally altered lesion, and was associated with higher rates of healed destructions in the lungs, and faster culture conversion. Based on the above-mentioned, we developed a method of RLTT for pulmonary MDR-TB, wherein lymphotropic administration of isoniazid with photophoresis is used on top of standard chemotherapy regimen for MDR-TB (regimen IV).

Statistical processing of results was performed using IBM SPSS Statistics 22 software suite. Due to absence of normal distributions for most of the parameters, and due to small study group sizes, measure of central tendency and measure

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of spreading are presented as medians (Me) and quartile distributions (Q1; Q3). Comparisons of quantitative variables and qualitative characteristics between groups were done using Kruskall-Wallis test, and Pearson's chi-squared test, respectively.

Material and methods. Drug susceptibility to isoniazid was determined based on urine samples, using absolute concentration method and solid medium, in the presence of 1 mcg/mL and 10 mcg/mL of isoniazid.

Urine samples were tested for isoniazid acetylation using L.I. Grebennik's modification of Wollenberg's test (1961, 1965) in 189 patients. According to procedure description, patients can be referred to one of the following types: slow, intermediate, or rapid inactivators (acetylators). Test result was determined based on amount of active isoniazid excreted in urine. Amounts below 10%, between 11 and 15%, or above 16% were interpreted correspondingly, as rapid, intermediate, or slow acetylators.

Serum isoniazid levels and dynamics were estimated using HPLC (high-performance liquid chromatography) in 96 slow and intermediate acetylators, using different drug administration routes: regional lymphotropic (n=32), intravenous drip (n=28), intramuscular (n=19), and oral (n=17). Blood samples were collected at specified time after drug administration via different routes (regional lymphotropic (1), intravenous drip (2), intramuscular (3), oral (4)): 1.5 hours later (1st sample), 6 hours later (2nd sample), 9 hours later (3rd sample).

Resources required for the proposed treatment include medications for anti-TB chemotherapy, market-authorized medical equipment, and standard equipment for procedure room and for laser therapy room.

1. Laser therapeutic device Uzor-A-2K, 2-channel, supplied with magnet applicator tips (Technical Specification TU TУ ТВО.290.001; Manufacturer: State-owned enterprise 'Voskhod', Kaluga; Reg. no. 94271-122). Light wavelength: 0.89 μm; number of channels: 2; pulse power per one channel: 4 W; pulse repetition rate: 80-300 Hz; weight: 5.5 kg; pulse duration: 300 nsec.

2. Medications: 10% isoniazid solution (amp): 5.0 mL; 0.5% novocaine injection solution (amp); heparin injection solution (amp): 5000 U/mL.

Treatment method is protected by patent RU2650633 'Method for treating infiltrative pulmonary tuberculosis with multiple drug resistance' [12].

Results and discussion. Cultures of MTB in all patients exhibited low levels of resistance to isoniazid (1 mcg/mL). As is seen in Table 1, rapid acetylators prevailed mostly among non-indigenous population (43.7%), intermediate acetylators were found at equal proportions among non-indigenous and indigenous population (47.9% and 48.2%), while the proportion of slow acetylators was reliably larger among indigenous population of Yakutia (45.4%).

As it is seen in Table 2, statistically meaningful differences were apparent in serum isoniazid concentrations after 1.5 hours: in group 1 (regional lymphotropic) compared to groups 3 (intramuscular) and 4 (oral); in group 2 (intravenous drip) versus group 4 (oral). Lowest serum isoniazid concentrations were observed in patients treated via lymphotropic route, and the highest concentrations – in patients who received oral treatment.

After 6 hours, no differences in serum concentrations between groups with different administration routes were noted. Concentrations remained at therapeutic levels irrespective of administration route, but tended to decrease in groups with intravenous drip, intramuscular, and oral administration, compared to lymphotropic route.

After 9 hours, group 4 (lymphotropic route) showed statistically reliable differences in serum isoniazid concentrations, compared to the rest of groups. The sus-

Table 1

Isoniazid acetylation types based on urine tests, among indigenous and non-indigenous population of extreme north

Population	Isoniazid acetylation type						Total	
	Rapid		Intermediate		Slow			
	абс.	%	абс.	%	абс.	%	абс.	%
Indigenous	9	6.4	68	48.2	64	45.4	141	100
Non-indigenous	21	43.7	23	47.9	4	8.4	48	100
Total	30	15.9	91	48.1	68	36.0	189	100
p*	$\chi^2 = 31.87$ df = 1 p = 0.001		$\chi^2 = 0.01$ df = 1 p = 0.894		$\chi^2 = 18.29$ df = 1 p = 0.001			

Note: *p – Pearson's χ2 test.

Table 2

Serum isoniazid concentrations for different administration routes, mg/L (Me (Q1; Q3))

Collection time	Isoniazid concentration (mg/L) for different administration routes:				p*
	1	2	3	4	
1st sample	4.2 (3.4; 5.0)	8.0 (5.3; 10.7)	12.5 (9.4; 15.6)	17.1 (23.8; 10.3)	$p_{1-3} < 0.001$ $p_{1-4} < 0.001$ $p_{2-4} = 0.030$
2nd sample	3.1 (2.0; 4.2)	2.2 (0.9; 3.5)	2.4 (1.0; 3.8)	2.2 (1.0; 3.4)	p = 0.321
3rd sample	2.2 (1.7; 2.7)	0.8 (0.2; 1.4)	0.8 (0.4; 1.2)	0.8 (0.6; 1.0)	$p_{1-2} = 0.003$ $p_{1-3} = 0.005$ $p_{1-4} = 0.008$
Isoniazid concentration decrease, %					
After 6 hours	27.5 (13.6; 41.4)	74.0 (63.7; 84.3)	79.0 (67.7; 90.3)	78.0 (66.3; 89.7)	$p_{1-2} = 0.012$ $p_{1-3} < 0.001$ $p_{1-4} = 0.002$
After 9 hours	48.5 (39.6; 57.4)	84.3 (74.7; 93.9)	92.6 (88.6; 96.6)	93.7 (89.2; 98.2)	$p_{1-3} < 0.001$ $p_{1-4} < 0.001$

Note: * Kruskall-Wallis test

tained therapeutic serum concentrations were observed in lymphotropic group, compared to decreased concentrations (below 1 mg/L) in groups with intramuscular and oral drug administration.

RLTT with photophoresis is indicated for patients with newly detected extensive destructive pulmonary MDR-TB, with minimally allowed level of resistance to isoniazid equal to 1 mcg/mL, and who are either slow (above 16%) or intermediate (11-15%) isoniazid acetylators.

Contraindications to RLTT include: intolerance/allergy to any agents used in treatment; pyoinflammatory diseases of skin and subcutaneous tissue; pronounced pain syndrome in response to drug administration.

Contraindications to photophoresis include: bleeding or hemoptysis; advanced concurrent diseases or complications (stage IIB-III heart failure, neoplasms, organic injury of central nervous system, stage II-III thyrotoxicosis, diseases of hematopoietic system); pregnancy; diseases associated with pronounced metabolic disturbances (decompensated diabetes mellitus) or dystrophy; disorders of blood.

RLTT with photophoresis was used on top of intensive phase of the chemotherapy regimen for pulmonary MDR-TB (regimen IV). RLTT is performed in combination with isoniazid, a highly lymphotropic anti-TB drug with remarkable capacity to reach and reversibly bind with cell structures of lymphatic tissue. Lymph-stimulating permeator agent is needed to ensure delivery of isoniazid to lymphatic bed. As permeator, we used heparin (1.0 mL, 5000 MU) dissolved in 4.0 mL of 0.5% novocaine solution.

Daily dose (10 mg/kg) of isoniazid solution is administered to subcutaneous tissue, alternating injection sites each time (axillary space; 5th intercostal space near the sternum edge; infraclavicular space in the projection of the joint between the first rib and sternum) 5 times a week, followed by photophoresis, during 25 days.

RLTT is performed in the procedure room, strictly adhering to the standards of aseptics and antiseptics.

Injection sites (axillary space, 5th intercostal space, infraclavicular space) are alternated every day, based on the extent of disease. Also, daily alternation of injection sites helps prevent injection site induration in subcutaneous tissue.

The 1st syringe is filled with 1.0 mL (5000 MU) of heparin and 4.0 mL of 0.5% novocaine solution; the 2nd syringe is filled with daily dose of 10% isoniazid solution (10 mg/kg) and 0.5% novocaine solution till a total amount of 10.0 mL is reached. Then the injection site is swabbed with alcohol swab, and a subcutaneous injection of heparin is performed, followed by injection of isoniazid solution using the same needle.

Injection to axillary space is performed in sitting position. The patient is sitting on the chair, the arm at the side of injection is placed behind the patient's head. Needle is inserted horizontally, parallel to costal surface, for two thirds of needle's length, stepping 4-5 cm. away from the axillary fossa and 1.5-2 cm. away from the edge of greater pectoral muscle (*musculus pectoralis major*).

Injection to the 5th intercostal space near the edge of the sternum is performed in supine position. The injection site is palpated, then a needle is inserted, stepping 1-1.5 cm. away from the edge of the sternum, subcutaneously, at an acute angle, parallel to the rib, for the half of the needle's length.

Injection to infraclavicular space is performed likewise in supine position, with the patient's head turned the opposite way to the injection side. The joint between the first rib and the manubrium of sternum is palpated, and stepping 1-1.5 cm. away, the needle is inserted subcutaneously, at acute angle, parallel to the rib, for the half of needle's length.

The injection site is covered with alcohol wipe and adhesive strip.

15-20 min. after the injection, body area where isoniazid was injected is further exposed to photophoresis. Photophoresis is performed in laser therapy room (pulse frequency 150 Hz, pulse power 2 W, exposure duration 256 sec.), 5 days a week, during a course of 25 seances.

Additionally, in the evening (18.30), patients received 0.3 g. of isoniazid, depending on their body weight.

On weekends, and after the completion of the course of RLTT with photophoresis, isoniazid was administered intramuscularly (daily dose of 10 mg/kg) in the morning (10.00), and orally (0.3 mg) in the evening (18.30), depending on patient's body weight.

X-ray and CT checkup was performed 21 days after the completion of RLTT with photophoresis. Based on indications, a course of RLTT with photophoresis was repeated.

The efficiency of the proposed treatment in newly detected infiltrative destructive pulmonary MDR-TB in terms of culture conversion estimated after 6 months of treatment was 89.1% (experiment group) vs. 61.5% (control group) ($p<0.05$).

Radiological assessment after 6 months of treatment among slow or intermediate acetylators with low levels of resistance to isoniazid (1 mcg/mL) showed reliably higher proportion of healed cavities in group treated with RLTT with photophoresis on top of standard chemotherapy (regimen IV): 74.5% (experiment) vs. 46.2% (control) ($p<0.05$).

Conclusions.

1. Bacteriological examination of *M.tuberculosis* isolated from patients participating in the study showed that all patients had low levels of resistance to isoniazid (1 mcg/mL).

2. Indigenous residents of Yakutia, in the majority, were either slow (45.4%) or intermediate (48.2%) isoniazid acetylators ($\chi^2 = 18.29$ df = 1 p = 0.001).

3. Regional lymphotropic administration of isoniazid in combination with photophoresis allowed more long-lasting bactericidal concentration of isoniazid in serum, assessed 9 hours after drug administration (2.2 (1.7; 2.7) mg/L) vs. baseline (4.2 (3.4; 5.0) mg/L)), compared to other administration routes ($p<0.001$).

4. Lymphotropic administration of isoniazid with photophoresis on top of intensive phase of standard chemotherapy regimen IV, in patients with newly detected infiltrative pulmonary MDR-TB with low resistance to isoniazid, substantially improved treatment efficiency after 6 months of treatment: time to eradication of clinical manifestations shortened by a factor 1.3 (OR 6.31; 95% CI 1.31-30.37); time to culture conversion shortened by a factor of 1.4 (OR 5.1; 95% CI 1.85-14.09); time to cavity healing reduced by a factor of 1.6 (OR 3.42; 95% CI 1.51-7.72); duration of hospitalization needed for intensive phase shortened by a factor 1.2 ($p<0.01$).

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