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"IZMEROV RESEARCH INSTITUTE OF OCCUPATIONAL MEDICINE"

(FSBSI "RI OM")

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STUDY REPORT

"STABILIZATION OF FUNCTIONAL CONDITION

"Evaluation of efficacy of transcutaneous electrostimulator for blood pressure correction "ABP-051"for stabilization of functional condition and blood pressure in persons working in the conditions of increased emotional overstrain, stress situations, also in persons working in hazardous and harmful labor conditions"

Head of the research work
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Moscow
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LIST OF THE EXECUTORS

Executors
from FSBSI “RI OM”:

1. *Elena L. Lashina, the study coordinator: professional pathologist of the prophylactic examination unit, head of clinical trial unit;*
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Consultant:

1. *Elena A. Shindyakova, the director of the “Inter-Industrial Center of Specialized Services by Economic Unities” LLC.*

Introduction

Over 72 million of working people of working age mainly determine the demographic picture and social welfare of the country in general.

Depopulation of working population exceeds depopulation of the entire population in Russia in 2.5 times. Based on the forecasts of the Federal State Statistics Service, up to 2030, the decrease of the population of the working age exceeds 13 mln. persons. 80% of the loss will occur in period up to 2020 – on average, 1 mln. persons annually.

The progressive working incapacity is determined as one of the main long-term strategic risks and threats of national safety in economic growth. Meanwhile, it is found that 20 to 40% of working losses is provided by unsatisfactory labor conditions, over 20% among people newly acknowledged as disabled have become incapable in the age of 45-50 years.

As estimated by WHO experts, such risk factors as stress and arterial hypertension play the most important role in development of diseases in population of the Russian Federation, the contribution of the latter amounts to 35.5%.

Variable human exposures, increase of information loads, psychoemotional overstrain, and well as hypokinesia leads to transformation of the existing professional diseases and expand the range of production-mediated disorders, the most of which are non-infectious diseases.

The International Labor Organization accepts that professional stress is nowadays a serious factor influencing workers’ health. The World Health Organization, largest employees unions and labor unions play the closest attention to the problem.

According to the estimates of the Research Institute of Occupational Medicine of RAS, over 10% of the working population in Russia live in the conditions of constant social and psychoemotional stress.

According to the definition of the Research Institute of Occupational Medicine of RAS, “professional stress (stress condition at work) – a special functional condition of a human body related to exposure primarily to pronounced nerve-emotional strain which is characterized with the increased activation or suppression of regulatory physiological body systems, development of tension or tiredness, as well as in accumulation of unfavourable shifts, overstrain or fatigue.

The long-term overstrain from exposure to intensive neuroemotional strains promotes development of production-related diseases: atherosclerosis, coronary heart disease, essential hypertension, neurotic disorders, etc. The pronounced nerve-emotional work intensity related to hazard classes 3.2-3.3, leads to depletion of adaptation body mechanisms, functional nerve and endocrine system disorders, metabolism disorders and, finally, to diseases. All these events aggravate with the increase of working experience.

The scientific research and data of insurance companies in the USA show that these are working problems that are the main reason of health complaints. Though mental strains and stress situations exist both in labor and private life but stress at work affects humans even to a greater extent than financial problems or family troubles.

Problems of stress at work are presented as priority in many developed countries and on the international level. In developed countries, they are of great importance both for labor unions and employers as both are interested in prevention or minimization of a negative exposure of mental strains on health of hired workers, and finally – on economic efficiency.

Stress at work may be induced almost by all hazardous and harmful factors of labor conditions - injuries, intensive noise, high or low temperature, exposure of toxic substances, etc., and such factors as danger, conflict, joy, etc. The body develops biochemical changes of the same kind aimed to overcome action of the factors and body adaptation to the imposed requirements. The typical particularities of all modern types of labor activity are insufficient level of general motor activity (hypokinesia) and stay in physiologically irrational working positions (uncomfortable, fixed, forced). However, in some cases, severe physical loads are also the cause of stress at work.

Depending on the intensity of exposure of stress fact, the incidence of essential hypertension

is 10.4% to 36.2%, and of coronary heart disease – 3.9 to 43.8%.

It should be mentioned that cardiovascular diseases are the causes of over 1/3 death cases in working age. The values of ultra-high mortality level in working age (predominantly, men) differ Russia from developed countries and are the main cause of the demographic crisis in Russia.

Moreover, there are results showing the exposure of psychogenic stress factors on female reproductive health. Infertility, spontaneous miscarriage, pregnancy complications and threatened miscarriage is directly related to the level of work intensity. The significant values of a relative infertility risk and relationship of the events varying from 51.5 to 89.7% are established.

Therefore stress at work may be classified not only as a health threat to an individual but also considering its global incidence, also as national and state safety threat.

The aim of occupational medicine is the search of effective, inexpensive and available methods for reduction of influence of negative factors of stress exposure and risk factors of a cardiovascular disorder in workers.

Materials and methods

Name of the test device: "Transcutaneous electrostimulator for blood pressure correction "ABP-051" per TU-9444-005-12342964- 2015".

Marketing authorization issued by the Federal Service for Surveillance in Healthcare, № RZN 2016/3776 dated March 31, 2016.

Certificate for conformity to the European standards per Directive 93/42/EEC dated 01.09.2017.

Manufacturer: Limited Liability Company "Inferum", INN 6612040385, "Inferum" LLC, 620026, Russia, Sverdlovsk Region, Yekaterinburg, Belinsky Str., 86-487.

Manufacturer's site: 623417, Russia, Sverdlovsk Region, Kamensk - Uralsky, Mechanisatorov Str., 74.

Medical organization performing medical tests of the medical device: Federal State Budgetary Scientific Institution "Izmerov Research Institute of Occupational Medicine", INN 7719022912, 105275, Moscow, Bydenny Avenue, 31.

Study coordinator: Elena L. Lashina, professional pathologist of the prophylactic examination unit, head of clinical trial unit

Applicant: Limited Liability Company "Schwabe-Moscow", INN 7717768215, 129366, Moscow, Prospekt Mira, 176

The clinical study is carried out in accordance with the finalized and approved draft project and approval of the local ethics committee.

Terms of the research work stage:

July 12, 2019 – October 15, 2019.

List of abbreviations

OS – occupational safety
HRV- heart rate variability
SI – Baevsky stress index
TP – total power spectrum of heart rate variability
CVS – cardiovascular system
EH – essential hypertension
AH – arterial hypertension
BP – blood pressure
HR – heart rate
DBP – diastolic blood pressure
SBP – systolic blood pressure
p – level of statistical significance
m > - mean squared deviation (MSD)

Study objective:

- to evaluate efficacy of transcutaneous electrostimulator for blood pressure correction "ABP-051" for stabilization of a functional condition and blood pressure in persons working in the conditions of increased psychoemotional strains, stress situations, as well as in persons working in harmful and hazardous labor conditions.

As the main criteria for efficacy evaluation, the following parameters and approaches were used:

- efficacy evaluation of stabilization and normalization of blood pressure levels as the consequence of exposure of stress factors, production environmental factors unfavorable and harmful for health;

- evaluation of heart rate variability values, in particular, numerical values of stress index SI (the range of 50-150 c.u. is normal) and adaptation resource as a total power of regulation spectrum TP (the range of 1000 - 2500 ms^2 is normal) in the range of frequencies

0.0033- 0.4 Hz;

- evaluation of changes in psychological conditions and stress level based on the analysis of psychological standard testing and survey using SAN and Spielberger questionnaires.

For the research work on efficacy evaluation of medical device “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU-9444- 005-12342964-2015”, the following documents are presented:

1. marketing authorization dated March 31, 2016 № RZN 2016/3776;
2. certificate of conformity;
3. instruction for use INFE05.01-03.70-01Hn;
4. plan of the research work on efficacy evaluation “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU-9444-005-12342964-2015” dated April 15, 2018.

Device “ABP-051” is intended for a therapeutic course exposure to the left wrist areas with the method of transcutaneous electroneurostimulation for correction of blood pressure and functional body condition as the main treatment or an adjunct to complex drug therapy.

Electrostimulator “ABP-051” has class IIa of potential risk of medical device use in accordance with GOST 31508 and order of the Ministry of Health of RF dated 06.06.2012 № 4n, as well as, pursuant to rule 9 of annex IX of directive 1993/42/CEE as amended 2007/47/CE.

The type of the medical device in accordance with the nomenclature classification of medical devices: 181480 (in accordance with Order of MoH RF dated 06.06.2012 №4n “On approval of nomenclature classification of medical devices”).

Code of the All-Russian Product Classifier for the medical device: 944410.

In the groups of placebo (false) control, devices “ABP- 051” visually not differing from working devices were used. In false devices, electrodes were switched off, with sound and light indication preserved, electrostimulation program was not performed.

Study plan

In the randomized placebo controlled study, 99 patients took part in the study, their mean age was 47.5±8 years, there were 16 women and 83 men.

The subjects were divided to three groups by the following criteria:

- group №1: 30 relatively healthy persons working in the conditions of harmful and hazardous production factors, psychoemotional strain without the established diagnosis of arterial hypertension, whose mean SBP was less than 130 mm Hg and DBP less than 80 mm Hg. The group consisted of the subgroup of 20 subjects (group №1) who received the course BP correction, and subgroup of 10 subjects (group № 1a) for placebo control;
- group №2 of 33 subjects with complaints to episodic BP increase with the established diagnosis of arterial hypertension (degree 1, 2, 3) receiving standard antihypertensive therapy. Group №2 consisted of 19 subjects who had the course BP correction and 14 subjects for placebo control (group №2a);
- group 3: 29 persons working in the conditions of production noise and psychoemotional strains (flight attendants), among which 19 persons were in the treatment group (group №3), and placebo control group comprised of 10 persons (group №3a).

Seven persons failed to complete the correction course due to organization reasons therefore they were withdrawn from the statistical analysis sample. Therefore the total number of study subjects was 92.

Devices “ABP-051” were used twice a day for 10 days. If any products were indicated, ABP-051 was used during the anti-hypertensive therapy.

The nonparametric Wilcoxon signed rank test and Mann-Whitney test was used for the data analysis as the normal distribution test showed the nonconformity of individual samples in the series to the Gaussian distribution.

Results

Below, the correction efficacy evaluation in each group is given separately.

Table № 1 Results of the course exposure in group №1 and group №1a

Group № 1				
Ref.№	Parameter	Prior to the course	After the course	Changes and level of their statistical significance
1	SBP	120± 16.3	122 ±15.8	±2 p = 0.31
2	DBP	77.8 ± 11.1	75.8 ± 10.4	-2 p = 0.2
3	HR	72.3 ±98	71.3 ± 10	-0.9 p»0.05
4	SI	165 ±41	144±39	-21 (-13%) p < 0.05
5	TP	1256 ±143	1420 ±210	±164 (±13%) p < 0.05
Group №1a Placebo				
6	SBP	123 ±7.9	118± 12.3	-5 p > 0.09
7	DBP	81 ±5.6	77.5 ±8.3	- 3.5 p > 0.05
8	HR	73.6 ± 7	75.7 ± 9	±2.1 p » 0.05
9	SI	172±38	168±62	- 4 (-2 %) p = 0.06
10	TP	1391±143	1410 ±320	±19 (±1.3%) p = 0.12

As table №1 showed, group №1 and №1a did not have any significant BP changes as a result of the course exposure regarding healthy persons with normal BP. Group №1 had the decrease of stress values from the slightly increased to normal level and the increase of total power spectrum of the regulatory systems which showed the increase of vital force reserve. In placebo group №1a, there was a slight decrease of stress level with the increased MSD, but the obtained result was not significant. The control group had the increase of total power spectrum of the regulatory systems by the mean value and amounted to 19 ms^2, however, MSD was increased, but the changes were within the normal, and the changes were not significant. HR changes were also not significant.

Table № 2 Results of the course exposure in group №2 and №2a

Group №2				
Ref.№	Parameter	Prior to the course	After the course	Changes and level of their statistical significance
1	SBP	148± 13.3	131 ±8	- 17 p< 0.001
2	DBP	92.8 ± 10.1	82.8 ± 6.9	-10.0 p< 0.001
3	HR	83.4 ± 12	81.3 ± 11	-2.1 p»0.05
4	SI	262 ±41	210±39	-52 (-20%) p<0.05
5	TP	680 ±113	945±186	±265 (+39 %) p < 0.05
Group №2a Placebo exposure				
6	SBP	150 ± 12.5	135 ± 12.3	-15 p» 0.05

7	DBP	90.7 ± 9.3	84.1 ±8.3	- 6.6 p » 0.05
8	HR	82.2 ± 13.1	79.9 ± 21	- 2.3 p » 0.05
9	SI	271 ±34	229 ± 36	-42 (-15%) p < 0.05
10	TP	710±122	845± 192	+ 135 (+19%) p < 0.05

Group №2 with the established diagnoses of arterial hypertension (degree 1, 2, 3) had the significant decrease of BP values, both systolic by 17 mm Hg and diastolic by 10 mm Hg. In control placebo group №2a, BP decrease (systolic and diastolic) was not significant. The changes in the control group were significantly lower.

Group №2 has the decrease of stress level by 20% from baseline and the increase of power spectrum of the regulatory systems by 39% which shows the significant increase of vital force resource and the increase of ability to environmental adaptation. HR changes were not significant.

Table № 3 Results of course exposure in group №3 and №3a

Group 3				
Ref.№	Parameter	Prior to the course	After the course	Changes and level of their statistical significance
1	SBP	132± 13.2	125 ±7.2	- 7 p < 0.01
2	DBP	84.0 ± 8.2	80.9 ±5.9	-3.1 p< 0.001
3	HR	77.1 ±11	75.3 ± 10	-2.6 p » 0.05
4	SI	190± 38	144+39	- 46 (+24 %) p < 0.05
5	TP	1120 ±127	1386 ±198	+ 266 (+24 %) p < 0.05
Group 3a Placebo exposure				
6	SBP	145 ± 13.8	129 ± 9.0	-16 p > 0.05
7	DBP	90.5 ± 9.3	80.0 ±8.3	-10.5 p > 0.05
8	HR	76.2 ± 14.1	77.5 ± 17	+1.3 p » 0.05
9	SI	201± 39	186+45	- 15 (-7%) p<0.05
10	TP	712+131	848 ±187	+ 136 (+ 19%) p<0.05

Group №3 consisted of employees working in the conditions of the increased noise and has on average a normal BP, and control group №3a had the increased BP. Device "ABP-051" does not decrease BP if the pressure corresponds to the normal one, due to that, there was the difference in the results of BP decrease in group №3 and №3a. In placebo group №3a, BP decrease was not significant.

Groupe №3 had the significant decrease of stress level by 24 % from baseline and the significant increase of power spectrum by 29% which shows the increase of vital force resource and ability to adaptation in aggressive environment. HR changes were not significant.

Efficacy evaluation of course use of device “ABP-051” using SAN method and Spielberger test

The method as a questionnaire (test) serves as an operative evaluation of Well-being (“W”), Activity (“A”), Mood (“M”) prior to and after patient’s exposure. The changes in situational (SA) and personal (PA) anxiety levels were evaluated prior to and after the exposure course by the Spielberger test.

The efficacy of course exposure was compared by groups №1 and №1a, №2 and №2a, №3 and №3a.

Groups№1 - №1a

When groups №1 and №1a (group of relatively healthy subjects) were compared, no significant differences in SAN and Spielberger were shown prior to and after course exposure. In group №1, any significant difference in either “SA” or “PA” was not shown. In group №1a, the significant difference in SA prior to the course was – 2.09 scores and after the course -1.72 scores.

Groups №2 - №2a

Groups №2 and №2a (patients with arterial hypertension) showed significant differences in SAN test by parameters “A” and “M”. Differences by activity “A” on average in group 2 – 5.59 scores, and in group №2a – 4.73 scores, i.e. group №2a is less activea. Differences by mood “M” on average in group №2 were 5.96 scores, in group №2a – 5.48 scores which means that the mood is slightly lower than in group №2.

Group №2 had significant differences in situational anxiety. The mean “SA” value was -1.85 scores, after -1.7 scores, and the mean “PA” value prior to the course was – 1.99 scores, after the course – 1.95.

Group №2a had significant differences in personal anxiety (mean “PA” value prior to the course – 2.21 scores, after the course – 2.08 scores).

Groups №3 - №3a

When groups №3 and №3a (work in the conditions of increased noise) were compared, group №3 showed significant differences in the dynamics only in situational anxiety. The mean “SA” value prior to the course was – 1.78 scores, after the course -1.56. Therefore, “SA” value to the end of the study was significantly reduced.

In group №3a, no significant differences either in situational or personal anxiety were shown.

Method safety

It has been established that the stimulation therapy is not accompanied with unfavorable reactions and adverse effect. No complaints to local application reactions were received.

To evaluate safety, BP changes were analyzed in patients with initially normal values not exceeding SBP 130 mm Hg and DBP 90 mm Hg. As well, minimal SBP and DBP values found during the therapy were analyzed both in combination and without combination with antihypertensive drugs. Minimal SBP values in neither of cases were lower than 110 mm Hg and DBP lower than 65 mm Hg.

Conclusions

1. The most pronounced and significant results in BP decrease, normalization of HRV parameters by SAN and Spielberger test in course ABP-051 exposure were shown in group №2 in which in general initially more unfavorable blood pressure and stress values were recorded compared to groups № 1 and №3.
2. In group №2, positive significant changes in activity, mood, anxiety corresponding to positive changes in course exposure as the statistically significant decrease of stress level SI and the increase of total power spectrum TP of the regulatory systems which were subjectively felt as the increase of life tone, working capacity and improved mood, were found.
3. The course use of device “ABP-051” in groups №1 and №1a showed the method safety as SBP in group №1 was not decreased below 115 mm Hg, and DBP below 75 mm Hg, however the significant decrease of stress level and increase of total power spectrum was shown. In group №1a, the significant decrease of situational anxiety was found.
4. In group №2, the significant SBP decrease by 17 mm Hg was shown. DBP values were significantly decreased by 10.0 mm Hg.
5. The use of electrostimulator “ABP-051” in patients in group №3 working in harmful and hazardous labor conditions was accompanied with the small but significant decrease of stress level SI, increase of power spectrum TP which was favorable for blood pressure normalization in general in group №3 and №3a. Positive changes of the values allow to conclude the increase of unspecific adaptation body resources and possibility to tolerate unfavorable stress factors.
6. Therefore, the method for BP correction with device “ABP-051” has a positive effect of activation of stress-limiting structures, the increase of adaptation body abilities and decrease of probability of disadaptation, improvement of psychoemotional background which concludes a high therapeutic and prophylactic effect of the method to preserve working capacity and increase stress resistance.
7. The use of device “ABP-051” during antihypertensive therapy did not influence its exposure on the autonomic nervous system and psychoemotional background.
8. The use of electrostimulator “ABP-051” may be considered safe as it was not accompanied with local or general adverse reactions and did not lead to unfavorable and critical BP decrease regardless of their use during antihypertensive therapy.

CONCLUSION

With regards to a normalizing effect to the body driven by reflector mechanisms of exposure, electrostimulator “ABP-051” can be recommended for individual prophylactic use by persons both with a normal blood pressure and the established diagnosis of hypertension who may be exposed to

the increased risk of professional stress conditions, disadaptosis due to the increased loads and psychoemotional overstrain, unfavorable factors related to the nature of work, shift method, necessity of frequent business trips and other harmful, and hazardous labor conditions.

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