Ratified by

Chief Medical Officer of
Clinical hospital № 83
N. Matveev
“ ”_____ 1996 yr

Report
on the results of clinical study of the medication Polyoxidonium in patients with purulent-septic diseases of lungs and pleura (Phase II)

Executors:

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Report

Clinical study of Polyoxidonium injections at 6 mg dose in patients with purulent-septic diseases of lungs and pleura

Type of study: Double blind, placebo-controlled

The present research conduction is based on the decision of the Pharmacological Committee of Ministry of Health and Medical Manufacturing, Russian Federation made on 03.10.95.

Phase of study: II

Number of patients: 60

Serial number of medication: 030995

Sponsor: "Scientific-Medical Center Petrovaks"
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Research institution:
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Regulating standards:
The research is carried out in accordance with the requirements of Pharmacological Committee, Ministry of health, Russian Federation
The BS project "Regulations of conduction of high-quality clinical studies in Russian Federation".

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1. Grounds for the phase II clinical research conduction

In compliance with the instruction of the State Pharmacological Committee of Ministry of Health and Medical Manufacturing, Russian Federation (Meeting protocol № ___ of the State Pharmacological Committee (SPC), MHMM, RF, held ___" _____"_____yr) phase II clinical study of the medication Polyoxidonium in patients with purulent-septic diseases of lungs and pleura was carried out at the department of thoracic surgery, Municipal Clinical Hospital № 83. 350 flasks containing 6mg Polyoxidonium each (in total 2100mg) as well as adequate quantity of placebo and the "Instructions of "Polyoxidonium" study" ratified on 23.02.1995yr by the SPC of MHMM, RF were provided by the developer – Institute of Immunology, MHMM, RF for purposes of phase II clinical trial conduction.

2. The aims and objectives of the present research

The present research that implied testing (II phase) of Polyoxidonium in patients with purulent-septic diseases of lungs and pleura was primarily aimed to evaluate the clinical effectiveness of Polyoxidonium use in this category of patients as well as to develop the optimal dosage regimens of the given medication applicable to the combined treatment of purulent-septic disorders. The following tasks were undertaken to achieve the research goals:

1. Comparative assessment of clinical efficacy of Polyoxidonium use at different course doses and regimens in patients with suppurative-septic disorders of lungs and pleura.
2. Investigation of influence of Polyoxidonium administration at different course doses and regimens on a number of hematological and biochemical values of patients with the purulent-septic disorders of lungs and pleura.
3. Evaluation of Polyoxidonium therapy influence on the immunological status values in patients with the purulent-septic disorders of lungs and pleura.
4. Assessment of severity of probable toxic adverse effects of Polyoxidonium use during the combined treatment including different course dosages and regimens of the probationer medication in patients with the purulent-septic disorders of lungs and pleura.

3. The general plan of the phase II clinical research conduction

1. Eligibility criteria of patients included in the present research

Patients with the purulent-septic disorders of lungs and pleura that had previously undergone thoracic surgical intervention of different extent were enrolled in the present study. Results of clinical and laboratory examination including evaluation of overall health status of patients, body temperature, alterations of complete blood count and etc. served to be the criteria for the adequate diagnosis establishment. The data of more sophisticated laboratory methods such as chest X-ray, bronchoscopy, bronchography, and ultrasonography were used on diagnosing. Purposeful selection of patients according to gender, age and characteristics of the primary disease was not accomplished (Table 1 demonstrates the patient distribution in accordance with gender, age as well as primary disease characteristics). Clinical status of patients by the moment of Polyoxidonium therapy commencement was evaluated conjointly with the treating doctors in compliance with the 3- grade scale (3 – "severe"; 2 - "moderate"; 1 – "satisfactory"). Patient distribution to groups depending on the status severity is depicted in the table 1.

All patients participated in the research as volunteers. All patients had received the written information on medication Polyoxidonium and subsequently, they had given the written informed consent to take part in the study.

The patients with critical status as well as those suffering from the decompensated hepato - renal failure manifestations were excluded from the study.

2. Polyoxidonium treatment schedules

The phase II clinical study was conducted in "double-blind" manner, in other words, neither patients nor the treating physicians were informed whether patients would receive Polyoxidonium or placebo. Doctors participating in the clinical trial had at disposal the numbered and sealed envelopes that contained special codes. Research plan intended to unseal the envelopes exceptionally in cases of development of undesirable adverse effects. All envelopes that remained sealed as well as unutilized flasks containing medication were sent back to the developer – Institute of Immunology, MHMM, RF.

Identical flasks containing either 6mg Polyoxidonium or placebo produced by the Institute of Immunology, MHMM, RF were used during research. Each flask was marked with identification number, which corresponded to the questionnaire number of patient enrolled in the study. All medications were kept in a locked refrigerator at $+4^0$ C.

By the moment of study completion and subsequent unsealing of envelopes all participants of the clinical trial were distributed in 2 clinical groups: **main** group (patients treated with Polyoxidonium) and **control** group (placebo recipients). Patients within the both study groups were further divided in clinical subgroups depending on the characteristics of used course dosages and regimens of either Polyoxidonium or placebo. Thus, the main clinical group patients were divided in two subgroups designated as "M"1 and "M"2. Patients attributed to "M"1 subgroup were treated with Polyoxidonium given intramuscularly at single dose of 6mg/day in the earlier half of the day, for five successive days. Hence, Polyoxidonium course dose equaled 30mg for the "M"1 subgroup patients and the total dose was divided into 5 intramuscular injections, performed at a time lag of 24 hours during workweek. Patients from the "M"2 subgroup also received Polyoxidonium given intramuscularly at 12mg single dose on alternate days in the earlier half of the day, for 10 days. Course dose of Polyoxidonium equaled 60mg for the patients assigned to "M"2 subgroup and the total dose was divided into 5 intramuscular injections, performed at a time lag of 48 hours during workweeks.

Course dosages/regimens of placebo administration in the "C"1 and "C"2 clinical subgroups of the control group were identical to those of Polyoxidonium therapy in "M"1 and "M"2 subgroups, respectively, of the main clinical study group.

Immunomodulatory treatment other than Polyoxidonium was not administered to study participants during the trial. Parallely to Polyoxidonium (or placebo) therapy patients undertook

combined treatment targeted at postoperative purulent-septic complications, including infusions and antibiotic treatments in accordance with the schemes that were approved by the research clinic.

The main and control clinical groups as well as “C”1, “C”2, “M”1, “M”2 subgroups were comparable in extent of previous surgical intervention and in the type and volume of infusion and antimicrobial therapies (Tables 2 and 3).

Polyoxidonium injections were performed in the mornings under the supervision of treating doctor.

3. The criteria for the evaluation of clinical and laboratory effectiveness of the medication Polyoxidonium

The accurate records of the data retrieved during the present research were kept using “Patient’s Forms” and all information was, subsequently, analyzed by means of mathematical statistics using PC UC-AT and the pack of computer software named “statgrafics”. If the patient was expelled from the study for any reasons all required documentation was filled in and the exclusion motives were deliberately pointed out.

3.1. Clinical values

The following clinical status parameters such as body temperature twice a day (in the mornings and evenings), heart rate as well as overall state of health (in compliance with conventional 3-grade scale: 3-“severe”, 2-“moderate”, 1-“satisfactory”) of patients enrolled in the study were evaluated daily.

3.2. Hematological values

The complete blood count including assessment of hemoglobin level, erythrocyte and leukocyte counts as well as differential white blood cell count implying quantification of lymphocyte, immature (young, band) and mature (segmented) neutrophils, eosinophil, basophil, monocyte percentages by means of cellular morphology review following routine staining of the blood smear using Giemsa-Romanovsky stain were taken by the study participants the day before Polyoxidonium therapy commencement and 2-3 days after immunomodulating treatment course completion.

3.3. Biochemical values

Biochemical tests of blood samples were accomplished by means of apparatus “Minilab” (“Labsystems”). Total protein, albumin, bilirubin, creatinine, blood urea nitrogen (BUN) levels as well as the activity of transaminases (ALT, AST) were assessed using standard biochemical diagnostic sets produced by the same company.

3.4. Immunological values

Immunological testing included assessment of the cellular immunity values as follow: evaluation of peripheral blood mononuclear cell subpopulations by means of flow cytometry using monoclonal antibodies to CD3, CD4, CD8, CD16, CD72 clusters of differentiation produced by “Sorbent”; assessment of in vitro phytohemagglutinin-induced proliferative activity of peripheral blood mononuclear cells by means of blast transformation reaction and subsequent estimation of [3H] thimidine inclusion into DNA by scintillation radiometry; characterization of the functional activity of peripheral blood neutrophils according to the plastic adhesion, superoxide-anion production on NTB-tests and to the production of active forms of oxygen in luminole-dependent chemiluminescence reaction (spontaneous and zymosan-induced NTB-test and LDCL). The

serum immunoglobulin – IgG_1, IgM, IgA levels were assayed using Manchini method of radial immunodiffusion.

3.5. Clinical and laboratory data evaluation scheme

Patients included in the phase II study of Polyoxidonium were subjected to thorough physical examination and laboratory tests the day before immunomodulatory therapy commencement and 2-3 days after it's completion.

4. The criteria for the evaluation of clinical and laboratory effectiveness of the medication "Polyoxidonium"

1. Criteria for the evaluation of clinical effectiveness of the medication Polyoxidonium

The features of dynamic changes in the course of primary suppurative-septic process served to be the basic criteria for the clinical efficacy of Polyoxidonium administration during the combined treatment of postoperative suppurative-septic complications in patients that had underwent thoracic surgical intervention.

Polyoxidonium efficacy was considered to be "excellent" (5 grades) – if the patient had exhibited the apparent tendency towards the regression of purulent-septic process, improvement of patient's general status, disappearance of intoxication symptoms as well as normalization of body temperature and laboratory findings during Polyoxidonium (or placebo) treatment period.

"Good" (4 grades) was designated to the treatment result – if the general patient status had improved and manifestations of intoxication had diminished considerably following the Polyoxidonium (or placebo) therapy completion, but the subfebrile body temperature and moderate leukocytosis remained though.

Polyoxidonium efficacy was "satisfactory" (3 grades) – if the slight improvement of patient status, body temperature reduction at a slow pace, gradual normalization of laboratory findings had been observed during and after the Polyoxidonium course completion.

Polyoxidonium "ineffectiveness" was proved (2 grades) - if Polyoxidonium use had not yielded any changes in patient status and laboratory findings.

"Process progression" was registered (1 grade) – in the cases of progressive aggravation of patient status due to spreading of suppurative-septic process.

In addition, mortality and hospitalization period shortening in present research participants were taken into account on Polyoxidonium effectiveness evaluation.

2. The laboratory criteria of treatment efficacy assessment

The laboratory criteria for the effectiveness of Polyoxidonium (or placebo) administration turned out to be the normalization of hematological, biochemical and immunological values manifested by:

- decrease in leukocyte count,
- diminusion of band neutrophil percentage,
- stabilization of hemoglobin level
- reduction in bilirubin, blood urea nitrogen (BUN), creatinine concentrations to the normal values,
- normalization of activity of liver enzymes – alanine aminotransferase and aspartate aminotransferase,
- positive changes in quantitative as well as functional characteristics of immune system.

5. The results of phase II clinical trial of the medication Polyoxidonium

60 patients suffering from the purulent-septic diseases of lungs and pleura were examined and treated during the research. Control (placebo) group was comprised of 10 patients. 40 patients received different dosages of Polyoxidonium. 16 patients were given medication at course dose 30mg. Study group of Polyoxidonium therapy at 60 mg course dose was composed of 24 patients (Table. 1).

Evaluation of clinical effectiveness of Polyoxidonium therapy

The data on suppurative-septic process course, laboratory as well as other objective data, mortality rate and hospitalization duration were used to assess the clinical effects of Polyoxidonium as an adjuvant to the combined treatment of suppurative-septic diseases of lungs and pleura.

Polyoxidonium treatment resulted in considerable decrease in number of hospitalization days, improvement of general patient status, body temperature normalization on $2^{nd} – 3^{rd}$ days of agent application. However, these favorable changes lacked statistical authenticity. Patients from the both study groups showed authentic reduction in evening body temperatures whereas the statistically significant decrease in evening fever was not observed in placebo group patients. Moreover, patients treated with Polyoxidonium demonstrated statistically significant reduction in heart rate. At the same time, control group participants could achieve only slight decline in tachycardia (table 5).

Findings of clinical efficiency evaluation of Polyoxidonium treatment are listed in the table 4.

Clinical-hematological influence of Polyoxidonium therapy

Polyoxidonium recipients exhibited more prominent decrease in leukocyte count and reduction of band neutrophil percentage in comparison with control groups. The rest hematological parameters failed to show considerable changes.

Polyoxidonium influence on the biochemical values of blood test

Decrease in serum levels of bilirubin, creatinine and blood urea nitrogen as well as reduction of AST and ALT activities appeared to be the most noticeable effects of Polyoxidonium therapy that were revealed during analysis of biochemical blood test findings in all patients treated with immunomodulating agent. The same parameters either remained constant or showed even slight increase in control group participants. Levels of total protein as well as albumin were not affected considerably in any study group (table 6).

Impact of Polyoxidonium therapy on immune status values

The majority of patients that received Polyoxidonium at either 6mg or 12mg single doses as an adjuvant to the combined treatment achieved favorable changes in immune status findings that were manifested by the enhancement of lymphocyte counts (CD3+, CD4+, CD16+) as well as elevation of the functional activities of neutrophils and lymphocytes (table 7).

Data enumerated in table 7 demonstrate that authentic enhancement of CD3+, CD4+, and CD16+ lymphocytes' quantities was revealed in the both main groups whereas control group patients failed to show even tendency towards the elevation of the same parameters. Levels of CD8+ and CD72+ lymphocytes remained stable in all study groups.

Authentic increase in the induced LDCL and plastic adhesion provides evidence for the stimulation of functional activity of neutrophils under the influence of Polyoxidonium. Results of spontaneous as well as mitogen-induced blast transformation reactions corroborate the functional activation of lymphocytes under the effects of immunomodulating therapy.

Comparative assessment of dynamic changes in immune status values of patients treated with different course doses of Polyoxidonium showed that administration of Polyoxidonium at

60mg course dose (12 mg single dose given on alternate days) produced more pronounced favorable changes in patients' immune status findings compared to the baseline levels of respective parameters as well as to the immune status values of control group patients.

Conclusion

Phase II clinical trial that was aimed at investigation of clinical effectiveness of the novel immunomodulatory agent - Polyoxidonium as an adjuvant to the combined treatment of purulent-septic diseases of lungs and pleura has demonstrated beneficial influence on the clinical and biochemical values of blood tests in this category of patients as well as on the dynamic changes in immune status parameters (including functional activities and absolute numbers of peripheral blood immunocompetent cells as so as reconstitution of the quantitative ratio of peripheral blood lymphocyte subpopulations) in comparison with control cohort patients receiving placebo.

Clinical effectiveness of the medication Polyoxidonium proved to be mediated by the immunomodulating capacity and by the profound detoxicant properties documented by the regression of clinical (reduction in tachycardia and body temperature) and laboratory (decrease in blood levels of creatinine and blood urea nitrogen) signs of intoxication.

The most prominent favorable alterations of clinical and laboratory findings were observed in patients treated with Polyoxidonium at course dose 60mg (12mg single dose given on alternate days) contributing to the decision that the schedule implying administration of the probationer medication at this course dosage/regimen gave the best account of itself as promotes the most advantageous efficiency of Polyoxidonium.

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Table 1

Patient distribution in compliance with gender, age, characteristics of the primary disease as well as with the features and severity of subsequent purulent-septic complications

Patient groups	**Control group**	**(placebo)**	**Main group**	**Polyoxidonium**
	Subgroup "K"1	**Subgroup "K"2**	**Subgroup "O"1**	**Subgroup "O"2**
In total	9	11	16	24
Male	5	5	9	13
Female	4	6	7	11
		M E A N	A G E	
	59,5	56,7	58,1	58,6
	Characteristics	**of the**	**primary**	**disease**
Abscessed pneumonia	3	4	6	11
Lung carcinoma	2	2	4	6
Bronchiectasis	1	2	1	1
Suppurative airy cyst	2	2	2	3
Others	1	1	3	3
Features	**of the**	**purulent**	**septic**	**complications**
Stagnant pneumonia	3	4	7	8
Broncho-pleural fistula	1	2	1	1
Pleural empyema	2	3	5	8
Suppuration of postoperative wound	3	1	3	6
Mediastinitis	-	1	-	1
Severity	**of the**	**purulent**	**septic**	**complications**
Severe status	3	4	6	8
Moderate severity	3	3	4	9
Satisfactory	3	4	6	7

Table 2

Patient distribution in accordance with the type of surgical intervention

Types of surgical intervention	**Control group**	**(Placebo)**	**Main group**	**(Polyoxidonium)**
	Subgroup "K"1	**Subgroup "K"2**	**Subgroup "O"1**	**Subgroup "O"2**
Drainage of pleural cavity	3	4	6	8
Abscess drainage	2	2	4	5
Lobectomy	1	2	3	5
Sparing resection of lung	2	2	2	5
Other operations	1	1	1	2

Table 3

Patient distribution depending on the character and volume of antimicrobial therapy

Medications	**Control group**	**(Placebo)**	**Main group**	**(Polyoxidonium)**
	Subgroup "K"1	**Subgroup "K"2**	**Subgroup "O"1**	**Subgroup "O"2**
Semi-synthetic penicillins	9	8	9	14
Cephalosporins	2	3	2	4
Aminoglycosides	5	6	7	19
Macrolides	1	2	2	2
Levomicetin	2	0	2	3
Dioxidin	1	1	1	2
Number of agents				
I	2	3	4	8
II	4	4	5	11
III	2	3	5	4
IV	1	1	0	1

Table 4

Evaluation of clinical effectiveness of Polyoxidonium therapy and mortality

Treatment results (grades)	**Control group**	**(Placebo)**	**Main group**	**(Polyoxidonium)**
	Subgroup "K"1	**Subgroup "K"2**	**Subgroup "O"1**	**Subgroup "O"2**
"Excellent" - 5	2 (22,2%)	2 (18,8%)	5 (31,25%)	9 (37,5%)
"Good" - 4	2 (22,2%)	3 (27,27%)	4 (25%)	6 (25%)
"Satisfactory" - 3	1 (11,1%)	3 (27,27%)	5 (31,25%)	5 (20,83%)
"Ineffectiveness"-2	2 (22,2%)	2 (18,8%)	1 (6,25%)	2 (8,33%)
"Progression" - 1	2 (22,2%)	1 (9,09%)	0 (0%)	0 (0%)
Mortality	2 (22,2%)	3 (27,27%)	1 (6,25%)	2 (8,33%)

Table 5

Influence of Polyoxidonium therapy on the clinical findings

	Subgroup "K"1		Subgroup "K"2		Subgroup "O"1		Subgroup "O"2	
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Duration of p/o hospitalization (days)	38,6±7,5		37,9±6,3		29,5±5,8		26,8±6,7	
Body temperature (mornings)	37,2±0,33	36,7±0,11	37,3±0,2	37,0±0,1	36,9±0,2	36,7±0,1	37,1±0,1	36,8±0,2
Body temperature (evenings)	38,1±0,4	37,7±0,2	38,4±0,4	37,5±0,4	38,3±0,4	36,8±0,3	38,4±0,2	36,7±0,2
Heart rate	88,7±1,9	86,3±1,3	89,4±1,8	83,9±1,7	88,9±2,1	82,6±2,3	90,7±2,3	81,7±1,9

Table 6

Influence of Polyoxidonium therapy on the hematological and biochemical values

	Subgroup "K"1		Subgroup "K"2		Subgroup "O"1		Subgroup "O"2	
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Leukocytes	12,6±1,8	9,6±1,4	11,7±1,2	10,1±1,0	11,9±1,6	8,2±1,3	12,3±1,1	7,3±0,9*
Neutrophils	78,9±3,4	74,6±2,8	76,5±3,7	75,1±1,9	77,5±2,6	73,6±2,3	75,9±3,1	72,9±1,85
Band neutrophils	13,6±1,9	9,7±1,7	12,7±2,3	10,6±1,6	14,9±2,5	7,6±1,75*	13,1±2,0	8,7±2,1
Monocytes	3,6±0,7	3,5±0,9	3,4±0,8	3,7±0,85	3,2±0,5	2,9±0,7	3,6±0,8	3,3±0,5
Hemoglobin	97,3±4,8	97,6±5,3	91,6±5,3	89,8±6,7	88,9±3,9	95,8±4,8	87,5±4,6	96,9±5,8
Total protein	62,7±5,6	61,9±4,8	63,6±6,4	64,3±3,9	66,8±5,7	69,3±4,4	67,6±3,2	71,7±5,2
Albumin	38,3±3,6	35,7±2,9	30,7±1,8	36,5±2,6	38,7±2,3	39,7±4,9	37,3±3,5	38,5±3,9
Bilirubin	12,6±3,9	11,7±2,3	9,9±2,15	10,3±3,6	11,2±1,7	9,3±1,55	10,8±2,1	8,6±1,7
BUN	6,8±1,1	6,7±0,85	6,1±0,7	5,8±1,2	6,6±1,8	5,1±1,35	5,8±0,9	4,7±0,6
Creatinine	156,6±18,9	167,3±26,7	143,8±17,1	137,7±21,4	149,9±18,0	105,6±18,8	131,8±23,8	99,6±13,1
AST	33,9±6,1	32,8±5,4	29,3±5,5	28,6±4,9	36, 1±5,7	28,3±3,9	37,6±9,8	18,6±4,9
ALT	26,5±4,8	25,9±6,1	24,8±3,7	25,7±3,7	28,8±3,2	22,3±4,8	31,0±7,2	17,9±2,7

Table 7

Influence of Polyoxidonium therapy on the immunological values

	Subgroup "K"1		Subgroup "K"2		Subgroup "O"1		Subgroup "O"2	
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
CD3+	44,8±5,1	45,6±4,7	46,3±3,5	48,4±3,9	43,7±2,6	54,6±3,1*	42,8±3,5	57,3±2,95*
CD4+	32,3±2,4	31,9±2,6	29,5±1,9	30,1±2,1	28,6±1,8	35,4±2,2*	27,7±1,95	33,9±2,17*
CD8+	21,8±1,7	22,7±1,9	24,3±1,65	22,3±2,0	20,7±1,3	20,9±1,55	22,3±1,8	23,8±2,0
CD4/CD8	1,76±0,17	1,69±0,14	1,53±0,22	1,49±0,31	1,67±0,18	1,55±0,21	1,65±0,16	1,57±0,29
CD16+	9,8±2,4	8,6±1,9	8,3±2,8	9,1±2,5	7,1±2,1	12,6±2,9	6,8±1,1	11,3±1,75*
CD72+	3,6±0,5	3,7±0,9	4,0±0,35	4,6±0,7	3,4±0,25	3,6±0,4	4,1±0,75	4,2±0,8
IgG	876,5±68,9	913,8±57,6	863,7±54,5	898,8±67,3	928,3±76,7	1025,0±59,3	885,6±45,4	1038,7±65,6
IgA	365,8±36,7	344,4±29,3	385,6±27,5	331,7±38,9	369,7±45,6	335,6±31,6	286,5±29,7	311,7±26,7
IgM	171,9±19,8	185,6±20,4	165,6±15,7	193,6±21,2	175,7±16,3	169,5±25,4	157,5±22,9	161,3±29,8
LDCL sp.	874,2±11,4	1151,6±269,4	1012,4±217,7	1263,3±145,2	896,4±103,6	1121,2±98,4	976,8±96,7	1236,7±235,4
LDCL ind.	3275,6±475,6	3368,4±531,6	3075,3±527,4	3268,4±375,3	2996,8±306,5	4358,2±698,1	3105,1±358,3	5028,4±863,7*
Adhesion	44,4±6,8	47,5±8,2	45,3±7,4	48,2±7,2	44,1±8,3	67,2±3,7	48,4±6,1	74,5±3,8*&
NTB sp.	68,7±8,8	63,2±12,3	73,4±8,2	75,1±5,7	67,2±5,4	83,9±11,4	76,2±9,4	94,1±11,8
NTB ind.	123,3±7,6	110,8±14,0	133,1±11,4	142,0±15,8	96,6±4,3	115,7±12,1	108,1±9,2	136,4±14,5
RLBT spont.	386,3±98,9	412,4±112,6	378,9±146,3	409,7±86,9	429,6±111,7	695,7±153,6	356,7±95,6	806,35±137,7*&
RLBT ind.	7651,7±1035,6	6986,3±1127,5	6384,5±936,3	7039,7±1058,6	7381,6±793,6	12035,6±1313,3*&	7286,5±1195,6	11836,5±1286,5*&

The findings marked with * showed statistically significant differences within group (before and after the treatment).
Parameters marked with & showed statistical difference between the main and control groups following therapy.