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Report on II phase clinical trial of Polyoxidonium in patients with generalized surgical infections

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Report

Clinical study of Polyoxidonium injections 3 mg, 6 mg doses in patients with generalized forms of surgical infections

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: 110

Serial number of medication: 020995, 030995

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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 present research conduction

The decision of the Pharmacological Committee of Ministry of Health and Medical Manufacturing, RF, made on 03.10.95., gave grounds for the II phase clinical study of medication "Polyoxidonium". According to the Protocol #18 of Pharmacological committee Meeting held on 3 October 1996, the City Clinical Hospital # 24 was approved to be the research-center of the Polyoxidonium clinical trials.

2. The aim and objectives of the present trial

The present research was primarily aimed to evaluate the effectiveness and the safety of Polyoxidonium use in patients with surgical purulent-septic complications. The objectives of the study were as follow:

1. Assessment of safety and clinical efficacy of different Polyoxidonium doses use in patients with surgical infections.
2. Investigation of Polyoxidonium influence on the hematological values in patients with purulent-septic disorders.
3. Investigation of the medication impact on a number of biochemical parameters.
4. Evaluation of Polyoxidonium therapy influence on the immunological values in patients with surgical infections.
5. Evaluation of dose-dependent effect of Polyoxidonium on clinical, hematological, biochemical and immunological characteristics of patients with surgical infections.
6. Selection of optimal dosages as well as development of the best medicate scheme on injections based on acquired data.

3. The general research plan

3.1. Patient eligibility criteria

Patients with the generalized surgical infections such as sepsis, peritonitis, pancreatic necrosis, pneumonia, abdominal abscesses and infiltrative processes, pelvic suppurative-inflammatory disorders and etc. were enrolled in the study. The physical examination results and laboratory findings of patients (general status, differential white blood cell count, body temperature etc.) served to be the diagnostic criteria. The bacteriological blood tests followed when suspecting sepsis clinically. The data acquired on surgical intervention as well as laboratory test results (chest and abdomen X-ray, ultrasonography, laparoscopy and etc.) were also taken into account as diagnostic information. The gender, age, as well as primary disorder that had resulted in the development of generalized surgical infection were disregarded on patient enrollment in the study groups (Table 1). The general statuses of patients at the Polyoxidonium treatment commencement were evaluated together with the treating physicians in accordance with the conventional 3-grade scale (3 – "severe", 2- "moderate", 1-"satisfactory"). Status severity - dependent allocation of patients to the study groups is shown on the Picture 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 agreement to take part in the study.

The patients with critical status, those with evident signs of hepato - renal failure as well as patients suffering from the unsanified surgical infectious processes were excluded from the study.

3.2. Treatment schedules

The II phase of the clinical trial had a "double-blind" character, in other words, neither patients nor physicians knew whether patients would receive Polyoxidonium or placebo. Research supervisor randomized the patients. Researchers had at disposal the numbered and sealed envelopes that contained special codes. In cases of undesirable adverse effects development the envelopes were unsealed under the researchers decision. All envelopes that remained sealed as well as unutilized flasks containing medication were sent back to the developer. The special forms were filled in cases of adverse effect manifestation.

Identical flasks containing either 3mg or 6mg Polyoxidonium or placebo produced by the Institute of Immunology, Ministry of Health and Medical Manufacturing, RF, were used during research. Each flask was marked with identification number, which corresponded to the patient's questionnaire number. Medications were kept in a locked refrigerator at $+4^0$ C.

Polyoxidonium injection schedules:

I group – single dose 3 mg intramuscular injections given in the mornings for 5 days (course dose –15mg);

II group - single dose 6 mg intramuscular injections given in the mornings for 5 days (course dose –30mg);

III group - single dose 9 mg intramuscular injections given in the mornings for 5 days (course dose –45mg);

IV group - intramuscular 6mg injections given in the mornings and evenings for 5 days (course dose –60mg);

V group - single dose 12 mg intramuscular injections given in the mornings once in two days for 10 days (course dose –60mg).

Immunomodulatory treatment other than Polyoxidonium was not administered during the trial.

In parallel to polyoxidonium therapy patients undertook infusions, detoxification and antibiotic treatments in accordance with the schemes that were approved by the research clinic. The surgical intervention volumes as well as that of infusions and antimicrobials were comparable in all study groups (Tables 2 and 3). Patients received Polyoxidonium injections under the doctor's supervision.

3.3. Patient status evaluation criteria

The accurate records of the data retrieved during research were kept using "Patient's Forms" and all information was, subsequently, analyzed by means of mathematical statistics. The required documentation was filled and the exclusion motives were adequately pointed out if the patient was expelled from the study.

3.3.1. Clinical values

The following values of clinical status of each patient were evaluated daily: body temperature twice a day (mornings and evenings), heart rate, systolic and diastolic blood pressures as well as overall patient status according to the conventional 3-grade scale - "severe", "moderate", "satisfactory".

3.3.2. Hematological values

The complete blood counts and the differential white blood cell counts including assessment of hemoglobin level, erythrocyte and leukocyte counts, lymphocyte, immature and mature neutrophils' (young, band and segmented neutrophils), eosinophil, basophil, monocyte percentages as well as the review of cellular morphology following routine staining of the blood smear using Giemsa-Romanovsky stain were taken by all study participants the day before Polyoxidonium treatment commencement.

3.3.3. Biochemical values

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

3.3.4. Immunological values

Immunological status evaluation included flow cytometry studies of subpopulations of peripheral blood lymphocytes (CD3+, CD4+, CD8+, CD16+, CD72+ lymphocytes) using monoclonal antibodies produced by the Institute of Immunology, MH, RF; The functional activity of peripheral blood neutrophils was assessed according to the plastic adhesion activity of neutrophils, superoxide-anion production on NTB-tests using specter photometry and luminole-dependent chemiluminescence reaction by CL3604 apparatus (“Mir-Dialog” Moscow) (spontaneous and zymosan-induced NTB-test and LDCL); The serum immunoglobulin levels were assayed using Manchini method of radial immunodiffusion.

3.4. Clinical and laboratory data evaluation scheme

Physical examination and laboratory tests to evaluate the patient status were performed the day before the immunomodulatory therapy commencement and 2-3 days after it’s completion.

4. The medication safety evaluation criteria

The severity and the rate of systemic as well as local adverse effects (allergic reaction, intoxication aggravation, development of inflammatory or infiltrative reactions on the injection sites, exacerbation of hematological, biochemical, immunological characteristics) were primarily evaluated for Polyoxidonium safety assessment.

The patients who developed adverse effects were excluded from the research group, medication use was discontinued, treatment of side effects was carried out if required, the envelope containing the special code was unsealed and finally, the form of adverse effects was filled.

5. Effectiveness evaluation criteria

5.1. The criteria of clinical efficacy

The characteristic properties of course of primary suppurative-septic process served to be the basic criterion for the efficacious application of Polyoxidonium during the combined treatment of suppurative-septic processes in surgical patients.

Polyoxidonium treatment result was considered to be “excellent” (5 grades) – if the patient had exhibited the apparent tendency towards the regression of purulant-septic process, improvement in general status, reduction in intoxication as well as normalization of body temperature and laboratory findings early in the Polyoxidonium treatment period.

Treatment result was registered to be “good” (4 grades) – if the general patient status had improved and intoxication had diminished following the Polyoxidonium therapy completion, but the subfebrile body temperature and moderate leukocytosis remained though.

Polyoxidonium efficacy was “satisfactory” (3 grades) – if the slight though stable improvement of patient status, reduction in body temperature, 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 determined (1 grade) – in the cases of progressive aggravation of patient status, infectious process advancement, development of primary disease related complications (pneumonia development, generation of purulant leakage and phlegmon in cases of local suppurative lesions).

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

5.2. The laboratory criteria of treatment efficacy assessment

Normalization of hematological, biochemical and immunological values (manifested by the decrease in leukocyte count and band neutrophil percentage, stabilization of hemoglobin level and erythrocyte count, reduction in bilirubin, blood urea nitrogen, creatinine concentrations to the normal values, normalization of activity of liver enzymes as well as positive changes in quantitative and functional characteristics of immune system) served to be laboratory criteria for the treatment effectiveness.

6. Results

Clinical results of Polyoxidonium inclusion into the combined treatment of purulant-septic processes in surgical patients

110 patients with surgical infections were examined and treated during the research. Control (placebo) group comprised 19 patients. 91 patients received different dosages of Polyoxidonium. 19 patients were given medication at course dose 15mg (single dose – 3mg). Study groups of Polyoxidonium therapy at 30 mg, 45 mg and 60 mg total doses given daily at 6mg, 9mg, 12mg, single doses, respectively, consisted of 20 patients each. Additional 12 patients received Polyoxidonium 60 mg (given on alternate days at single dose 12 mg) (Table. 1)

6.1. Assessment of treatment safety

None of patients suffered from any local or systemic adverse effects resultant from Polyoxidonium injections at 15 mg, 30 mg, 45 mg or 60 mg total doses. Moreover, none of adverse effects related to other treatment agents were observed in study participants.

6.2. Clinical evaluation of treatment effectiveness

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 results of Polyoxidonium inclusion into the combined treatment of suppurative-septic complications in surgical patients.

Polyoxidonium treatment resulted in significant decrease in number of hospitalization days, the general patient status improvement on 2^{nd} – 3^{rd} days of agent application. However, these favorable changes lacked statistical authenticity. The patients of all study groups showed authentical reduction in evening body temperatures. At the same time, the statistically significant decrease in evening fever was not observed in patients of placebo group. In addition, the patients who had taken Polyoxidonium at 15 mg, 45 mg or 60 mg total dose demonstrated statistically significant reduction in heart rate unlike control group participants.

Fatal outcomes were not observed among patients, who had received 12 mg daily Polyoxidonium injections. Thus, Mortality rate equaled 0 % in this study group. Moreover, none of patients showed “progression” of purulant-septic complication. “Ineffectiveness” took place in 2 (10%) patients. Though it’s remarkable that the primary surgical infectious lesion appeared impossible to be adequately drained in both patients. “Satisfactory” effect was observed in 2 (10%) participants, “good” – in 5 (25%) and “excellent” effect – in 13 (65%) patients.

In a group of patients taking 12 mg Polyoxidonium injections on alternate days (total dose – 60mg) mortality rate also was 0%. The “process progression” was not observed in this group (0%). The “ineffectiveness” rate equaled 8,3% (1 case), “satisfactory” effect was registered in 2 patients (16,7%), “good” – in 4 (33,3%) and “excellent” - in 5 (41,7%) cases.

One patient out of those taking 9 mg Polyoxidonium daily injections (total dose – 45 mg) died afterwards. At that the general status of given patient had remained severe but stable during the treatment period and 5 days following the course accomplishment, though the manifestations of purulant-septic process (pneumonia, peritonitis, sepsis) progression did not become apparent. Time lag between the treatment completion and patient's death lasted 11 days. Therefore, this case was attributed to Polyoxidonium "ineffectiveness". Thus, the mortality rate equaled 5,5% in this study group. None of patients showed "process progression" and the treatment "ineffectiveness" was registered in 2 (10%) patients (including lethal outcome). Polyoxidonium promoted "good" results - in 5 (25%) patients, "satisfactory" effects - in 3 (15%) patients and "excellent" - in 10 (50%) patients.

Among recipients of Polyoxidonium injections at 30 mg total dose one patient died also and mortality rate was 5% in this group. General status of this patient had remained stable during treatment period and 10 days after therapy completion without progression of existing peritonitis and pneumonia. However, the patient succumbed subsequently to status deterioration. Treatment result was ascribed to the medication "ineffectiveness" in the given case. None of patients showed "progression" of purulant-septic complication in this group either. "Ineffectiveness" was observed in the mentioned case of lethal outcome solely. "Good" effect was registered in 8 (40%), "satisfactory" - in 3 (15%) and "excellent" - in 8 (40%) patients.

One patient from the first group (15 mg Polyoxidonium) gained transitory effect, though aggravation of patient's general status; recommencement of fever as well as other intoxication signs were observed shortly after the discontinuation of Polyoxidonium injections. The given patient had been sustaining the unsanified infectious process (decomposed and abscessed cancer of rectum). This condition as well as the intoxication resultant from diffuses fibrous-suppurative peritonitis and severe bilateral pneumonia followed by the development of multisystem failure and fatal outcome. Thus, the mortality rate was 10,5% in I group. Disease "progression" was observed in one (5,2%) patient, treatment "ineffectiveness" – in one more (5,2%) case. The treatment result was thought to be "satisfactory" in 3 (15,8%), "good" - in 5 (26,3%) and "excellent" in 9 (47,5%) patients.

Rate of suppurative-septic process "progression" in control group was 5,2% (1 patient). The given patient succumbed 2 days after the treatment course completion to the pelvic phlegmon spreading and intoxication reinforcement. The therapy "ineffectiveness" was observed in 5 (26,3%) patients. One of these patients died due to heart and respiratory failures 25 days after the end of treatment. Mortality rate came to 10,5% in this group. The treatment yielded "satisfactory" effect in 5 (26,3%), "good" effect - in 4 (21,1%) and "excellent" - in 4 (21,1%) patients.

The data mentioned above are listed in the Table 5.

6.3. Clinical-hematological effectiveness of therapy

The leukocytosis and band neutrophil reduction rates exceeded in Polyoxidonium recipients compared to placebo group. Tendency towards the elevation of peripheral blood monocyte count was observed in patients of all Polyoxidonium study groups. However, the placebo group patients showed the decrease in monocyte number following therapy. The hemoglobin levels remained stable in all group.

6.4. Polyoxidonium treatment influence on biochemical values

Decrease in serum bilirubin, creatinine, and blood urea nitrogen levels as well as in activity of transaminases (ALT, AST) was revealed in all patients treated with Polyoxidonium. These findings remained constant or even enhanced slightly in control group patients. In all study groups evaluation of serum levels of total protein and albumin did not demonstrate significant changes (Table 6).

6.5. Influence of Polyoxidonium therapy on the values of patients' immune status

Polyoxidonium therapy led to the lymphocyte percentage elevation in all study groups. However, the incremental tendency was exhibited mostly in Polyoxidonium treated patients. Statistically significant enhancement in lymphocyte percentage was revealed in patients, who had received Polyoxidonium at total doses 60mg, 45 mg. The absolute lymphocyte count has shown to remain stable in control group and to increase slightly in Polyoxidonium groups.

Percentage as well as absolute count of CD3+ lymphocytes did not change in placebo group. On the contrary, Polyoxidonium recipients showed significant increase (though lacked statistical authenticity) in abovementioned values. CD4+ and CD72+ lymphocyte counts remained constant in all groups. Considerable rise in CD8+ lymphocytes was observed in all patients that had undertaken the immunomodulatory treatment. Moreover, this alteration appeared statistically significant in group III.

Statistically authentical increase in CD16+ lymphocytes was revealed in all 5 Polyoxidonium groups in comparison with that of placebo group, in which CD16+ cell values remained constant.

The CD4+/CD8+ ratio showed slight decrease in Polyoxidonium treated persons as well as in control groups.

Considerable dynamic changes in of IgG, IgA, IgM serum levels were not found in study groups.

Cell adherence to plastic was constant in placebo group, though it exhibited significant increase in Polyoxidonium groups. Moreover, plastic adherence enhancement had statistically authentical character in patients who had received 45 mg and 60 mg Polyoxidonium per course. Evaluation of spontaneous and zymosan-induced NTB-test results revealed the decline in neutrophil activity in control group, whereas the both parameters increased in Polyoxidonium therapy groups. Increase in spontaneous and reduction in induced chemiluminescence was observed in patients of placebo group. Among patients treated with Polyoxidonium those from the first group exhibited reduction in spontaneous and elevation of induced chemiluminescence, whereas the enhancement of spontaneous as well as induced chemiluminescence was revealed in patients from the rest groups. Moreover, the increase in LDCL proved to be statistically significant.

Evaluation of patients, who had exhibited the altered baseline values of immune status, demonstrated the Polyoxidonium capacity to improve these impairments. Thus, all patients with low baseline CD3+ and CD4+ lymphocyte counts (less than 40% and 30%, respectively) gained statistically authentic expansion of these T-cell subpopulations, whereas the CD3+ and CD4+ lymphocyte numbers remained constant in control group. Percents of CD8+ and CD16+ cells increased in all groups of Polyoxidonium use, though these changes lacked statistical significance. The control group demonstrated moderate elevation of plastic adherence capacity of cells following therapy, whereas the patients in Polyoxidonium treatment groups exhibited the significant enhancement in similar test values. Moreover, the statistical authenticity was observed in groups of Polyoxidonium use at 30mg, 45mg, and 60mg total doses. Increase in induced NTB-test and induced LDCL values was revealed in all patients.

7. **Conclusion**

II phase clinical trial aimed at the investigation of effectiveness of novel immunomodulatory agent - Polyoxidonium - inclusion into the combined treatment of surgical patients with the purulant-septic processes has demonstrated the absence of local and systemic adverse effects and allergic reactions as well as the beneficial influence on the biochemical and hematological findings in these patients and favorable dynamic changes in immune status values – mostly, the functional activity of peripheral blood immunocompetent cells – in comparison with placebo group patients.

Clinical effectiveness evaluation has revealed increase in a number of patients who had achieved "good" result on medication use in all Polyoxidonium groups compared to control cohort. The most pronounced dynamic changes in laboratory findings and improvement in treatment results was observed in patients with lowered baseline values of immune status.

We consider it to be remarkable that Polyoxidonium use contributed to the reduction of clinical (diminished fever and decreased heart rate) as well as laboratory (reduction in serum levels of blood urea nitrogen, creatinine) manifestations of intoxication providing the trustworthy evidence of detoxicant activity of medication and favoring clinical effectiveness.

Polyoxidonium inclusion in combined treatment of surgical patients with suppurative-septic processes yields beneficial influence on the immune status values, in particular, on the functional activity of immunocompetent cells. Moreover, the novel medication reconstitutes the quantitative ratio of peripheral blood lymphocyte subpopulations.

Comparison of different schedules of Polyoxidonium application proved 60 mg total dose of medication given daily or on alternate days (IV group and V group, respectively) to produce the most beneficial treatment results. Moreover, in our opinion, the schedule implying daily injections of Polyoxidonium (IV group) gave the best account of itself, as the rate of positive effects was 90% (maximal value) on evaluation of patients' status. Besides, the favorable dynamic changes in laboratory findings were predominantly apparent in this study group. However, statistical distinction in laboratory values of patients in IV and V groups was not observed.

The worse effectiveness was revealed in patients who had received Polyoxidonium injections at 15 mg total dose (I group). This treatment schedule resulted in the least amount of "good" and "excellent" effects (74%). Besides, the improvement in laboratory findings lacked statistical authenticity. However, even this schedule showed slight positive changes in comparison with control group. The efficiency of Polyoxidonium application schedules implying the research agent injections at total doses 30 mg and 45 mg was inferior to that of 60 mg Polyoxidonium use, though exceeded the effectiveness of medication given at 15 mg total dose (I group) and treatment results in polyoxidonium groups were significantly more advantageous compared to that of control group.

Thus, in our opinion, Polyoxidonium application during the combined therapy of suppurative-septic conditions in surgical practice proved to be perspective. The medication does not diminish treatment results and in a number of cases it contributes to the achievement of patient status improvement. The total absence of adverse reactions on medication, the complex immunocorrective and detoxifying activity of Polyoxidonium, the prompt advent of clinical and immunological effects conferred regards on the immunomodulatory agent – Polyoxidonium as one of the alternative medications for mainline immunotherapy in surgical clinics.

The fact that Polyoxidonium produces beneficial effect on immune status in a majority of surgical patients including those who exhibit profound immunodeficiency caused by the advanced septic complications, promotes conclusion about the pronounced immunomodulatory activity of medication and the perspectiveness of it's inclusion in a combined treatment of surgical septic conditions as well as in the treatment of other disorders accompanied by the manifestations of secondary immunodeficiency.

Table 1

Distribution of patients according to the gender, age, purulant-septic processes and primary disorders

Patient groups	**Placebo**	**Polyoxidonium** (Total course dose)				
		15 mg (3 mg daily)	30 mg (6mg/day)	45 mg (9 mg/day)	60 mg (12 mg/day)	60 mg (12 mg on altern. days)
Male	7	9	8	9	13	8
Female	12	10	12	11	7	4
Mean age	54,3	56,8	59,2	56,7	59,7	57,6
Primary diseases						
Cancer of the colon	8	9	12	11	11	6
Acute pancreatitis	4	3	3	3	2	1
Acute appendicitis	2	1	1	1	3	2
Gastric and/or duodenal ulcer	1	2	1	1	1	0
Others	4	4	3	4	3	1
Purulant - septic process						
Peritonitis	5	5	4	5	5	2
Abdominal abscesses, infiltrates	5	7	6	7	7	2
Pneumonia	2	2	2	3	3	2
Purulant lesions	4	3	2	4	4	2
Pelvic inflammatory diseases	5	5	7	7	5	3
Sepsis	2	3	2	3	2	0

Table 2

Distribution of patients according to the type of surgical intervention

Patient groups	Placebo	Polyoxidonium (Total course dose)				
		15 mg	30 mg	45 mg	60 mg/daily	60 mg/alt. days
Operations for:						
Colon cancers	8	9	12	11	11	6
Diseases of pancreas and bile ducts	5	3	3	3	5	2
Stomach and small intestine disorders	3	4	3	2	1	1
Others	2	1	1	2	3	1
Without operation	1	2	1	2	0	0

Table 3

Distribution of patients according to antibiotic therapy (agent and dosage)

	Placebo	Polyoxidonium (Total course dose)				
		15 mg	30 mg	45 mg	60 mg/daily	60 mg/alt. days
Penicillin	6	8	9	10	8	4
Cephalosporins	8	9	8	10	9	5
Aminoglycosides	16	8	11	11	10	5
Metronidazole	6	8	8	9	6	4
Semi – synthetic penicillins	3	3	3	4	3	2
Dioxidin	1	2	1	2	2	2
Levomicetin			1			
Number of agents						
I	5	6	6	4	3	2
II	8	7	7	7	7	4
III	5	6	7	8	9	6
IV	1			1	1	

Table 4

Influence of Polyoxidonium therapy on the clinical values

	Placebo		Polyoxidonium (Total dose)									
			15 mg		30 mg		45 mg		60 mg daily		60 mg alt/days	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Duration of p/o hospitalization (days)		33,9±6,4		36,7±6,5		30,6±2,3		26,4±3,1		27,1±2,5		26,9±2,9
Body temperature (mornings)	36,9±0,1	36,8±0,1	37,1±0,1	37,0±0,1	36,9±0,1	36,7±0,3	36,9±0,1	36,8±0,1	37,1±0,1	36,8±0,1	36,7±0,1	36,8±0,1
Body temperature (evenings)	37,9±0,1	37,0±0,6	37,9±0,2	37,4±0,1	38,2±0,2	38,5±0,8	38,3±0,2	37,4±0,2	38,6±0,2	37,1±0,1	37,9±0,2	36,6±0,1
Heart rate	89,6±1,7	85,4±1,4	93,1±3,0	83,5±1,8	88,2±1,9	83,2±1,9	91,6±2,4	82,9±2,1	92,1±2,0	82,4±2,1	88,6±1,8	80,2±1,8

Treatment effectiveness and mortality

Table 5

Treatment results (Grades)	Placebo	Polyoxidonium (Total dose)				
		15 mg (1)	30 mg (2)	45 mg (3)	60 mg (4)	60 mg (5)
"Excellent" - 5	4 (21,1%)	9 (47,5%)	8 (40,0%)	10 (50,0%)	13 (65,0%)	5 (41,7%)
"Good" - 4	4 (21,1%)	5 (26,3%)	8 (40,0%)	5 (25,0%)	5 (25,0%)	4 (33,3%)
"Satisfactory" - 3	5 (26,3%)	3 (15,8%)	3 (15,0%)	3 (15,0%)	2 (10,0%)	2 (16,7%)
"Ineffectiveness"-2	5 (26,3%)	1 (5,2%)	1 (5,0%)	2 (10,0%)	2 (10,0%)	1 (8,3%)
"Progression" – 1	1 (5,2%)	1 (5,2%)	-	-	-	-
Mortality	2 (10,5%)	2 (10,5%)	1 (5,0%)	1 (5,0%)	-	-

Influence of Polyoxidonium therapy on hematological and biochemical values

Table 6

	Placebo		Polyoxidonium (Total dose)									
			15 mg		30 mg		45 mg		60 mg daily		60 mg alt/days	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Leukocytes	11,5±1,4	10,6±1,2	12,3±1,9	9,7±1,0	10,3±1,8	9,2±0,8	10,9±1,2	8,2±1,0	12,4±1,8	9,2±0,7	11,4±1,5	8,3±1,7
Band neutrophils	12,8±1,7	8,6±1,7	13,7±3,2	6,4±1,5	11,3±2,3	7,3±1,5	11,9±2,1	7,3±1,6	11,5±2,0	7,1±1,5	12,0±1,2	7,4±2,1
Segmented neutrophils	77,1±1,8	75,3±1,8	78,3±3,0	69,1±3,2	77,7±2,8	73,8±2,9	76,3±2,4	69,9±2,4	78,1±2,3	70,0±2,5	77,4±2,6	69,5±2,2
Monocytes	3,8±0,9	3,1±0,7	3,5±0,5	3,7±0,7	2,3±0,3	2,8±0,5	3,2±0,5	3,6±0,7	2,6±0,5	2,9±0,6	2,8±0,7	3,1±0,3
Hemoglobin	97,9±4,5	97,2±5,6	88,9±7,0	89,5±6,7	82,8±4,3	90,8±4,9	97,7±4,5	100,9±4,4	87,7±3,6	90,7±3,0	86,8±3,9	90,1±3,6
Total protein	62,9±5,0	58,9±2,0	62,4±3,4	66,8±3,1	65,2±5,2	62,8±5,5	70,0±3,1	73,0±3,3	65,6±5,5	66,7±4,6	61,8±3,2	60,9±4,5
Albumin	33,3±2,0	30,9±1,6	36,4±2,0	34,5±2,0	38,7±4,7	35,4±2,0	38,3±2,0	39,9±1,9	36,7±3,5	37,8±4,1	34,0±4,3	36,7±3,4
Bilirubin	21,1±7,6	20,5±8,6	4,7±0,8	4,7±0,8	11,8±2,2	8,9±1,7	10,3±1,3	7,2±1,0	12,3±1,7	10,8±1,6	11,9±2,1	10,7±2,3
Blood urea nitrogen	6,6±1,1	6,7±1,5	5,7±0,4	4,4±0,4	6,5±0,8	5,3±0,5	4,5±0,6	4,0±0,4	6,4±1,5	5,6±0,8	5,9±1,5	5,0±1,2
Creatinine	137,3±23,3	160,3±37,7	127,1±16,3	99,4±8,0	130,2±18,8	111,0±8,3	107,3±6,6	97,7±6,3	120,3±5,9	111,2±3,7	130,1±5,6	119,9±8,7
AST	36,5±4,7	39,0±3,8	28,9±5,1	28,1±2,0	33,4±5,3	32,7±3,9	30,3±9,2	17,4±2,8	33,6±2,6	31,5±1,9	29,9±2,3	27,7±2,0
ALT	28,5±3,5	32,3±2,8	24,2±7,0	26,1±2,8	28,7±4,3	25,3±2,7	29,3±7,3	18,4±2,9	33,5±4,2	29,8±2,9	28,5±1,9	20,8±1,9

Influence of Polyoxidonium therapy on Immune status values

Table 7

	Placebo		Polyoxidonium (Total dose)									
			Schedule I		Schedule II		Schedule III		Schedule IV		Schedule V	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
CD3+	43,7±3,8	45,5±4,0	49,4±3,1	60,3±3,9	43,1±3,7	50,6±3,6	34,9±5,0	45,1±4,7	43,3±4,1	49,9±4,2	35,8±3,5	44,7±3,1
CD4+	30,9±2,7	32,2±3,2	33,7±2,3	32,8±3,0	27,9±3,5	33,0±2,1	25,6±3,9	29,7±3,4	27,7±3,9	30,6±2,9	23,7±3,5	28,7±3,1
CD8+	19,3±2,9	21,4±2,5	25,4±3,0	34,6±4,6	20,4±2,7	23,5±2,1	14,8±1,8	22,5±2,0	17,7±1,7	21,5±1,5	19,8±2,1	24,5±2,1
CD4/CD8	1,81±0,14	1,64±0,17	1,59±0,2	1,38±0,3	1,66±0,24	1,46±0,16	2,09±0,3	1,32±0,17	1,75±0,17	1,59±0,2	1,95±0,2	1,53±0,25
CD16+	6,7±1,3	7,6±1,3	7,2±2,7	14,6±1,7	6,0±0,6	10,8±2,9	6,2±1,1	10,7±2,1	7,1±1,2	12,3±1,1	6,5±1,4	10,9±1,0
CD72+	3,6±0,6	3,9±0,6	7,1±1,6	4,7±2,3	4,0±0,6	3,4±0,6	4,1±0,6	4,0±0,5	4,0±0,7	3,9±0,5	4,1±0,6	3,9±0,5
IgG	898,4±52,0	977,6±57,7	880,2±98,6	1038,2±66,9	944,2±63,3	1136,9±101,8	1061,3±149	973,6±86,9	1178,0±120	1211,9±121	1076,6±123	1233,5±102
IgA	353,4±28,0	341,8±27,6	267,8±29,8	285,7±23,6	268,5±27,6	330,0±21,6	243,8±37,3	216,2±14,9	236,6±33,4	233,7±34,6	256,7±23,7	249,5±19,9
IgM	183,6±23,0	183,7±24,4	133,4±23,0	169,7±21,6	161,8±22,5	175,2±21,1	121,4±19,7	118,1±13,9	132,4±15,6	129,6±13,7	121,7±19,9	122,5±15,6
LDCL sp.	877,1±113,3	1359,6±279,9	1386,3±264,3	1156,9±131	875,5±102	1014,7±96,1	1007,9±90,3	1226,8±251	877,8±98,6	1235,9±122	932,8±89,0	1301,8±96
LDCL ind.	3450,9±528,9	3174,0±375,5	3785,2±527,7	4366,5±917	2992,4±271	5182,9±461,0	2942,1±307	5063,3±431	1978,8±309	3978,2±348	2100,5±431	4121,6±423
Adhesion	45,5±7,9	49,8±8,7	44,6±12,1	65,5±14,1	67,5±7,4	81,2±5,9	32,4±2,7	41,0±2,8	44,7±2,6	59,1±2,9	45,3±2,6	64,8±3,0
NTB sp.	98,0±11,4	83,7±11,2	81,3±12,9	88,8±14,6	44,2±4,5	58,2±5,8	79,4±12,3	76,8±11,4	69,9±11,4	81,6±10,8	76,4±12,7	91,0±11,2
NTB ind.	148,0±19,0	115,4±15,0	120,4±15,3	138,8±17,2	75,2±8,1	100,9±9,3	111,0±14,7	143,9±17,4	116,5±13,7	156,5±14,6	123,6±12,1	153,7±11,6