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Comparative study of the effects of fresh and canned Naftussya bioactive water on neuro-endocrine-immune complex and metabolism in chronic pyelonephritis patients

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Background. There are several patented methods of preservation of medicinal waters of the Naftussya type. The authors of the patents as evidence of the correctness of the methods cite the facts of preservation of the ability of canned water to enhance motility rat's v. portae in vitro and/or increase diuresis. However, such tests are not attributive. The most characteristic manifestation of the biological activity of Naftussya water is the stimulation of phagocytosis through the mediation of the nervous and endocrine systems. Another "Method of preservation of hydrogen sulfide mineral waters" was recently patented. The purpose of this study is to compare the impact of fresh and canned by this method Naftussya water on its targets in patients with chronic pyelonephritis. **Materials and Methods.** The object of clinical-physiological observation were residents of the city of Truskavets' (21 men aged 24-67 years and 8 women 33-76 years) with chronic pyelonephritis in remission. The subject of the study were the phagocytic function of neutrophils, excretory function of kidneys, leukocyturia and bacteriuria levels, components of microbiota of feces as well as HRV and endocrine parameters. **Results.** Weekly use of fresh Naftussya water causes an increase in the reduced content of probiotics in the microbiota and a decrease in the increased content of conditionally pathogenic microflora, which is accompanied by an increase in reduced bactericidal capacity of neutrophils against both E. coli and Staph. aureus, normal diuresis, phosphaturia, magnesiumuria, ureauria while reduction of bacteriuria and leveling of leukocyturia as well as decrease in concentration of uric acid in urine and creatinine and cholesterol in plasma. Favorable changes in neuro-endocrine regulation were revealed. The beneficial effect on the listed parameters of canned Naftussya water is less pronounced, but

the differences are statistically insignificant. **Conclusion.** The obtained results confirm the effectiveness of the Dovzhenko[®] method for Naftusya water conservation and provide grounds for continuing research into the effects of canned Naftusya water on the body of urological patients.

Keywords: Naftusya bioactive water, Dovzhenko[®] conservation method, chronic pyelonephritis, urinary syndrome, microbiota, phagocytosis, diuresis, saluresis, HRV, adaptation hormones.

INRODUCTION

Balneotherapy has its rightful place in the arsenal of means of treatment of chronic pyelonephritis [1]. The universally recognized gold standard of balneofactors is Naftusya bioactive water. The issue of the loss of its healing properties by Naftusya water after extraction from the subsoil, the possibility of its preservation and transportation remain debatable and relevant [11,15,24,26-28].

There are several patented methods of preservation of medicinal waters of the Naftusya type. The authors of the patents as evidence of the correctness of the methods cite the facts of preservation of the ability of canned water to enhance motility rat's v. portae in vitro and/or increase diuresis (even without recording urinary excretion of electrolytes and nitrogenous metabolites!?) [15,24]. However, it is well known that even fresh Naftusya water affects such tests ambiguously [11,22,28], so they do not reflect the inherent properties of Naftusya water, that is, they are not attributive. The Truskavetsian Scientific School has shown that the most characteristic manifestation of the biological activity of Naftusya water is the stimulation of phagocytosis in both rats and humans [11,14,20-22,25] caused by its organic substances, in particular, polyphenols [4,10] as Ah receptor ligands [22]. Such an effect of organic substances on phagocytes is realized not directly, but through the mediation of the nervous and endocrine system, the mediators and hormones of which activate phagocytosis [13,14,21,22].

Another "Method of preservation of hydrogen sulfide mineral waters" [16] was recently patented.

The purpose of this study is to compare the impact of fresh and canned by this method Naftusya water on its targets in patients with chronic pyelonephritis.

MATERIALS AND METHODS

The object of clinical-physiological observation were residents of the city of Truskavets' (21 men aged 24-67 years and 8 women 33-76 years) with chronic pyelonephritis in remission. The day before, samples of morning urine and feces was collected, in which was determined the leukocyturia and bacteriuria levels and components of microbiota respectively. Unified methods are applied. Urinary syndrome was assessed by quantitative and qualitative levels of bacteriuria and leukocyturia [7,20]. The inclusion criteria were the presence of pronounced urinary syndrome (bacteriuria: $0,285 \div 0,715$ points; leukocyturia: $0,1 \div 0,5$ points) with preservation of functional renal reserve ($>10\%$), previously assessed by the Gozhenko AI method [6].

In daily urine was determined the concentration of electrolytes: calcium (by reaction with arsenase III), magnesium (by reaction with colgamite), phosphates (phosphate-molybdate method), chloride (mercury-rhodanidine method), sodium and potassium (flaming photometry); nitric metabolites: creatinine (by Jaffe's color reaction by Popper's method), urea (urease method by reaction with phenolhypochlorite), uric acid (uricase method). The same metabolic parameters were determined in plasma as well as total cholesterol (by a direct method after the classic reaction by Zlatkis-Zack). The analysis carried out according to

instructions [5] with the use of analyzers "Reflotron" (BRD) and "Pointe-180" (USA) with corresponding sets of reagents, and flaming photometer "CФ-47".

To assess the state of the endocrine system we determined the plasma levels of main adaptation hormones as Cortisol, Aldosterone, Testosterone, Calcitonin, and Triiodothyronine (by the ELISA with the use of corresponding sets of reagents from "Алкор Био", XEMA Co Ltd, and DRG International Inc). The analyzes were carried out according to the instructions. The analyzers "RT-2100C" (PRCh) used. To assess the state of the autonomic nervous system the parameters of heart rate variability (HRV) have been recorded [2] during 7 min (software-hardware complex "CardioLab+HRV", KhAI-MEDICA, Kharkiv).

Parameters of phagocytic function of neutrophils estimated as described by Kovbasnyuk MM [14,21]. The objects of phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index Phi), intensity (number of microbes absorbed one phagocytes - Microbial Count MC or Right's Index) and completeness (percentage of dead microbes - Killing Index KI). On the basis of the registered partial parameters of phagocytosis, taking into account the content of neutrophils (N) in 1 L of blood, the integral parameter - the bactericidal capacity of neutrophils (BCCN) - was calculated by the formula [20]:

$$BCCN (10^9 \text{ Bact/L}) = N (10^9/L) \cdot \Phi I (\%) \cdot MC (\text{Bact/Phag}) \cdot KI (\%) \cdot 10^{-4}.$$

Every day, 6 patients were examined, who were divided into two groups, approximately equal in terms of gender, age and severity of urinary syndrome. After the initial testing, the members of the main group received a weekly course of balneotherapy [26] with fresh Naftussya water (taken directly from the field), instead, for the experimental group, Naftussya water, previously preserved by Dovzhenko[©] method [15], was used. On the second day after the end of the drinking course, repeated testing was carried out.

Normal (reference) values of variables are taken from the database of the Truskavetsian Scientific School of Balneology [19]. For statistical analysis used the software package "Statistica 6.4".

RESULTS AND DISCUSSION

Both groups were equal in terms of gender (4 women each), age (M±SD: 52±15 and 50±10 years), body mass index (26,8±4,2 and 27,8±3,3 kg/m²) as well as of the initial symptoms of urinary syndrome and components of the microbiota of feces, parameters of phagocytosis, metabolism [18,19], as well as autonomous and endocrine status. A fragment of the obtained results was published earlier [18,19], but in order to preserve the integrity of the picture, we consider it necessary to repeat it.

Screening of changes in the registered parameters revealed a significant decrease in some parameters, instead of an increase in others (Tables 1-4). Other parameters did not change significantly, so they are not analyzed further.

Table 1. Comparative characteristics of the microbiota of feces and urine

| Parameters | | Actual value | Z-score | Mean Cv/SD |
|---------------------------------|--------------------|--------------|------------|------------|
| Lactobacilli, lg CFU/g | Before treatment | 5,38±0,25*** | -1,87±0,17 | 8,10 |
| | Effect of fresh N | +1,49±0,51** | +1,03±0,35 | 0,179 |
| | Effect of canned N | +0,96±0,47* | +0,66±0,33 | |
| Bifidobacteria, lg CFU/g | Before treatment | 4,83±0,21*** | -1,86±0,19 | 6,94 |
| | Effect of fresh N | +1,26±0,44** | +1,11±0,39 | 0,164 |
| | Effect of canned N | +0,73±0,38 | +0,64±0,34 | |
| Escherichia coli | Before treatment | 76±3*** | +3,34±0,19 | 17 |

| | | | | |
|--|--------------------|---------------|------------|-------------|
| attenuated, % | Effect of fresh N | -27±8** | -1,55±0,46 | 1,0 |
| | Effect of canned N | -9±7 | -0,52±0,42 | |
| Escherichia coli hemolytic, % | Before treatment | 34±8** | +1,35±0,32 | 0 |
| | Effect of fresh N | -21±14 | -0,86±0,55 | 25 |
| | Effect of canned N | -25±15 | -0,99±0,59 | |
| Klebsiela & Proteus, % | Before treatment | 19±4*** | +1,72±0,32 | 0 |
| | Effect of fresh N | -9±5 | -0,80±0,50 | 11 |
| | Effect of canned N | -8±6 | -0,76±0,57 | |
| Bacteriuria, lg CFU/mL | Before treatment | 2,11±0,08*** | +2,16±0,09 | 0 |
| | Effect of fresh N | -1,10±0,21*** | -1,13±0,21 | 0,98 |
| | Effect of canned N | -0,79±0,20*** | -0,81±0,21 | |
| Leukocyturia, lg L/mL | Before treatment | 3,56±0,11*** | +0,88±0,18 | 3,00 |
| | Effect of fresh N | -0,46±0,18* | -0,73±0,29 | 0,21 |
| | Effect of canned N | -0,16±0,17 | -0,25±0,28 | |

Note. Significant deviations from the norm as well as changes are indicated by stars ($p < 0,05^*$, $< 0,01^{**}$, $< 0,001^{***}$).

Table 2. Comparative characteristics of the phagocytosis parameters

| Parameters | | Actual value | Z-score | Mean Cv |
|--|--------------------|--------------|------------|---------|
| Killing Index vs Staph. aureus, % | Before treatment | 45,2±1,0*** | -3,28±0,25 | 58,9 |
| | Effect of fresh N | +9,5±2,4*** | +2,26±0,56 | 0,142 |
| | Effect of canned N | +4,8±2,1* | +1,14±0,49 | |
| Killing Index vs E. coli, % | Before treatment | 40,1±1,2*** | -4,53±0,25 | 62,0 |
| | Effect of fresh N | +10,5±3,0** | +2,18±0,61 | 0,156 |
| | Effect of canned N | +3,6±2,3 | +0,75±0,48 | |
| Bactericidity vs E. coli, 10⁹ Bacteria/L | Before treatment | 74±2*** | -2,55±0,20 | 99 |
| | Effect of fresh N | +24±6*** | +2,42±0,56 | 0,100 |
| | Effect of canned N | +19±4*** | +1,88±0,45 | |
| Bactericidity vs Staph. aureus, 10⁹ Bacteria/L | Before treatment | 81±3*** | -2,32±0,30 | 106 |
| | Effect of fresh N | +26±6*** | +2,44±0,59 | 0,100 |
| | Effect of canned N | +17±8* | +1,62±0,75 | |

Table 3. Comparative characteristics of the neuro-endocrine parameters

| Parameters | | Actual value | Z-score | Mean Cv |
|--|--------------------|--------------|-------------|---------|
| Baevskiy's ARS Index, Z-units | Before treatment | | 3,92±0,50** | 0÷3 |
| | Effect of fresh N | | -1,04±0,66 | |
| | Effect of canned N | | -1,43±0,62* | |
| Baevskiy's Stress Index Male, units | Before treatment | 209±31 | +1,18±0,59 | 140 |
| | Effect of fresh N | -88±25* | -1,14±0,53 | 0,426 |
| | Effect of canned N | -53±58 | -1,31±0,94 | |
| Baevskiy's Stress Index Female, units | Before treatment | 66±8*** | -1,23±0,16 | 140 |
| | Effect of fresh N | +34±9*** | +0,56±0,11 | 0,426 |
| | Effect of canned N | +47±22* | +0,88±0,41 | |
| Cortisol Male, nM/L | Before treatment | 358±30 | -0,11±0,27 | 370 |
| | Effect of fresh N | +86±87 | +0,77±0,77 | 0,303 |
| | Effect of canned N | +20±57 | +0,18±0,51 | |
| Cortisol Female, nM/L | Before treatment | 303±32* | -0,60±0,28 | 370 |
| | Effect of fresh N | +256±91** | +2,29±0,82 | 0,303 |
| | Effect of canned N | +129±61* | +1,15±0,54 | |
| Testosterone Male, nM/L | Before treatment | 14,0±1,6 | +0,09±0,35 | 13,7 |
| | Effect of fresh N | -3,8±1,5* | -1,04±0,41 | 0,266 |
| | Effect of canned N | -3,6±1,7* | -1,01±0,47 | |
| Testosterone Femalee, nM/L | Before treatment | 3,18±0,34* | +0,78±0,33 | 2,37 |
| | Effect of fresh N | -1,31±0,64* | -1,26±0,62 | 0,438 |
| | Effect of canned N | -0,73±0,50 | -0,70±0,48 | |

| | | | | |
|---|--------------------|-------------|------------|-------|
| Triiodothyro- nine, nM/L | Before treatment | 2,28±0,17 | +0,16±0,33 | 2,20 |
| | Effect of fresh N | -0,38±0,18* | -0,77±0,36 | 0,227 |
| | Effect of canned N | -0,37±0,21 | -0,75±0,42 | |

Table 4. Comparative characteristics of the metabolic parameters

| Parameters | | Actual value | Z-score | Mean Cv |
|--|--------------------|--------------|------------|---------|
| Diuresis, L/24 h | Before treatment | 1,61±0,13 | +0,56±0,33 | 1,40 |
| | Effect of fresh N | +0,39±0,11** | +1,03±0,28 | 0,274 |
| | Effect of canned N | +0,40±0,17* | +1,06±0,44 | |
| Urea Excretion, mM/24 h | Before treatment | 462±38 | +0,05±0,45 | 458 |
| | Effect of fresh N | +96±46* | +1,12±0,54 | 0,186 |
| | Effect of canned N | +113±55* | +1,32±0,65 | |
| Phosphate Excretion, mM/24h | Before treatment | 18,3±1,7*** | -0,93±0,23 | 25,2 |
| | Effect of fresh N | +9,7±3,5** | +1,31±0,48 | 0,294 |
| | Effect of canned N | +5,9±3,3 | +0,80±0,44 | |
| Calcium Excretion, mM/24 h | Before treatment | 3,74±0,42 | -0,68±0,45 | 4,38 |
| | Effect of fresh N | +2,92±0,89** | +3,12±0,95 | 0,214 |
| | Effect of canned N | +0,61±0,77 | +0,65±0,82 | |
| Magnesium Excretion, mM/24 h | Before treatment | 4,00±0,31 | -0,09±0,30 | 4,10 |
| | Effect of fresh N | +0,91±0,46 | +0,87±0,44 | 0,256 |
| | Effect of canned N | +0,76±0,59 | +0,73±0,56 | |
| Uric Acid Urine Concentration, mM/L | Before treatment | 2,20±0,14 | +0,12±0,27 | 2,14 |
| | Effect of fresh N | -0,36±0,22 | -0,67±0,41 | 0,250 |
| | Effect of canned N | -0,49±0,19* | -0,92±0,35 | |
| Creatinine Plasma, μM/L | Before treatment | 87,6±2,9*** | +1,34±0,20 | 77,0 |
| | Effect of fresh N | -6,6±2,9* | -0,46±0,20 | 0,167 |
| | Effect of canned N | -3,4±2,5 | -0,24±0,17 | |
| Cholesterol Plasma, mM/L | Before treatment | 5,60±0,21 | +0,08±0,20 | 5,44 |
| | Effect of fresh N | -0,55±0,30 | -0,55±0,30 | 0,193 |
| | Effect of canned N | -0,09±0,32 | -0,08±0,31 | |

Adhering to the Truskavetsian Scientific School's analytical algorithm [22,25], the actual/raw parameters were normalized by recalculation by the equations:

$$Z = 4 \cdot (V - N) / (\text{Max} - \text{Min}) = (V - N) / \text{SD} = (V/N - 1) / \text{Cv}, \text{ where}$$

V is the actual value; N is the normal (reference) value; SD and Cv are the standard deviation and coefficient of variation respectively.

This methodical approach makes it possible to visualize the initial state and dynamics of parameters expressed in different units.

Figs. 1-4 visualizes how a weekly intake of fresh Naftussya water causes an increase in the significantly reduced content in the microbiota of feces/gut of classical probiotics [3,9,23] to the lower normal zone. This is accompanied by a significant increase (but without normalization) of the reduced bactericidal activity of neutrophils/microphages against both gram-positive and gram-negative bacteria; at the same time, the bactericidal capacity of blood neutrophils is completely restored, due to an increase in their content. Instead, the marginally increased content of the E. coli strain capable of hemolysis is almost completely normalized; the less elevated content of conditionally pathogenic Klebsiella&Proteus decreases to the upper normal zone; the extremely high content of the E. coli strain with weakened enzymatic activity remains in the pessimistic zone. Obviously, this is a manifestation of antagonistic activities of lactobacilli and bifidobacteria against microbial pathogens [23].

With regard to the cohort of patients with chronic pyelonephritis observed by us, the data that **pyelonephritogenic** Escherichia coli was highly suppressed by Lactobacillus rhamnosus and both Bifidobacteria strains [9] are of particular interest. This gives us reason to assume that inhibition of the growth of **pyelonephritogenic** Escherichia coli in the intestine by probiotics reduces its translocation to the kidneys via lymph and/or blood. In addition,

circulating bacteria are destroyed by neutrophils, whose bactericidal capacity increases significantly. The result is a decrease in bacteriuria, as well as leukocyturia as a marker of pyelonephritis.

As expected [8,11,20,22,25-28], the daily diuresis and excretion of urea, phosphates, calcium, and magnesium increases, but not uric acid, the concentrations of which in the urine decrease. At the same time, the elevated plasma level of creatinine as well as normal level of cholesterol decreases, which is clearly interpreted as beneficial effects.

The described effects are accompanied by a decrease in elevated markers of maladaptation, namely: Baevsky's Activity of Regulatory Systems (BARS) and Stress Index (BSI, in male only). Instead, the reduced levels of cortisol and BSI in women increase within the normal range, that is, there is a normalizing effect. At the same time, the initially upper limit or normal levels of testosterone and triiodothyronine decrease, which also is evaluated as physiologically favorable changes [17,22,25].

It can be seen that the effect of canned Naftussya water on the 11 parameter are almost the same, and on the 16 parameters are somewhat weaker, but the differences are statistically insignificant.

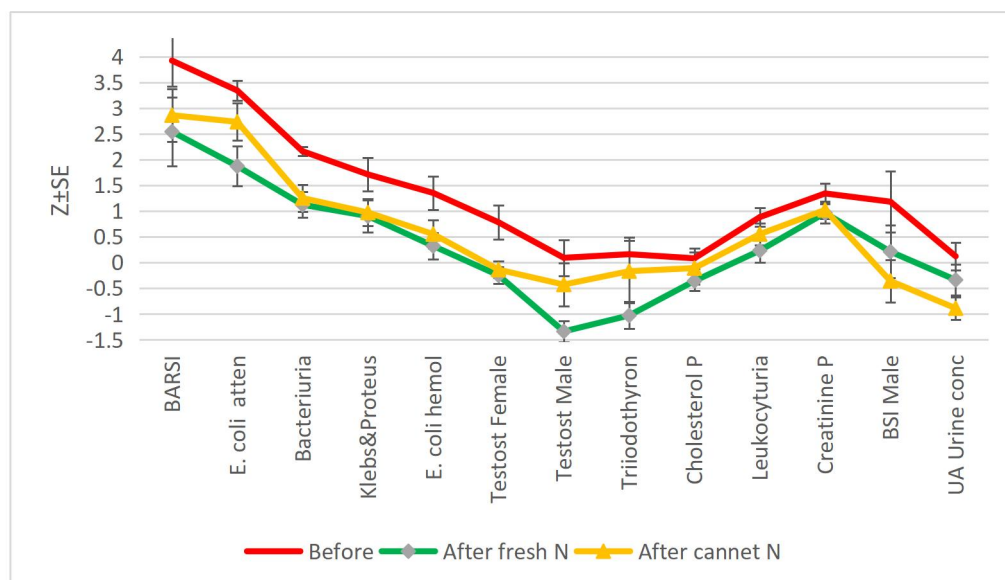


Fig. 1. Profiles of patients before and after a course of balneotherapy by fresh and canned Naftussya bioactive water. Initial elevated and normal parameters are given

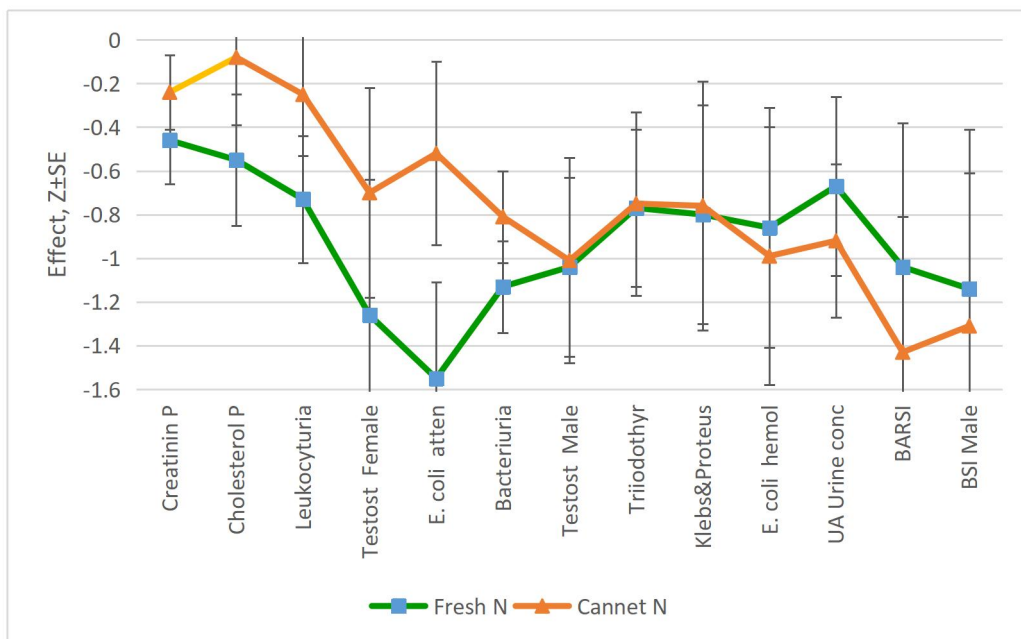


Fig. 2. Profiles of downregulating effects on parameters in patients with chronic pyelonephritis caused by course of balneotherapy with fresh and canned Naftussya water

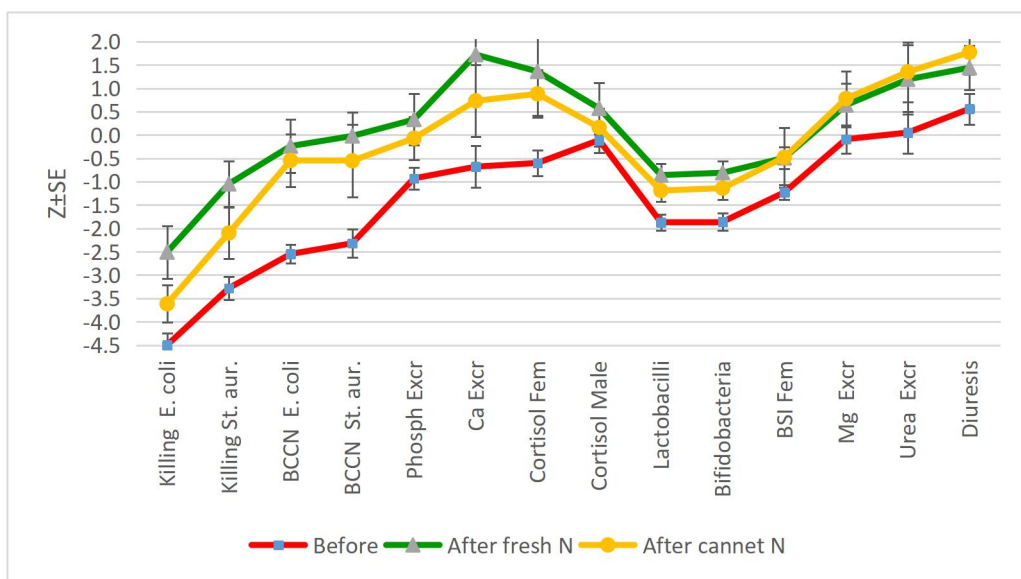


Fig. 3. Profiles of patients before and after a course of balneotherapy by fresh and canned Naftussya bioactive water. Initial reduced and normal parameters are given

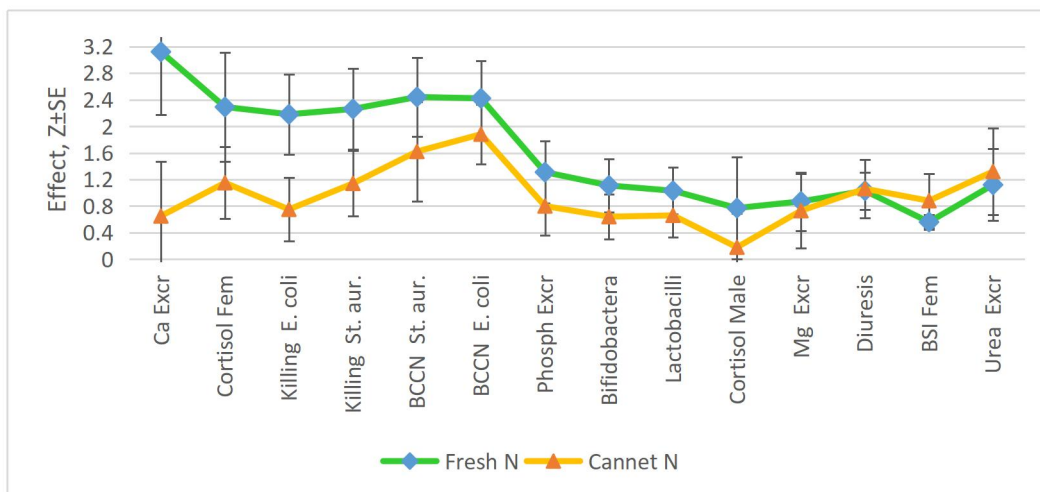


Fig. 4. Profiles of upregulating effects on parameters in patients with chronic pyelonephritis caused by course of balneotherapy with fresh and canned Naftussya water

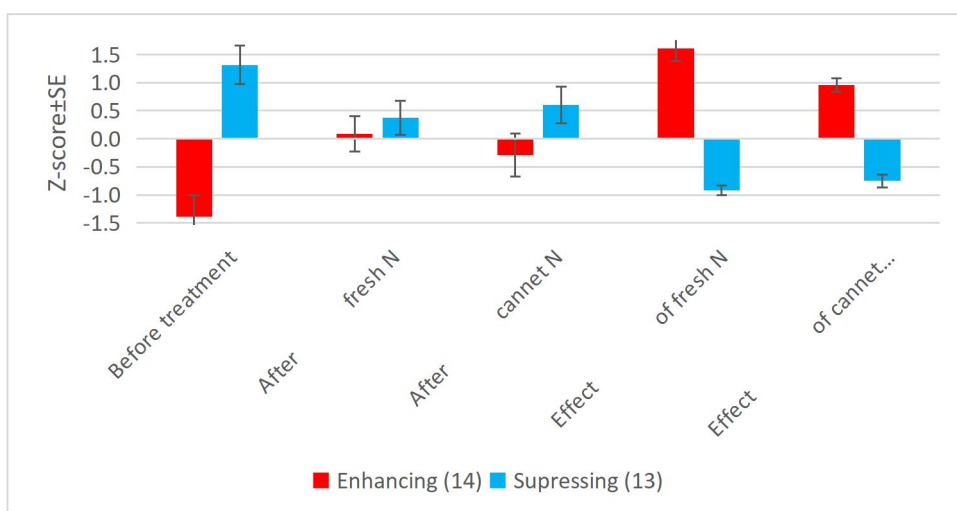


Fig. 5. Integral normalizing effects of fresh and canned Naftussya bioactive water on abnormal parameters of patients with chronic pyelonephritis

Візуальне враження підтверджується обчисленням інтегральних нормалізуючих ефектів бальнеотерапії (рис. 5). As you can see, the inhibitory/limiting effects of canned water are almost as good as those of fresh water, and the enhancing effects are somewhat weaker.

The obtained results confirm the effectiveness of the Dovzhenko's[©] method [16] used for Naftusya water conservation and provide grounds for continuing research into the effects of canned Naftusya water on the body of urological patients [1,26].

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of

scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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