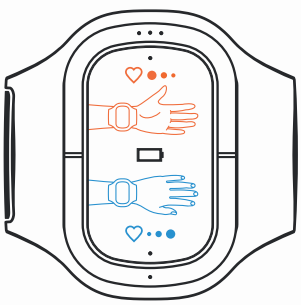
CITY HOSPITAL No. 175 OF THE HEALTHCARE DEPARTMENT
State-Financed Health Institution
Moscow
2018 and 2019

ABP 051



Зарегистрирован
в качестве **медицинского**
изделия в РФ и ЕС

Регистрационное удостоверение
РЗН 2016/3776 от 31.03.2016.
EC Certificate № 1942/MDD от 01.09.2017.

"APPROVED"
Chief physician
SBHI "Municipal outpatient health facility № 175
of the Moscow Health Department"

«Городская поликлиника № 175 Департамента здравоохранения города Москвы»

A.P. Ternavsky

«17» 10 2018

CLINICAL STUDY PROTOCOL

Name of the study device: "Trascutaneous electrostimulator for blood pressure correction "ABP-051" per TU-9444-005-12342964-2015" (hereinafter referred to as Electrostimulator "ABP-051"). Model: ABP-051.

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

EU Certificate for Conformity under Directive 93/42/EEC dated 01.09.2017.

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

Manufacturing site: 623417, Russia, Sverdlovsk Region, v. Kamensk-Uralsky, Mechanizatorov Str., 74.

Medical organization carrying out the medical study of the medical device:

State Budgetary Healthcare Institution of the Moscow Health Department "Municipal outpatient health facility № 175 of the Moscow Health Department" (SBHI "Municipal outpatient health facility № 175 of the Moscow Health Department"), Russia, 105568, Moscow, Chelyabinsk Str., 16, bld. 2, 1.

The license for medical activity: LO-77-01-015019 dated 17 October 2017 issued by the Moscow Health Department.

The study was carried out in outpatient settings on the base of therapeutic unit of branch № 1 of SBHI "Outpatient health facility № 175 of the Moscow Health Department". The study coordinator: physician – Methodist I.V. Kirichok.

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

The clinical study is carried out in accordance with the agreed and approved study protocol.

The study period: 27 April 2018 to 2 August 2018.

Aims and goals of the medical study:

- To assess efficacy of blood pressure (BP) correction when device "ABP-051" is administered in outpatient settings by elderly patients with three or more chronic diseases, one of which is arterial hypertension, as an adjunct to the main drug therapy.
- To establish terms and efficacy level for achievement and stabilization of target BP in hypertensive patients having three daily procedures with working devices "ABP-051" within 14 days compared to sham devices.
- To determine duration of an effective course of the device exposure for achievement and stabilization of target BP in the study groups.
- Conclusions on the study results.

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

1. Application for the medical study dated 15 April 2018.
2. Marketing authorization of the medical device dated 31 March 2016, № RZN 2016/3776.
3. Certificate for Conformity.
4. Clinical study protocol represented by the analysis and assessment of clinical data of medical study № 15122017-02 dated 15 December 2017 “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU-9444-005-12342964-2015” (Budgetary Healthcare Institution “Republican clinical – diagnostic center of the Ministry of Health of the Udmurt Republic”, Izhevsk).
5. Instruction for use INFE 05.01-03.70-01 IP.
6. Plan of the medical study of medical device “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU-9444-005-12342964-2015” dated 15 April 2018.

1. ANALYSIS OF THE CLINICAL DATA, DOCUMENTS AND MATERIALS SUBMITTED BY THE APPLICANT:

Electrostimulator “ABP-051” is intended for non-drug therapy of diseases associated with blood pressure correction as an adjunct to complex drug therapy, is intended for therapeutic non-invasive (not impairing the skin) course exposure to the left wrist areas using the transcutaneous electrostimulation method.

Classification.

Electostimulator “ABP-051” has class IIa of potential risk of the medical device in accordance with GOST 31508 and Order of the Ministry of Health of the Russian Federation dated 06.06.2012 № 4n, as well in accordance with the rule 9 in the annex of Directive IX 1993/42/CEE as amended 2007/47/CE.

Type of the medical device in accordance with the nomenclature classification of medical devices: 181480 (in accordance with Order of Ministry of Health of the Russian Federation 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.

Device labeling.

The device labeling contains the following symbols and designations.

Administration of the medical device.

Electrostimulator “ABP-051” is intended for the use in health facilities, as well for individual use by patients in home settings for therapeutic exposure.

The device is not sterile.

Patient groups in accordance with the instruction for the use of the medical device:

Electrostimulator “ABP-051” is intended for therapeutic non-invasive exposure for blood pressure correction and normalization of general health condition.

The device is intended for persons above 14 years with labile arterial hypertension and patients with persistent increase of blood pressure as additional exposure during drug therapy.

For hypotonic patients.

Indications for the device administration:

√ persistent high blood pressure in patients with essential hypertension – as an adjunct to complex drug therapy;

√ episodes of blood pressure increase in stress situations, weather changes, etc. in persons with labile arterial hypertension;

√ low blood pressure in patients with essential hypotonia as an adjunct to complex drug therapy.

Contraindications to the device administration:

√ presence of an implanted pacemaker;
√ atrial fibrillation;
√ individual intolerability of the electric current;
√ skin injury on the left wrist;
√ neoplasms (tumors) of any etiology or location;
√ acute fevers of unknown origin;
√ acute psychotic, alcohol or drug-induced excitation.

Possible adverse actions.

Possible adverse actions of the medical device are not identified.

Technique of administration.

Electrostimulator "ABP-051" is used for a direct short-term contact with a patient's skin on the left wrist.

Principle of the device work:

Transcutaneous stimulation – the method of physiotherapy which is based on exposure to short frequency impulses on human wrists, namely:

- exposure to the internal left wrist surface, is used for lowering of blood pressure. Working frequencies of the program: 9.2 Hz and 77 Hz. Total time of the program exposure - 5 minutes.
- exposure to the external left wrist surface, is used for increase of blood pressure. Working frequencies of the program: 77 Hz and 140 Hz with magnitude modulation and frequency 4 Hz. Total time of the program exposure - 6 minutes.

The exposure occurs through the built-in electrodes in the device body while touching a patient's skin.

The device provides therapeutic exposure for correction in the following values of blood pressure:

- for patients with a high blood pressure, range of systolic BP over 130 mm Hg and diastolic over 80 mm Hg;
- for patients with arterial hypotonia and systolic BP less than 106 mm Hg and diastolic less than 70 mm Hg.

Safety of the medical device is confirmed by the marketing authorization of the device dated 31 March 2016 №RZN 2016/3776 issued by the Federal Agency for Surveillance over Healthcare based on the results of the expertise made during the registration of the medical device.

2. ANALYSIS OF THE CLINICAL STUDY RESULTS

During the clinical study, device "ABP-051" was administered in patients with high BP as an adjunct to the main complex therapy.

Procedure of the device administration in the clinical study.

1. Prior starting the work, BP was measured. Then the device was put on the internal left wrist so that the electrodes touched the skin closely.
2. The device was switched on with the button pressed, with three points and red mark which corresponded to the exposure program for BP lowering.
3. BP correction process lasted for 5 minutes and consisted of several exposure phases differing by frequency, exposure time and magnitude. After the session, a sound signal was

heard, the device was switched off automatically.

4. For a consistent result, a 14-day course treatment was selected, 3 procedures a day.
5. Then the device was removed from the hand, a patient had rest for 20-30 minutes, BP was measured, and a result is recorded.

During the complex medical studies to assess safety and efficacy of outpatient administration of device "ABP- 051", statistically significant results were established. It was assessed in elderly patients with several chronic diseases, one of which – essential hypertension.

28 patients divided to four groups took part in the study. Device "ABP-051" was clinically investigated in three groups of patients within 14 calendar days. In the control group of patients, a sham device was used in the analogous mode (with electrodes switched off). After treatment period (the period of the device administration), the patients were followed for 14 days with BP control.

The patients' registry is provided in Annex 1 "Study log".

All patients completed the study, one patient discontinued the study on the initial stage due to her individual intolerability and refusal (more detailed - below), other patients did not report any negative device effects and adverse reactions.

The patients received standard individual baseline therapy prescribed prior the clinical study. During the study, drug therapy was not changed. After exposure period with device ABP-051 thrice a day for 14 days, the patients were dynamically observed for a 14-day period. Considering that all patients were observed by a physician for a long time, as baseline BP, mean BP values were taken for the previous 5 months (based on office BP on the visit to the physician's recorded in the patients' registry in the district followed by the physician).

The results were assessed in groups of patients and in general with regards to total mean BP value (both systolic and diastolic) and pulse rate during the period when the device was administered, and in observation period. BP and heart rate flow charts were examined in each patient, tendency line was determined.

General patient's health condition based on subjective patient sensations was assessed prior and after the device administration using 10 score scale, where 10 – excellent health condition, mood, working capacity, and 1 - bad.

Table 1.

Study design scheme.

Group	**Number**	**ABP-051 administration**	**Observation**
Group 1	7 patients	14 days	14 days
Group 2	8 patients	14 days	14 days
Group 3	6 patients	14 days	14 days
Control	7 patients	14 days	14 days

Clinical study control:

- patient study log;
- patient observation registration card;
- clinical study protocol on device "ABP-051" for BP correction based on general clinical efficacy and administration methodology (observation diary in treatment period and observation period);
- patients' voluntary informed consent for the study and processing of personal data;
- recording card of adverse reactions.

Elderly patients (starting from 50 years) with three or more chronic diseases, one of which is arterial hypertension, observed by a physician constantly and receiving baseline treatment, were enrolled to the study. During the drug therapy, some patients enrolled to the study were

persistently normotonic (in this case, the study aim was possibility to decrease drug doses), some of them – had significant BP fluctuations.

Patients with maximal values of systolic BP (SBP) not exceeding 180 mm Hg, diastolic BP (DBP) - 110 mm Hg took part in the study. Anti-hypertensive effect was considered as achieved if BP was lowered for over 5% from baseline.

Flow charts were plotted for visual analysis of the study reflecting BP fluctuation in treatment period (period of the device administration thrice a day for 5 minutes) for 14 days (horizontal axis), in observation period (14 days) and significance level of approximation (R^2).

Analysis of the results in group 1.

Seven patients with AH (arterial hypertension), CAD (coronary artery disease) and CVD (cerebrovascular disease) were enrolled to group 1. Prior the study, mean blood pressure in the group was 148 mm Hg and 85 mm Hg.

Table 2.

Mean BP in group 1 prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	119.0+7.2	176.2±4.9	148.5±15.5
Diastolic BP (DBP)	72.8±2.6	96.4±7.76	84.5±.3

Table 3.

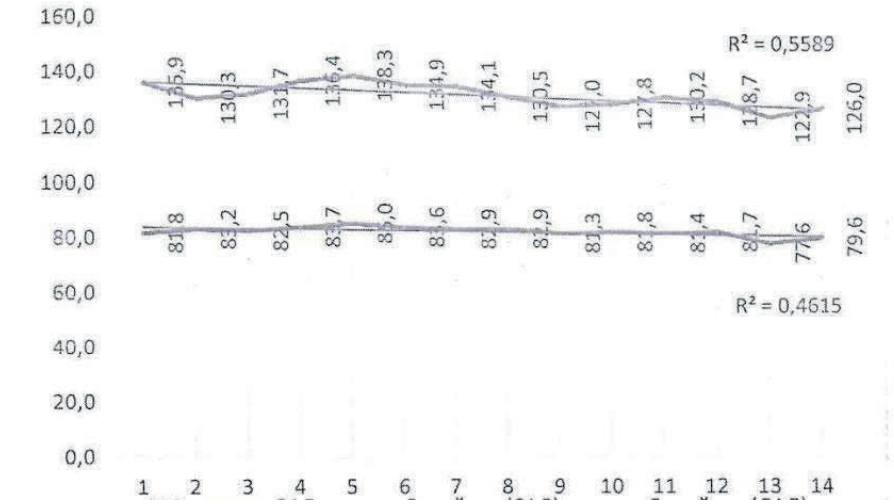
Dynamics of mean BP and pulse in group 1.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	148.5±15.5	84.5±3	No data
During the procedure	131.1±6.6	82.6±4.6	75±11.1
In observation period	128.4±7.9	80.6±6.4	73.1±8.3
General dynamics:	-20.1	-3.9	-1.9

Five patients achieved a good effect (a consistent BP lowering). Two patients whose mean BP during drug therapy was in the range 120-130 mm Hg did not have any significant effect.

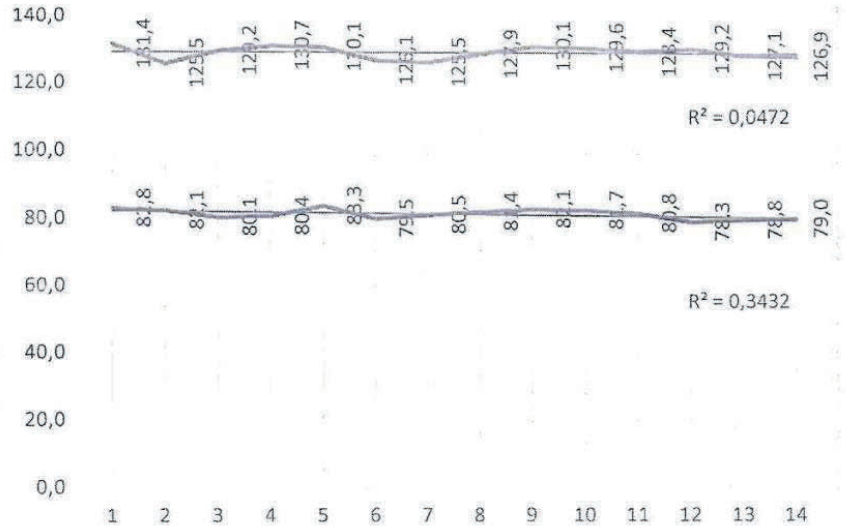
All patients stated improved health condition, decreased anxiety, sleep normalization. Health assessment after the procedure was increased on 3-4 scores and averaged to 7 scores with baseline 4 (out of 10 possible).

Figure 1 presents the flow chart with the correction results in group 1 in treatment period (mean daily BP), and Figure 2 – in observation period. In treatment period, the tendency line of mean daily BP, both systolic and diastolic, was decreased. Significance level of approximation was 0.5±0.05



Total efficiency of course BP correction in group 1; SBP; DBP, Linear (SBP); Linear (DBP)

Figure 1. BP dynamics in the study treatment period



BP dynamics in observation period in group 1; SBP; DBP, Linear (SBP); Linear (DBP)

Figure 2. Representation of BP dynamics in observation period.

In observation period, the tendency line of systolic BP was horizontal, i.e. BP lowering was maximally achieved in treatment and remained stable in observation period. The tendency line of diastolic BP tended to decrease in both periods, but was lower than in treatment period. In general, SBP was lowered in the group on 20 mm Hg (14 %), DBP - on 4 mm Hg (5 %), pulse rate was reduced on 2 beats/min. in relation to the study period. Anti-hypertensive effect was 71 %.

Analysis of the results in group 2.

Group 2 was comprised of patients with AH, CAD and 2 type DB (2 type diabetes mellitus). The number of patients taking part in the study - 8 persons. Diabetes mellitus was treated with hypoglycemic combined drugs.

During the treatment, mean blood pressure in patients of group 2 was 147 and 83 mm Hg with fluctuations of systolic BP ± 20 mm Hg and diastolic BP ±6 mm Hg.

Table 4.

Mean BP in group 2 prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	126.5±3.8	168.2±20.5	147.8±11.8
Diastolic BP (DBP)	75.4±1.3	88.4±5.1	83Д±5.0

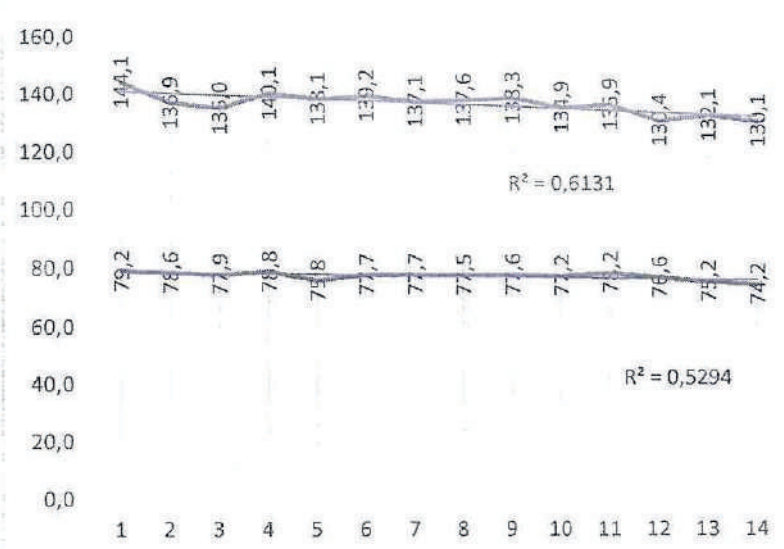
Seven patients (87.5%) achieved BP lowering. One patient with systolic BP lowered on 9 mm Hg (which was 6% of baseline) had the increase of diastolic BP on 9 mm Hg (which was 10% of baseline). No patient reported aggravated condition and negative dynamics.

Table 5.

Dynamics of mean BP and pulse in group 2.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	147.8±11.8	83.1±5.0	Нет данных
During the procedure	136.6±8.5	76.8±6.7	69±3.8
In observation period	132.6±8.8	75.0±7.8	66.8±3.2
General dynamics:	-15.2	-8.1	-2.2

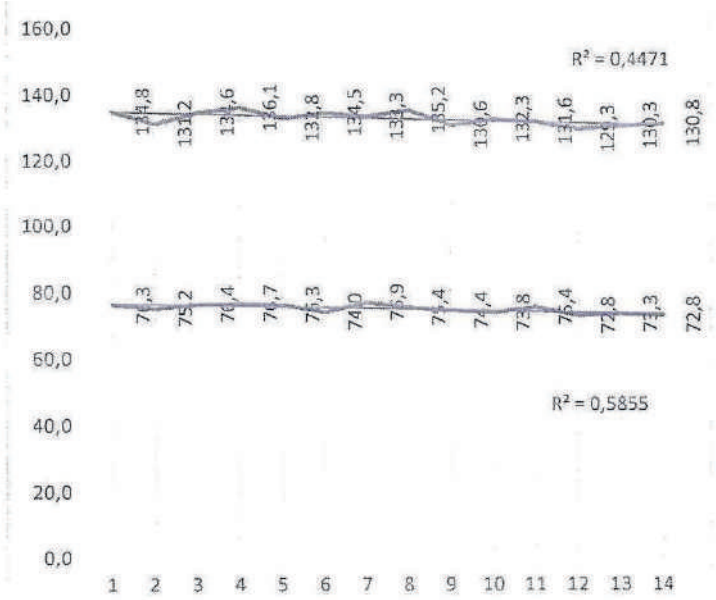
4 patients (50%) stated their improved health conditions, other patients considered that their health condition and working capacity did not change after therapeutic exposure to device “ABP-051”. Two patients assessed the device administration so positively (health condition improved on 5 scores compared to baseline) that were ready to use it multiple time. Their systolic BP was lowered on 16 and 37 mm Hg in relation to mean value for the previous 5 months.



Total efficiency of course BP correction in group 2; SBP; DBP, Linear (SBP); Linear (DBP)

Figure 3. BP dynamics in treatment period in group 2

Figure 3 presents the flow chart of correction results in group 2 in treatment period (mean daily BP), and Figure 4 – in observation period. The lowering of mean daily BP, both systolic and diastolic, was observed both in treatment period and observation period, but the lowering in treatment period was more profound.



BP dynamics in observation period in group 2; SBP; DBP, Exponential (SBP); Exponential (DBP)

Figure 4. BP in observation period in group 2.

In general, SBP was lowered on 15 mm Hg, DBP - 8 mm Hg in the group, pulse rate was changed on 2-3 beats/min in relation to the study period. Anti-hypertensive effect in group 2 was 88%.

Analysis of the results in group 3.

Group 3 was comprised of six patients with AH, CAD and chronic lung disease (COPD (chronic obstructive pulmonary disease) or mild bronchial asthma).

Mean blood pressure in patients of group 3 receiving the therapy was 157 and 84 mm Hg. Fluctuations of systolic BP were ± 28 mm Hg, diastolic ±12 mm Hg.

Significant BP fluctuations were observed in patients of group 3 during the drug therapy and in the study period. It was probably due to complexity of arterial hypertension correction in lung disorder. Most drugs for asthma and COPD treatment aggravate hypertension course, reverse reactions and adverse effects were observed. Long-term administration of beta adrenergic agonists in asthma induces a persistent increase of blood pressure.

Table 6.

Mean BP in group 3 prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	123.6±7.7	178.4±9.3	156.9±15.6
Diastolic BP (DBP)	75.0±3.2	10±2	83.6±1.6

After the treatment course, five out of six patients stated general health improvement on average on 2-3 scores. The patient that did not subjectively state health change had a significant lowering of mean BP: systolic on 17%, diastolic - on 8%.

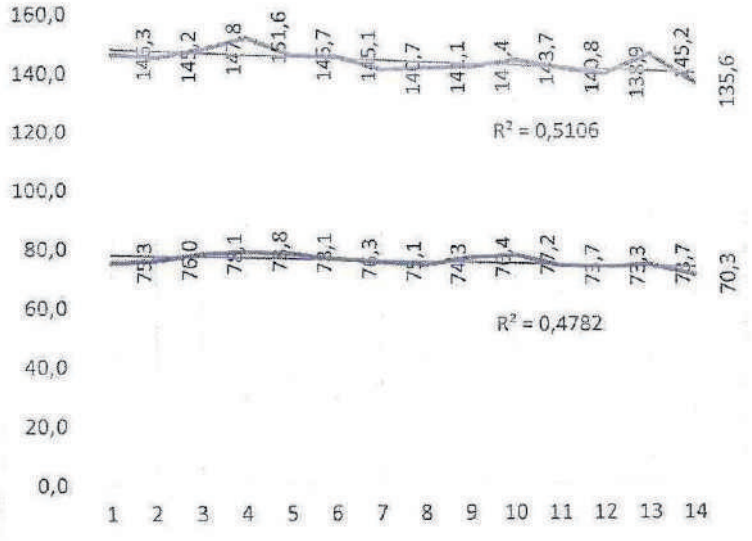
Table 7.

Dynamics of mean BP and pulse in group 3.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	156.9±15.6	83.6±1.6	No data
During the procedure	143.2±12.8	77.5±6.5	77.7±10.9
In observation period	140.3±8.9	75.7±4.1	75.1±9.8
General dynamics:	-16.6	-7.9	-2.6

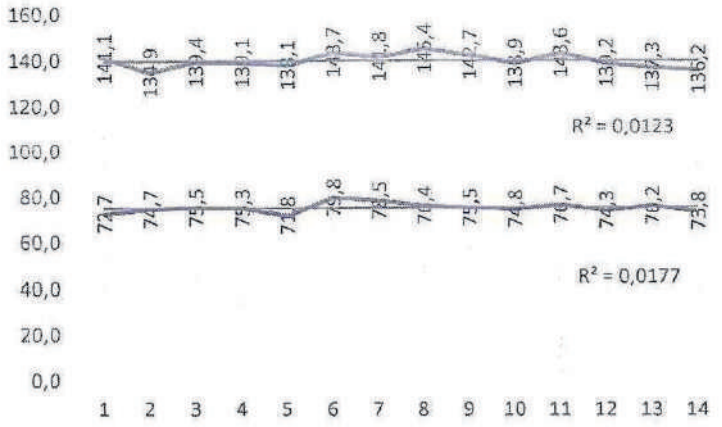
In general, SBP was lowered in the group on 16 mm Hg (10 %), DBP on 8 mm Hg (10 %). Pulse rate was reduced on 2 beats/min.

Figure 5 presents the flow chart of correction results in group 3 in treatment period (mean daily BP), Figure 6 – in observation period. The decrease of the tendency line of mean daily BP, both systolic and diastolic, was observed in treatment period. In observation period, BP was not lowered in group 3, conditional tendency line was horizontal, BP remained stable in observation period.



Total efficiency of course BP correction (group 3); SBP; DBP, Linear (SBP); Linear (DBP)

Figure 5. BP dynamics in group 3 in treatment period



BP dynamics in observation period (group 3); SBP; DBP, Linear (SBP); Logarithmic (SBP); Linear (DBP)

Figure 6. BP in observation period in group 3.

Anti-hypertensive effect was observed in 83% of patients from group 3. Any adverse events were not reported. Drug therapy was not corrected during administration of device ABP-051 and in observation period.

Analysis of results of device "ABP-051" administration.

The data analysis in all groups of patients receiving device "ABP-051" in the mode providing BP lowering showed that mean systolic BP was lowered on 17 mm Hg, 6% from baseline, mean diastolic BP was lowered on 7 mm Hg, 8% from baseline. Only four out of 21 patients did not achieve any significant effect of BP lowering. Systolic BP in 62% patients was lowered for more than 10 mm Hg, and diastolic BP fore more than 5 mm Hg.

More profound BP decrease was observed in patients with a higher baseline BP. BP lowering was negligible in baseline normotonia during drug therapy - within 1-3% from baseline. A significant anti-hypertensive effect among all patients was 81%.

Analysis of the results in the control group.

The control group using "sham device" was comprised of 7 elderly patients with three and more chronic diseases receiving baseline AH therapy for a long time. During the study, the device simulating the working one with all the features of active apparatus was used to detect a sham effect: a light emitting diode flashed, background sound worked, but electrodes were switched off from the scheme.

Mean blood pressure in patients of the control group during the treatment was 149 and 84 mm Hg.

Table 8.

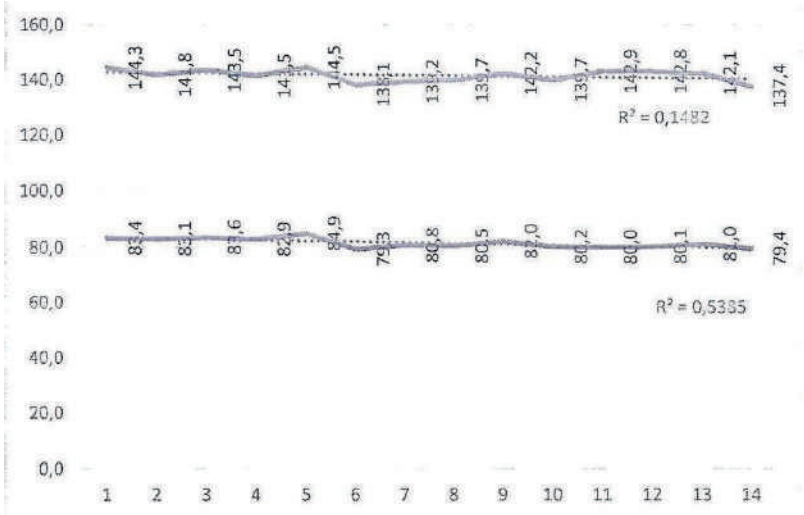
Mean BP in the control group prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	137.0±2.8	170.2±7.7	149.3±11.7
Diastolic BP (DBP)	76.0±6.0	92.2±6.24	84.4±6.3

After the course of procedures, three out of six patients stated improved health condition, two – on 1 score, one patient – on 4 scores, but her BP did not change, in general. Other patients did not feel any improvement, in general, SBP was lowered on 9 mm Hg in the group, 6% from baseline, DBP on 3 mm Hg, 3% from baseline, pulse rate was changed on 4 beats/min. and became more frequent, on 4 beats/min in relation to the study period.

Table 9. Dynamics of mean BP and pulse rate in the control group.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	149.3±11.7	84.4±6.3	No data
During the procedure	141.9±7.0	83.1±8.4	74.3+5.6
In observation period	139.7±6.2	81.8±6. 2	77.8±6.7
General dynamics:	-9.6	-2.6	+3.5

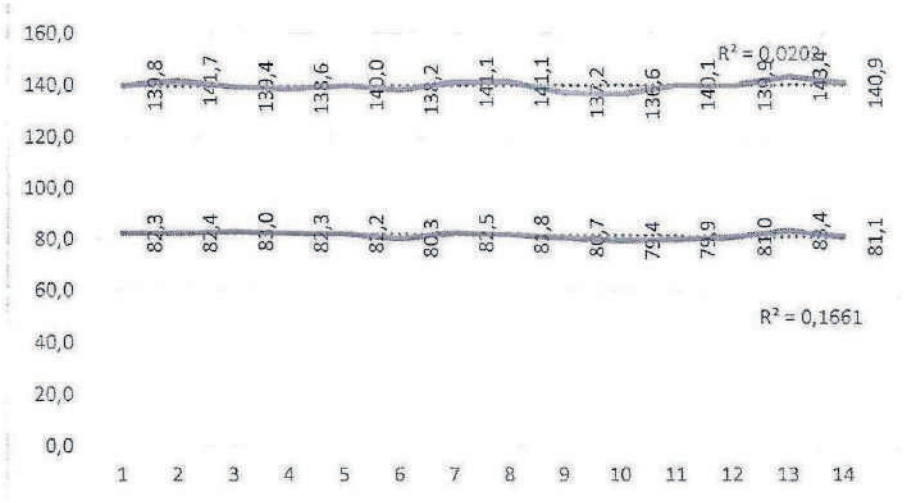


Total BP correction in treatment period - placebo group; SBP; DBP, Linear (SBP); Linear (DBP)

Figure 7. BP in the control group in treatment period

Figure 7 presents the flow chart of correction results in the control group in treatment period (mean daily BP), Figure 8 – in observation period. There is no evident tendency line of systolic mean daily BP, diastolic pressure was lowered on 4 mm Hg.

In observation period, BP lowering was not observed in the control group, the conditional tendency line remained horizontal, significance level of approximation (R^2) was less than 0,1. BP lowering for over than 5% was achieved by 2 patients, anti-hypertensive effect was 33 %.



BP dynamics in observation period in placebo group; SBP; DBP, Linear (SBP); Linear (DBP)

Figure 8. BP dynamics in observation period in placebo group

COMPARISON OF THE STUDY RESULTS ON DEVICE "ABP-051" AND THE RESULTS IN THE CONTROL GROUP

Comparing the results in the group of patients administering device "ABP-051" in a working mode and the results in the control group, you can state a significant BP lowering in the study group using working device "ABP-051" and insignificant BP fluctuations in the group using "placebo device". The results are summarized in table 10.

Table 10

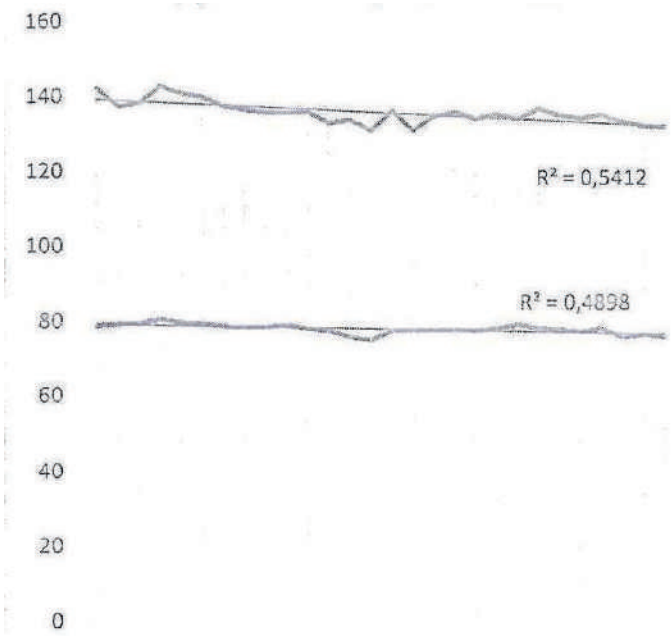
Comparison of the study results.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	150.6±14.2	83.7+5.7	No data
During the procedure	136.6±10.0	78.8+6.5	73.5+8.7
In observation period	133.4+10.2	77.1+6.2	71.3+7.9
General dynamics:	-17.2	-6.6	-2.2
"Placebo" dynamics	-9.6	-2.6	+3.5
Improvement (%)	+79%	+153%	

In the study group, SBP was decreased on 17 mm Hg, DBP on 7 mm Hg, pulse rate was changed negligibly - on 2 beats/min. In the control group, the lowering of mean BP was 9 mm Hg as for systolic and 2 mm Hg from diastolic.

The lowering of systolic BP compared to anti-hypertensive effect of the working electrostimulator and "placebo device" was 80% greater, and the lowering of diastolic BP – 150% greater. The change of pulse rate in both groups was negligible, but when the working device was used, RR became less frequent, on 2.2 beats/min on average, and when "placebo" device was used – more frequent, on 3.5 beats/min. on average.

The health assessment by patients was increased on 2.4 scores up to 7 scores in the study group, and on 1.4 scores up to 6 in the control group.

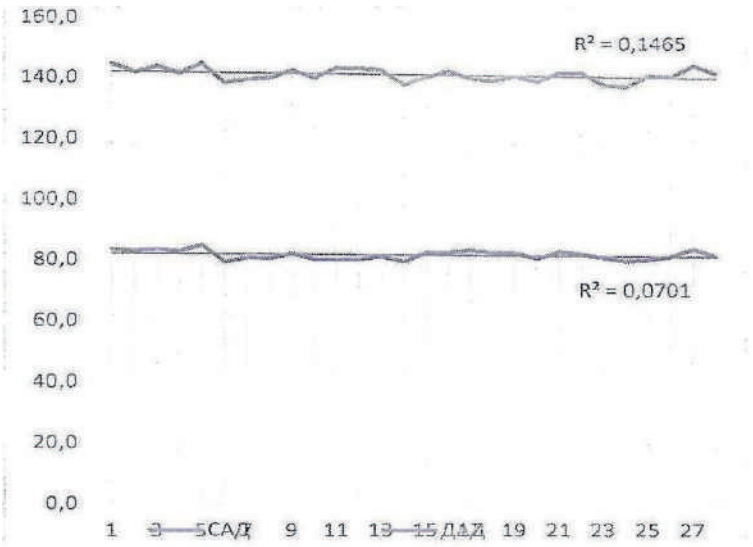


Dynamics of mean BP; study days; SBP; DBP; Linear (SBP); Linear (DBP)

Figure 9. Representation of BP dynamics in study groups during the study period on device "ABP-051"

Figure 9 presents a flow chart of BP dynamics during the treatment period and observation period. The tendency line of systolic and diastolic BP was deceased, as well systolic and diastolic BP was lowered. Significance level of approximation was more than 0.5.

Figure 10 presents BP dynamics in the control group. Dynamics of the tendency throughout the period was almost horizontal. Systolic BP was reduced negligibly, diastolic BP was not lowered. Significance level of approximation was about 0.1



BP dynamics in “placebo” group; Linear (SBP); Linear (DBP)

Figure 10. BP dynamics in the control group throughout the period (28 days).

All patients did not have contraindications set forth in the instruction for the use of the device.

If patients developed any unintended and adverse reactions, and events which could be related to the device, the study was discontinued. Headaches occurred in one study patient on the third day of the device administration, she herself refused from further device administration and examination to investigate reasons and relationship between the headache and device action.

Patient V., 81 years with the diagnosis: 3 grade arterial hypertension, degree 2. Risk of cardiovascular complications 3. Coronary artery disease. Atherosclerosis of the brachiocephalic arteries and cardiac vessels. II grade angina of effort. Cerebrovascular disease. Chronic cerebral ischemia. She mentioned headache, sleep disorder in the first days of the device administration. She treated the study with caution and distrust though she agreed to participate. Her arterial hypertension was corrected with three anti-hypertensive drugs and diuretic agent. Mean BP for the last six months: SBP 138±3.2 mm Hg; DBP 75.4±6.32 mm Hg. It could not be unanimously stated that the identified reaction was related to the device administration as the patient had reported such events before, and it was recorded in her medical records. Due to that, the patient was withdrawn from the study.

3. CONCLUSIONS ON THE CLINICAL STUDY RESULTS.

As a result of the medical study of medical device "Transcutaneous electrostimulator for blood pressure correction "ABP-051" in treatment of patients with increased BP, the following conclusions can be made:

1. When the device is administered as a course in patients with chronic arterial hypertension, a profound positive effect was observed, and systolic BP lowers on average on 17 mm Hg, and diastolic BP - on 7 mm Hg.

2. The most profound lowering of SBP was observed in patients with initially high SBP (above 140 mm Hg); patients that became normotonic during drug therapy, had a less profound lowering of BP.

3. The analysis of BP dynamics in the groups showed that systolic BP in the group of patients only with cardiovascular disorder (AH, CAD, CVD) was lowered on 20 mm Hg, and if patients had endocrine or respiratory disorders and, as a consequence, more extensive drug therapy, their systolic BP was lowered on 16 mm Hg, and diastolic BP - on 8 mm Hg.

4. The most significant anti-hypertensive effect was observed in group 2 (2 type diabetes mellitus) - 88 %, the lowest – in the group with cerebrovascular disorder - 71 %. Total anti-hypertensive effect was 81%, in control group - 33 %.

5. Pulse rate was changed negligibly in all the groups.

6. "Placebo" group had a subjectively positive dynamics, but BP was lowered negligibly in treatment period and was absent in observation period.

7. When patients assessed their health condition, the score was increased from 2 to 5 after the device administration. "Placebo" – health assessment was increased on 1 score.

8. Administration of the medical device is safe. Headaches reported by one patient could not be related with the device as she had had headache episodes before, the device was used for a short time (2 days), on this stage, the patient refused from the examination. Other patients did not report any adverse events.

9. To increase the effect consistency, it can be recommended to repeat the device administration in 1-1.5 month or increase the course duration.

10. One of the positive effects of the device administration is a sudden increase of patients' discipline and their treatment compliance. The necessity to administer the device and, due to that, more frequent BP control create a deliberate attitude to hypertension treatment, serve as a reminded for a timely drug administration.

11. On our opinion, the device for blood pressure correction "ABP-051" can be individually administered in elderly patients with several chronic diseases as an adjunct to the drug therapy.

12. The study results are reliable as we had the control group, and the patients were randomized by the "set" of chronic diseases.

Conclusion. Medical device "Transcutaneous electrostimulator for blood pressure correction "ABP-051" per TU-9444-005-12342964-2015 meets the requirements of regulatory documents, technical and operational documents of the producer.

The results of the medical study confirm efficacy and safety of the medical device administration.

Study coordinator  I.V. Kirichok

"APPROVED"
Chief physician
SBHI "Municipal outpatient health facility № 175
of the Moscow Health Department"

A.P. Ternavsky

«07» 06 2019

CLINICAL STUDY PROTOCOL

Name of the study device: "Trascutaneous electrostimulator for blood pressure correction "ABP-051" per TU-9444-005-12342964-2015" (hereinafter referred to as Electrostimulator "ABP-051"). Model: ABP-051.

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

EU Certificate for Conformity under Directive 93/42/EEC dated 01.09.2017.

Producer: Limited Liability Company "Inferum", 620026, Russia, Sverdlovsk Region, Yekaterinburg, Belinsky Str., 86-487

Manufacturing site: 623417, Russia, Sverdlovsk Region, v. Kamensk-Uralsky, Mechanizatorov Str., 74.

Medical organization carrying out the medical study of the medical device:

State Budgetary Healthcare Institution of the Moscow Health Department "Municipal outpatient health facility № 175 of the Moscow Health Department" (SBHI "Municipal outpatient health facility № 175 of the Moscow Health Department"), Russia, 105568, Moscow, Chelyabinsk Str., 16, bld. 2, 1.

The license for medical activity: LO-77-01-015019 dated 17 October 2017 issued by the Moscow Health Department.

The study was carried out in outpatient settings on the base of therapeutic unit of branch № 1 of SBHI "Outpatient health facility № 175 of the Moscow Health Department". The study coordinator: physician – Methodist I.V. Kirichok.

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

The clinical study is carried out in accordance with the agreed and approved study protocol.

The study period: 1 November 2018 to 31 March 2019.

Aim of the medical study

- To assess efficacy of blood pressure (BP) correction when device "ABP-051" is administered in outpatient settings by elderly patients with three or more chronic diseases, one of which is arterial hypertension, as an adjunct to the main drug therapy.

Goals of the medical study

- To establish terms and efficacy level for achievement and stabilization of target BP in hypertensive patients having daily two procedures with working devices "ABP-051" within 14 days compared to sham devices.
- To determine duration of effective course of the device exposure for achievement and stabilization of target BP in the study groups.

• Conclusions on the study results.

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

1. Application for the medical study dated 15 November 2018.
2. Marketing authorization of the medical device dated 31 March 2016, № RZN 2016/3776.
3. Certificate for Conformity.
4. Clinical study protocol represented by the analysis and assessment of clinical data of medical study № 15122017-02 dated 15 December 2017 “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU-9444-005-12342964-2015” (Budgetary Healthcare Institution “Republican clinical – diagnostic center of the Ministry of Health of the Udmurt Republic”, Izhevsk).
5. Instruction for use INFE 05.01-03.70-01 IP.
6. Plan of the medical study of medical device “Transcutaneous electrostimulator for blood pressure correction “ABP-051” per TU-9444-005-12342964-2015” dated 15 April 2018.

1. ANALYSIS OF THE CLINICAL DATA, DOCUMENTS AND MATERIALS SUBMITTED BY THE APPLICANT

Electrostimulator “ABP-051” is intended for non-drug therapy of diseases associated with blood pressure correction as an adjunct to complex drug therapy, is intended for therapeutic non-invasive (not impairing the skin) course exposure to the left wrist areas using the transcutaneous electrostimulation method.

Classification.

Electostimulator “ABP-051” has class IIa of potential risk of the medical device in accordance with GOST 31508 and Order of the Ministry of Health of the Russian Federation dated 06.06.2012 № 4n, as well in accordance with the rule 9 in the annex of Directive IX 1993/42/CEE as amended 2007/47/CE.

Type of the medical device in accordance with the nomenclature classification of medical devices: 181480 (in accordance with Order of Ministry of Health of the Russian Federation 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.

Device labeling.

The device labeling contains the following symbols and designations.

Administration of the medical device.

Electrostimulator “ABP-051” is intended for the use in health facilities, as well for individual use by patients in home settings for therapeutic exposure.

The device is not sterile.

Patient groups in accordance with the instruction for the use for the medical device:

Electrostimulator “ABP-051” is intended for therapeutic non-invasive exposure

for blood pressure correction and normalization of general health condition.

The device is intended for persons above 14 years with labile arterial hypertension and persistent increase of blood pressure as additional exposure during drug therapy.

For hypotonic patients.

Indications for the device administration:

- persistent high blood pressure in patients with essential hypertension – as an adjunct to complex drug therapy;
- episodes of blood pressure increase in stress situations, weather changes, etc. in persons with labile arterial hypertension;
- low blood pressure in patients with essential hypotonia as an adjunct to complex drug therapy.

Contraindications to the device administration:

- presence of an implanted pacemaker;
- atrial fibrillation;
- individual intolerability of the electric current;
- skin injury on the left wrist;
- neoplasms (tumors) of any etiology or location;
- acute fevers of unknown origin;
- acute psychotic, alcohol or drug-induced excitation.

Possible adverse actions.

Possible adverse actions of the medical device are not identified.

Technique of administration.

Electrostimulator “ABP-051” is used for a direct short-term contact with a patient’s skin on the left wrist.

Principle of the device work:

Transcutaneous stimulation – the method of physiotherapy which is based on exposure to short frequency impulses on human wrists, namely:

- exposure to the internal left wrist surface, is used for lowering of blood pressure. Working frequencies of the program: 9.2 Hz and 77 Hz. Total time of the program exposure - 5 minutes.
- exposure to the external left wrist surface, is used for increase of blood pressure. Working frequencies of the program: 77 Hz and 140 Hz with magnitude modulation and frequency 4 Hz. Total time of the program exposure - 6 minutes.

The exposure occurs through the built-in electrodes in the device body while touching a patient’s skin.

The device provides therapeutic exposure for correction in the following values of blood pressure:

- for patients with a high blood pressure, range of systolic blood pressure over 130 mm Hg and diastolic over 80 mm Hg;
- for patients with hypotonia and systolic pressure less than 106 mm Hg and diastolic less than 70 mm Hg.

Safety of the medical device is confirmed by the marketing authorization of the device dated 31 March 2016 №RZN 2016/3776 issued by the Federal Agency for Surveillance over Healthcare based on the results of the expertises made during the registration of the medical device.

2. ANALYSIS OF THE CLINICAL STUDY RESULTS

During the clinical study, device "ABP-051" was administered in patients with high BP as an adjunct to the main complex therapy.

Procedure of the device administration in the clinical study.

1. Prior starting the work, BP is measured. Then the device put on the internal left wrist so that the electrodes touch the skin closely.
2. The device is switched on with the button pressed having three points and red mark which corresponds to the exposure program for BP lowering.
3. BP correction process lasts for 5 minutes and consists of several exposure phases differing by frequency, exposure time and magnitude. After the session, a sound signal is heard, the device will switch off automatically.
4. For a consistent result, 14-day course treatment was selected, 2 procedures daily, in the morning and evening.
5. Then the device is removed from the hand, a patient has rest for 15-20 minutes, BP is measured, and a result is recorded.

During the complex medical studies to assess safety and efficacy of outpatient administration of device "ABP- 051", statistically significant results were established. It was assessed in elderly patients having several chronic diseases, one of which – essential hypertension.

49 patients were divided to four groups that took part in the study. Device "ABP-051" was clinically investigated in three groups of patients within 14 calendar days. In the control group of patients, sham device was used in the analogous mode (with electrodes switched off). After treatment period (period of the device administration), patients were followed up for 28 days with BP control.

All patients completed the study, any negative device exposure and adverse reactions were not recorded.

The patients had a standard individual basic therapy prescribed prior the clinical study. During the study, drug therapy was not changed. After exposure period with device "ABP-051" twice a day for 14 days, the patients were dynamically observed for a 28-day period. Considering that all patients were observed by a therapist for a long time, mean BP values for previous 5 months (based on office BP at physician' admission recorded in the patients' registry in the district followed by the physician, and patient's medical record) were taken as baseline BP.

The results were assessed in groups of patients in general with regards to general mean BP value (both systolic and diastolic) and pulse rate during the period when the device was administered, and observation period. BP and heart rate flow charts were examined in each patient, tendency line was determined.

General patient condition based on subjective patient sensations was assessed prior and after the device administration using 10 score scale, where 10 – excellent health condition, mood, working capacity, and 1 - bad.

Table 1.
Scheme of the study design model.

Group	Number	ABP-051 administration	Observation
Group 1	12 patients	14 days	28 days
Group 2	22 patients	14 days	28 days
Group 3	5 patients	14 days	28 days
Control	10 patients	14 days	28 days

Clinical study control:

- patient study log;
- patient observation registration card;
- clinical study protocol on device "ABP-051" for BP correction based on assessment of general clinical efficacy and administration methodology (observation diary in treatment period and observation period);
- patient's voluntary informed consent for the study and processing of personal data;
- reporting card for adverse reactions.

Patients aged 50 years and above with several chronic diseases, one of which is arterial hypertension, observed by a physician constantly and taking basic therapy were enrolled to the study. During drug therapy, some patients enrolled to the study were persistently normotonic (in this case, the study aim was possibility of decrease drug doses), some patients had significant BP fluctuations.

Patients with maximal values of systolic blood pressure (SBP) not exceeding 190 mm Hg, diastolic BP (DBP) - 110 mm Hg took part in the study. Anti-hypertensive effect was considered as achieved if BP was lowered for over 5% from baseline.

There were 12 men and 37 women among 49 patients, their mean age was 70.6 years. 25 patients below 70 years took part in the study, as well, 24 patients were aged over 71 years. Patients were randomly distributed into the groups.

Table 2.

Patient distribution by sex and age.

Group	Number of Patients	Men	Women	Below 70 years	Above 71 years
Group 1	12	2(17%)	10 (83%)	4	8
Group 2	22	6 (27%)	16 (73%)	13	9
Group 3	5	1 (20%)	4 (80%)	4	1
Control	10	3 (30%)	7 (70%)	4	6
	49	12 (24%)	37 (76%)	25 (51%)	24 (49%)

Flow charts were plotted for visual analysis of the study reflecting BP fluctuation in treatment period (period of the device administration twice a day for 5 minutes) for 14 days (horizontal axis), in observation period (28 days) and significance level of approximation (R^2).

Analysis of the results in group 1.

12 patients with AH (arterial hypertension), CAD (coronary artery disease) and CVD (cerebrovascular disease) were enrolled to group 1. Prior the study, mean blood pressure in the group was 151 mm Hg and 80 mm Hg.

Table 3.

Mean BP in group 1 prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	130.0±2.0	174.0±12.0	151.0±10.4
Diastolic BP (DBP)	68.8±2.88	89.4±6.04	80.0±4.2

Table 4.

Dynamics of mean BP and pulse in group 1.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	151.0±10.4	80.0±4.2	No data
During the procedure	143.3±11.3	79.0±4.5	72.2±5.0
In observation period	140.0±10.3	77.8±6.1	72.8±5.6
General dynamics:	-11.0	-2.2	0.6

All patients had systolic BP lowered from 16 to 6 mm Hg. A good effect (BP lowered for more than 5 %) was achieved in nine patients. Systolic BP in two patients lowered negligibly (on 4%), however diastolic BP lowered for more than 5%. One patient did not have any significant effect.

All patients but one stated improved health condition, decreased anxiety, sleep normalization. Health assessment after the procedure was increased on 2.6 scores and averaged to 7.7 scores with baseline 5.1 (from 10 possible).

Figure 1 presents the flow chart with correction results in group 1 in treatment period (mean daily BP), and Figure 2 – in observation period. In treatment period, the tendency line of mean daily BP was decreased, both systolic and diastolic. Significance level of approximation was 0.22±0.05

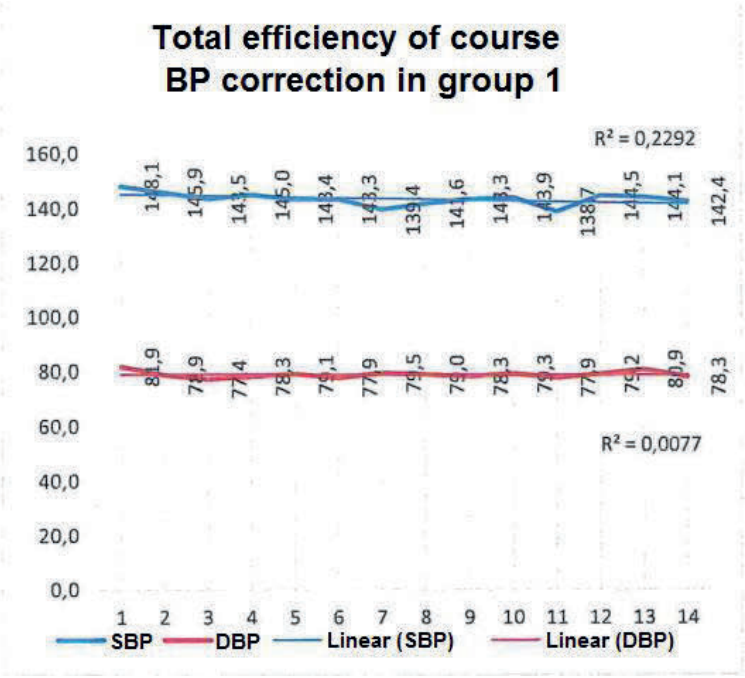


Figure 1. BP dynamics in the study treatment period.

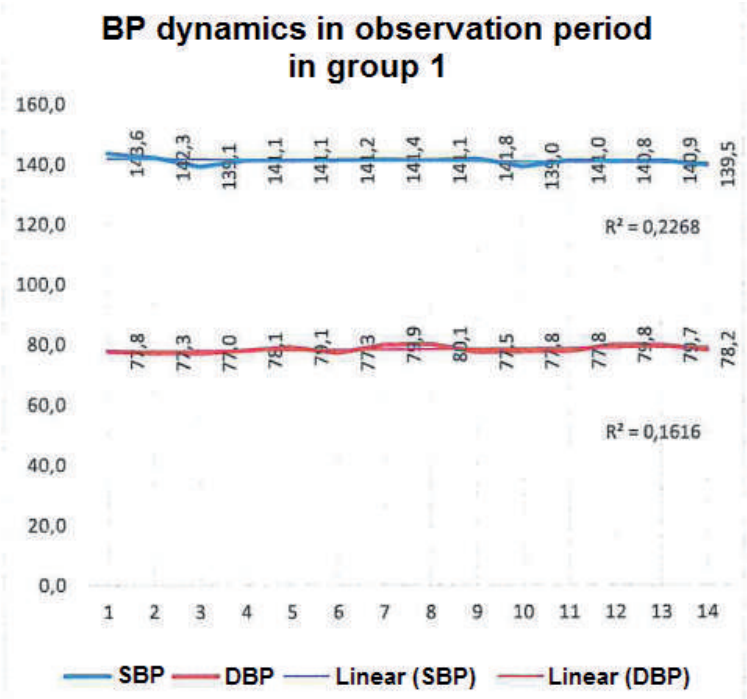


Figure 2. Representation of BP dynamics in observation period.

In observation period, tendency line of systolic BP was also slightly decreased (R^2 = 0.2268) which shows that stability of systolic BP was also achieved in observation period. The tendency line of diastolic BP was also slightly decreased in both periods.

In general, SBP in the group was decreased on 11 mm Hg (7.3 %), DBP on 2 mm Hg (3 %), pulse rate was not actually changed in relation to the study period. Anti-hypertensive effect was 80 %.

Analysis of the results in group 2.

Group 2 was comprised of patients with AH, CAD and 2 type DB (2 type diabetes mellitus). The number of patients taking part in the study - 22 persons. 4 patients were administered with insulin for diabetes, the remaining – hypoglycemic combined drugs.

Mean blood pressure in patients of group 2 receiving the therapy was 152 and 84 mm Hg.

Table 5.

Mean BP in group 2 prior the study

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	142.0±2.0	172.4±12.7	152.2±6.2
Diastolic BP (DBP)	74.2±3.0	99.8±3.4	84.3±5.6

22 patients achieved lowering of systolic BP for over 5%, on average on 9%.

Diastolic BP was lowered for over 5% in 16 patients (70%). Diastolic BP in six patients was not actually changed.

Table 6.

Dynamics of mean BP and pulse in group 2.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	152.2±6.2	84.3±5.6	No data
During the procedure	140.8±3.4	77.8±6.3	73.9±6.9
In observation period	138.1±5.4	77.5±5.3	72.4±5.6
General dynamics:	-14.1	-6.7	-1.5

18 patients (82%) stated their improved health condition, other patients considered that their health condition and working capacity did not change after therapeutic exposure to device “ABP-051”.

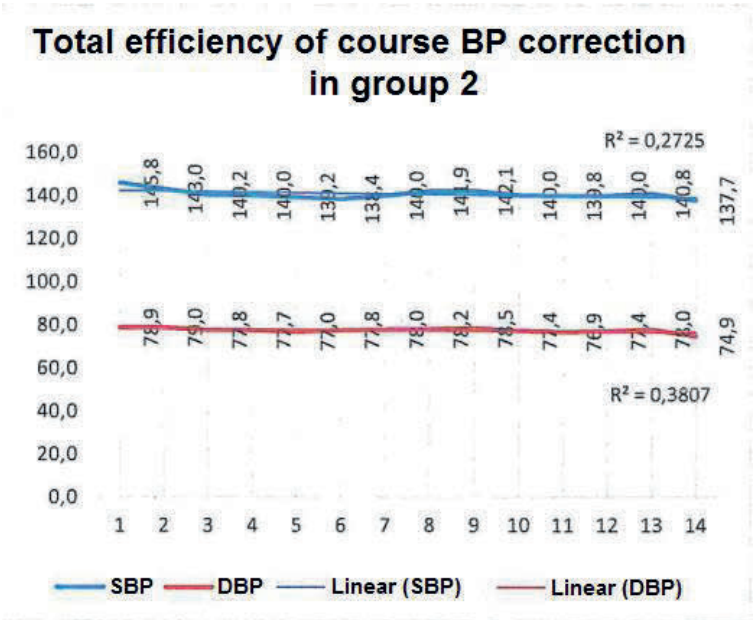


Figure 3. BP dynamics in treatment period in group 2

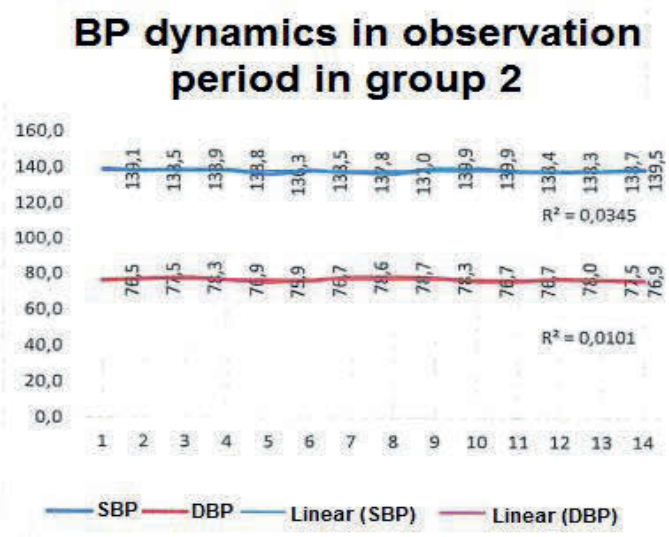


Figure 4. BP in observation period in group 2.

Figure 3 presents the flow chart of correction results in group 2 in treatment period (mean daily BP), and figure 4 – in observation period. The lowering of mean daily BP, both systolic and diastolic, was negligible in observation period.

In general, the lowering of SBP on 14 mm Hg (9%), DBP on 7 mm Hg (8%) was observed in the group, pulse rate did not change in relation to the study period. Anti-hypertensive effect in group 2 was 83%. Health improvement was observed in 18 out of 22 patients completing the therapy. The health assessment after the procedure was increased on average in the group on 2.8 scores and was 7.7 scores with baseline 4.9 (from 10 possible).

Analysis of the results in group 3.

Group 3 was comprised of five patients that had received already therapy course with device “ABP-051” six months ago.

Mean blood pressure in patients of group 3 receiving the therapy was 148 and 87 mm Hg.

Table 7.

Mean BP in group 3 prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	141.8±5.4	162.4±9.1	148.6±6.8
Diastolic BP (DBP)	81.8±5.4	97±3.6	87.±4.5

After the therapy course, all patients stated the improved health capacity, mood, health assessment was 8.6 out of 10 scores with average baseline 6.

Table 8.

Dynamics of mean BP and pulse in group 3 .

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	148.6±6.8	87±4.5	No data
During the procedure	140.6±8.1	82.0±5.6	73.6±3.9
In observation period	135.8±5.4	79.6±6.5	71.6±5.3
General dynamics:	-12.8	-7.4	-2.0

In general, SBP was lowered on 13 mm Hg (9 %), DBP on 7 mm Hg (9 %). Pulse rate was decreased on 2 beats/min.

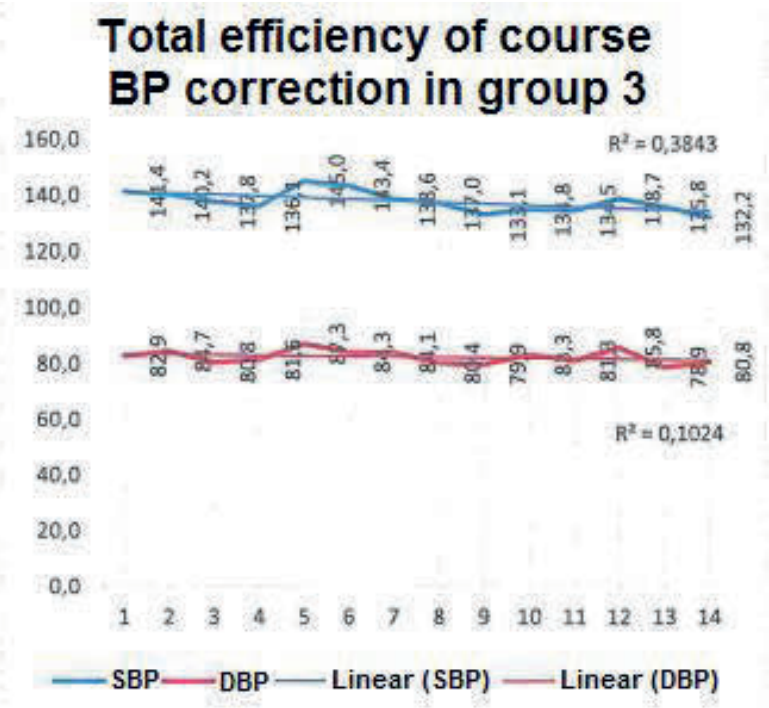


Figure 5. BP dynamics in group 3 in treatment period

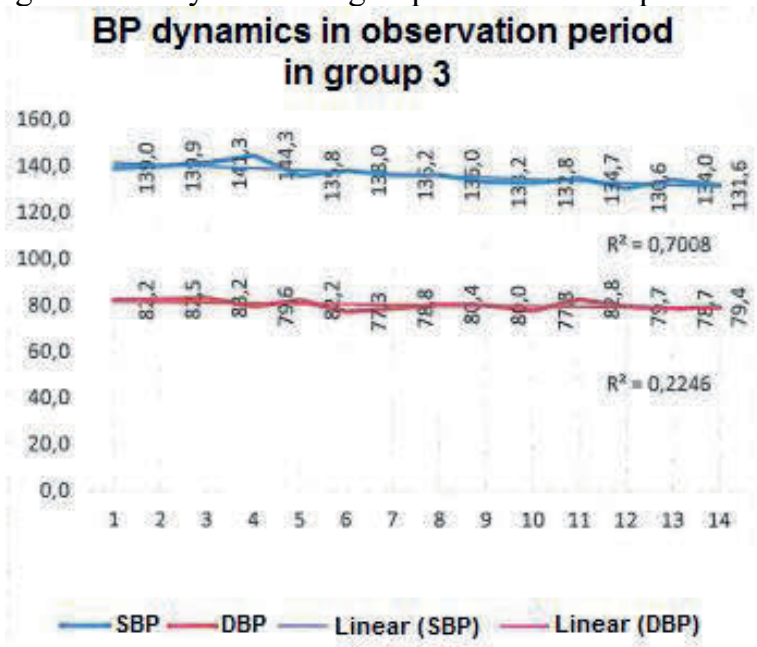


Figure 6. BP in observation period in group 3.

Figure 5 presents the flow chart of correction results in group 3 in treatment period (mean daily BP), figure 6 – in observation period. The decrease of tendency line of mean daily BP, both systolic and diastolic, was observed in treatment period and observation period.

Anti-hypertensive effect was observed in 100% of patients from group 3. Any adverse events were not recorded. Drug therapy was not corrected during administration of device “ABP-051” and in observation period.

Analysis of device "ABP-051" administration.

The data analysis in all groups of patients administering device "ABP-051" in the mode providing BP lowering showed that mean systolic BP was lowered on 13 mm Hg, 9% from baseline, diastolic on average on 5 mm Hg, 7% from baseline. A significant effect of BP lowering was not achieved only by four out of 39 patients. The lowering of systolic BP in 25 patients (51%) was over 10 mm Hg, and diastolic - over 5 mm Hg

Most profound BP lowering was observed in patients with a higher baseline BP. All 39 patients achieved lowering of systolic BP, minimally on 5 mm Hg, 3.6% from baseline. Anti-hypertensive effect in all patients was 87%.

Analysis of the results in the control group.

Control group using "sham device" comprised of 10 elderly patients receiving basic AH therapy for a long period. During the study, the device simulating the working one with all the features of active apparatus was used to detect a sham effect: a light emitting diode flashed, background sound worked, however, electrodes were switched off from the scheme.

Mean blood pressure in patients of the control group during therapy was 148 and 84 mm Hg.

Table 9.

Mean BP in the control group prior the study.

BP range in the group	Minimal (mm Hg)	Maximal (mm Hg)	Mean (mm Hg)
Systolic BP (SBP)	139.6±8.2	166.6±5.1	148.3±7.6
Diastolic BP (DBP)	77.4±5.6	93.2±6.24	83.6±4.4

After the procedure course, average health assessment in the group was 6.5 scores with baseline 5.5. Four out of 10 patients stated their improved health condition. On average, SBP was lowered on average in the group on 6 mm Hg, 4% from baseline, DBP on 3 mm Hg, 3% from baseline, pulse rate was not changed.

Table 10.

Dynamics of mean BP and pulse in the control group.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	148.3±7.6	83.6±4.4	No data
During the procedure	138.9±8.9	79.9±4.9	74.3±5.6
In observation period	142.3±6.4	80.9±4.5	73.2±5.8
General dynamics:	-6.0	-2.7	-1.1

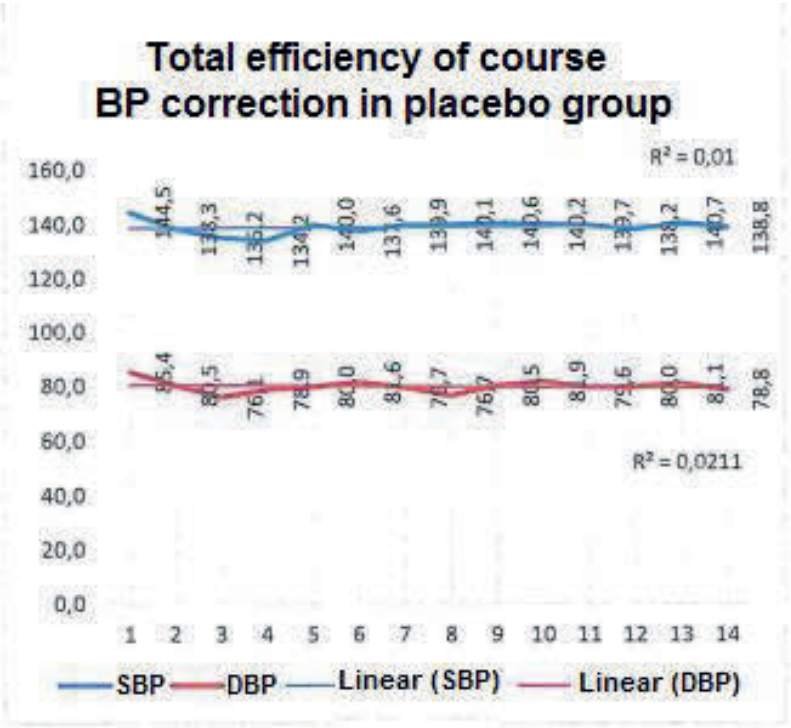


Figure 7. BP in treatment period in the control group.

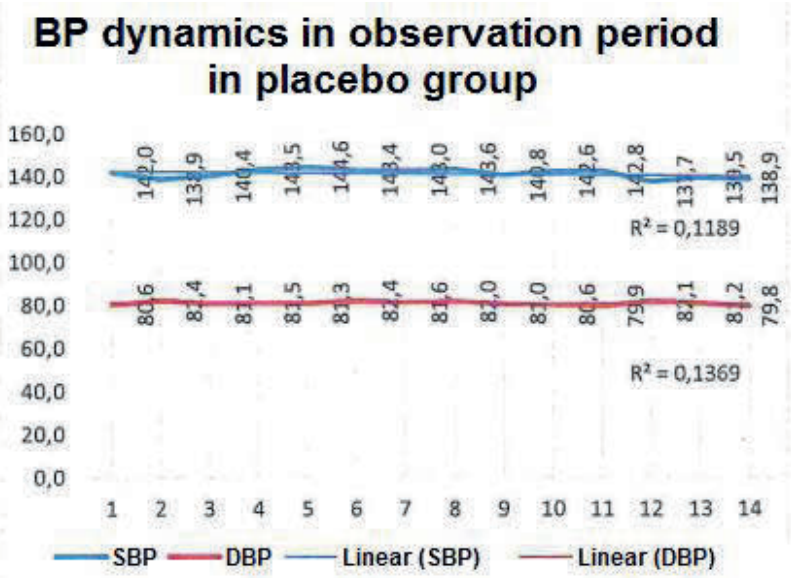


Figure 8. BP dynamics in observation period in placebo group

Figure 7 presents the flow chart of BP correction results in the control group in treatment period (mean daily BP), figure 8 – in observation period. There is no decrease of tendency line.

In observation period, no BP lowering was also observed in the control group, the conditional tendency remained actually horizontal, significance level of approximation (R2) was 0.1. BP was lowered in 4 patients for over 5%, anti-hypertensive effect was 40 %.

COMPARISON OF THE STUDY RESULTS ON DEVICE "ABP-051" AND THE RESULTS IN THE CONTROL GROUP

Comparing the results obtained in the group of patients administering device "ABP-051" in a working mode, and the results in the control group, you can state a significant BP lowering in the study group administering active "ABP-051", and negligible BP fluctuations in the group administering "placebo device". The results are summarized in table 11.

Table 11.

Comparison of the study results.

Mean value	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats per min)
Prior course correction	151.4±7.6	83.2+5.1	No data
During the procedure	141.5±8.6	78.7±5.3	73.3±5.3
In observation period	138.4+7.7	77.8±5.5	72.4+5.6
General dynamics:	**-13.0**	**-5.4**	**-0.9**
"Placebo" dynamics	-6.0	-2.7	-1.1
Improvement (%)	+60%	+100%	

In the study group, SBP was decreased on 13 mm Hg, DBP - on 5 mm Hg, pulse rate was changed negligibly - on 1 beat/min. In the control group, the mean BP was lowered on 6 mm Hg as for systolic, and on 3 mm Hg as for diastolic.

The lowering of systolic BP with anti-hypertensive effect of the active electrostimulator, compared to the sham device was 60% greater, and the lowering of diastolic BP - 100% greater. The change of pulse rate in both groups was negligible.

The health assessment by patients was increased on 2.7 scores up to 7.8 scores in the study group and on 1 score up to 6.5 in the control group.

BP dynamics in the study group (red and green) and control group (black and blue)

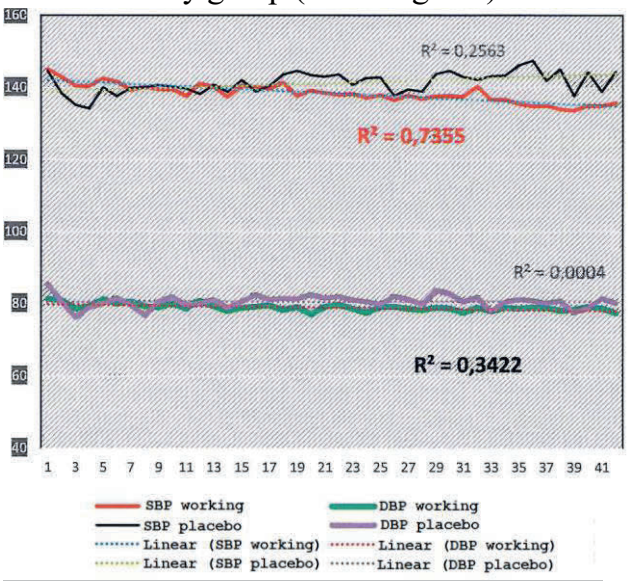


Figure 9. Representation of BP dynamics in the groups during the treatment period and observation period.

Figure 9 presents a flow chart of BP dynamics during the treatment period and observation period. The tendency line of systolic and diastolic BP was decreased in the active group. Significance level of approximation was 0.7 and 0.3, respectively.

In the control group, the dynamics of tendency line was negligible throughout the period: systolic BP tending to increase in the end of observation, diastolic BP – almost horizontal.

All patients did not have any contraindications set forth in the instruction for the device.

If patients developed any unintended, adverse reactions and events which could be related to the device, the study was discontinued.

3. CONCLUSIONS ON THE CLINICAL STUDY RESULTS.

As a result of the medical study of medical device "Transcutaneuos electrostimulator for blood pressure correction "ABP-051" in treatment of patients with increased blood pressure, the following conclusions can be made:

1. When the device is administered as a course in patients with chronic arterial hypertension, a profound positive effect was observed with the lowering of systolic BP on average on 13 mm Hg and diastolic BP on 5 mm Hg
2. The most profound SBP lowering was observed in patients with initially high SBP (above 145 mm Hg); BP was lowered less profoundly in patients becoming normotonic during the drug therapy.
3. The analysis of BP dynamics in the groups showed the average lowering of systolic BP in all patient groups on more than 10 mm Hg, the greatest lowering up to 14 mm Hg was observed in group 2 of patients with concurrent diabetes mellitus. Diastolic BP was less sensitive to the therapy and was lowered on 7 mm Hg in group 2 and 3, and only on 2 mm Hg – in group 1 of patients.
4. The most significant anti-hypertensive effect (100%) was observed in group 3, in which patients had the recurrent therapy course; in group 2 (2 type diabetes mellitus), it was 83 %, the less significant effect was observed in the group with cerebrovascular disorder - 80%. Total anti-hypertensive effect was 87%, in control group - 40 %.
5. Pulse rate was changed negligibly in all the groups.
6. Placebo group had subjectively a positive dynamic, but BP lowering was negligible in treatment period and absent in the observation period, and in some patients, it even tended to baseline BP.
7. When patients assessed their health condition, the assessment was increased on 2.7 scores on average. "Placebo" – health assessment was increased on 1 score.
8. Administration of the medical device is safe. Any adverse effects were not reported.
9. The device effect was observed for at least 14 days. To increase the effect consistency, the recurrent device administration can be recommended in 3-4 weeks.
10. The increase of patients' discipline and their treatment compliance appeared to be one of positive effects of the device administration. The necessity to use the device and, due to it, more frequent BP control create a deliberate attitude to hypertonia treatment, serve a reminder for a timely drug administration.
11. On our opinion, the device for blood pressure correction "ABP-051" can be individually administered in elderly patients with several chronic diseases as an adjunct to drug therapy.
12. The study results are reliable as we had the control group, and the patients were randomized by the "set" of chronic diseases.

Conclusion. Medical device "Transcutaneous electrostimulator for blood pressure correction "ABP-051" per TU-9444-005-12342964-2015 meets the requirements of regulatory documents, technical and operational documents of the producer.

The results of the medical study confirm efficacy and safety of the medical device administration.

Study coordinator [Signature] I.V. Kirichok

ANNEX TO CLINICAL STUDY PROTOCOLS
dated «17» October 2019, «07» June 2019

The clinical studies were carried out in accordance with the agreed and approved project design:

- in terms from 27 April 2018 to 2 August 2018 for a group of 28 persons;
- additional study of samples 39 persons in the treatment group and 10 persons with sham-control in terms from 1 November 2018 to 31 March 2019.

The data obtained during the research studies were used for the detailed statistical analysis.

The aim of the statistical analysis:

First part. Safety and efficiency study on increased BP correction in group of 28 patients (among which, 8 persons with 2 type diabetes mellitus) in treatment period 14 days and observation period 14 days.

Second part. Efficiency study on increased BP correction in group of 39 persons compared to sham control of 10 persons in period 14 days and further observation of BP dynamics in period of 28 days.

First part.

General group - a group of 28 persons which comprised of patients with BP close to normal and SBP increased for over 150 mm Hg. Subsequently, the group was represented by 4 subgroups per BP ranges.

Baseline data were presented as Excel tables for statistical processing of results of observation over BP course correction for 14 days, and results of further observations over BP dynamics for 14 days for one group and 28 for another one.

Package STADIA was used for statistical processing (A.P. Kulaichev, Methods and means for data analysis in Windows, NPO “Informatics and computers”, Moscow, 2002).

Depending on the study result for compliance of the sample with Gauss distribution, the assessment criterion was selected: parametric or non-parametric.

Table №1 provides the results of statistical processing of cumulative set of SBP and DBP data set using daily triple procedures and further 6 control BP measurements during the day throughout the entire 14-day course. BP dynamics was assessed by detection of significance of differences in paired data sample of the first and each subsequent day.

The non-parametric Wilcoxon test for shift (location) difference for paired data was used for the data analysis as the test in normal distribution showed non-compliance of some samples in this series with gauss distribution per one criterion from group, for example, Chi-square.

Moreover, Wilcoxon paired data test is intended for comparison of vales measured in two different conditions – prior exposure (correction) and exposure using the same sample of subjects.

The following designations are accepted:

- i – day number, at i=l... 14
- X – mean value of systolic blood pressure in mm Hg;
- Y – mean value of diastolic blood pressure in mm Hg;
- $\Delta 1 = Xi-X1$ – difference between the current mean SBP value in the treatment group on day i and mean SBP value on the first day X1;

- Δ2 = Xi+1-Xi – difference between the current mean SBP value on the current day i and mean SBP value on subsequent day i+1;
- Δ3 = Yi+1-Y1 – difference between the current mean DBP on day i+1 and mean DBP value on the first day Y1;
-σ – mean square value (dispersion);
- P- level of statistical significance;
- SBP ± σ – systolic blood pressure
- DBP ± σ – diastolic blood pressure

Table №1
Efficiency of BP lowering in general group.

Day i	SBP ± σ Mm Hg	-Δ1=Xi-Xi, i= 2.. .14 p <0.01	△2=Xi-Xi-i i= 2.. .14		DBP± σ	△3=Yi-Yi, i= 2.. .14	P
			Δ2	P			
1	144 ±15				77.7±9.8		
2	137 ±13.6	7	-7	-	78±9.2	+0.3	-
3	135 ±10.1	9	-2	-	76.4±8.9	-1.3	-
4	140 ±11.6	4	+5	-	77.3±9.4	-0.4	-
5	138 ±13.2	6	-2	-	76.1±7.3	-1.6	-
6	139 ±14.3	5	+1	-	78.1±8.4	+0.4	-
7	137 ±12.6	7	-2	<0.05	76.6±10.4	-1.1	-
8	138 ±17.2	6	+1	-	74.4±16.7	-3.3	-
9	138 ±11.7	6	0	-	76.7±9.5	-1	-
10	135 ±12.8	9	-3	<0.01	76±11.5	-1.7	-
11	136 ±13.6	8	+1	-	78.2±9.6	+0.5	-
12	130 ±11.6	14	-6	< 0.01	75.7±9.8	-2	-
13	132 ±9.6	12	+ 2	-	75±8.3	-2.7	<0.01
14	130 ±11.7	14	-2	<0.05	74.8±9.6	-3.1	<0.01

Based on the data provided in table №1, the following conclusions can be made:

1. Efficiency of course correction is confirmed, Δ1=Xi-Xi for SBP lowering on 14 mm Hg with significance P < 0.01
2. To achieve target SBP and its stabilization, course correction lasting for 10 days is required.
3. Statistically significant DBP lowering Δ3=Yi-Y1 observed on day 13 was 2.7 mm Hg with significance < 0.01 and on day 14 on 3.1 mm Hg with significance p < 0.01
4. During course correction, incremental lowering of mean SBP value was observed which was shown by Δ1 at p < 0.01, and Δ2 reflecting sensitivity to correction was not a constant value.
5. After the third session, a relative decrease of sensitivity to correction was observed by SBP on 5 mm Hg
6. No correlation was shown between parameters Δ1 and Δ3 which reflected actual sensitivity to daily correcting exposure.

Table №2 provides the results of the analogous statistical analysis of the same subjects and table №1, but the values were processed separately for each of four groups of one of SBP ranges:

- group l - less than 130 mm Hg;
- group 2 - 130 to 140 mm Hg;
- group 3 - less than 140 mm Hg;
- group4 - over 150 mm Hg

Table №2

Correction results by four groups of SBP ranges from general group

Day I	Systolic blood pressure ± σ mm Hg, Significance level P, (* less than 0.05) (** less than 001)								
	Group 1 SBP <130	P	Group 2 SBP 130÷ 140	P	Group 3 < 140	P	Group 4 ≥150	-Δ1= Xn-X1	P
1	124 ±5.4		134±3.8		128±7.4		160 ±9.7		
2	124 ±11.9		133±6.0		127±10.7		148 ±11.7	12	**
3	127 ±8.5		135±5.2		130±8.5	*	142 ±7.67	18	**
4	128 ±10.1		139±5.1	*	133±10.2		147 ±9.7	13	**
5	128 ±10	*	134±5.7		130±9.1		149 ±11.9	11	**
6	128 ±5.9	*	131±4.1		129±5.3	*	148 ±14.6	12	**
7	129 ±6.2		136±9.4		132±8.4		145 ±10.6	15	**
8	125 ±11.1		139±16.2		132±15.1		147 ±16.3	13	**
9	128 ±8.4		130±4.0	*	129±6.9		148±10.5	12	**
10	128 ±12.2		124±6.5	*	126±10.5		145 ± 8.8	15	**
11	123 ±8.6		128±5.4	*	125±7.9		147 ±11.9	13	**
12	120 ±11.1		127±8.1	*	123±10.7	*	138 ±10.1	22	**
13	127 ±11.7		130±7.0		128±10.2		135 ±5.8	25	**
14	121 ±10.6		127±6.7	*	123±9.8	*	137 ±9.4	23	**

Table №3.

Cumulative table of mean SBP lowering values by four groups

	Start	End	Decrease	P
Group 1	124	121	3	-
Group 2	134	127	7	<0.05
Group 3	128	123	5	<0.05
Group 4	160	137	23	0.01

It follows from tables №2 and №3:

1. Correction efficiency depends on initial (input) SBP value – the larger SBP value prior the procedure, the more significant is the lowering:
2. Lowering effect in group 1 is 3 mm Hg and is not statistically significant. On day 5 and 6, SBP increase effect on 3-4 mm Hg was observed, the increase effect was statistically significant.
3. In group 2, lowering effect was 7 mm Hg, but only in half of cases, statistically significant effect was observed.
4. In group 3, SBP effect was reduced significantly compared to group 2 and 5 mm Hg, and the patients less statistically significant results. It is likely to be related with the fact that group 3 consisted only of the first two groups, and the results were underestimated due to parameters of group 1.
5. In group 4, SBP lowering effect after the course was 23 mm Hg, with statistical

significance less than 0.01 for intermediate results on all days of course correction.

6. In group 4, SBP stabilization occurs after 10 correction sessions.
7. In group, a consistent SBP lowering was shown from each subsequent procedure in relation to the first Δ1 at significance level $P < 0.01$

Table №4 provides the results of statistical processing of the cumulative set of DBP data with daily procedures and subsequent control DBP measurements both during the day and throughout the entire course lasting for 14 days for subjects from the general group with DBP over 80 mm Hg. They were compared similarly as in previous studies.

Table №4

Efficiency of BP correction in patients from general group with DBP over 80 mm Hg and HR dynamics.

Day i	DBP ± σ	-Δ1=Yn-Y1, n=2...14 mm Hg	P *<0.05 **<0.01	HR, beats/min
1	86.3±5.6			69.6±6.2
2	85±7.2	1.3		67.1±5.9
3	82.9±8Д	3.4	*	67.4±6
4	84.7±7.2	1.6		71.2±8
5	80.4±7.2	5.9	**	71.1±5.5
6	83.9±6.9	2.4	*	69.6±5.4
7	82.4±10.7	3.9	*	67.6±6.4
8	81.7±9.9	4.6	**	68.5±6
9	82.5±9.5	3.8	**	67.4±5.2
10	83.6±10.3	2.7		67.6±10.8
11	85.9±7.6	0.4		70.9±7.3
12	82.1±9.4	4.2	*	68.1±8.6
13	80.7±7.2	5.6	**	68.3±6.7
14	81.6±9.2	4.7	**	70.3±7.6

1. It follows from table №4 that DBP lowering in a 14-day course on 4.7 mm Hg was stable without jumps and significant almost throughout the entire cycle which showed efficiency of DBP correction.
2. Heart rate throughout the course did not change significantly, and statistical HR analysis was not performed in these series.

General study conclusions and patterns in program "First part":

3. Electric impulse correction is safe. It is confirmed by the fact that the increased SBP with regards to mean square deviation was not lowered during the entire treatment period less than 108 mm Hg
4. Electric impulse correction is efficient in course correction lasting at least 10 days and is confirmed by a high statistical significance.
5. The higher SBP values, the higher is the correction result and its statistical significance.
6. Small transient SBP increases were observed in treatment period only in groups with SBP less than 140 mm Hg

Table №5 provides mean values of SBP and DAD samples in the general group in 14-day observation period after treatment period in the morning, day and evening.

Table №5
14-day observation period after correction course

	Morning	Day	Evening
SBP	134 ± 2.15	132 ±2.6*	132 ±2.85
DBP	75.3 ± 1.62	75.1 ±2.47	74.6 ± 1.56

*Statistically significant differences were shown with Wilcoxon paired test only by SBP between morning and daily measurements. In other samples, the differences were not shown.

It follows from table №5:

1. Course of 14-day correction was completed with SBP and DBP lowering up to values close to target ones.
2. Morning, day, evening results of SBP and DBP measurements did not almost differ. Only morning-day SBP measurements differed.
3. Evident decrease of mean square value (MSV) is of importance compared to MSV of input correction parameters. It shows greater stabilization of BP values after correction.

Table № 6 provides efficiency of SBP and DBP decrease for the general group of 28 morning BP measurements prior correction.

Table № 6
Efficiency of SBP and DBP lowering for general group 28

Day i	SBP ± σ mm Hg	- Δ1=Xi-X1, i= 2...14 mm Hg p < 0.01	DBP ± σ mm Hg	Δ3=Yi-Yi, mm Hg i= 2...14	P
1	149 ±16		82.3± 9.4		-
2	138 ±16	11	80 ±8.5	2.3	-
3	139 ±11	10	81.5± 9.1	0.8	-
4	146 ±13	3*	83.9 ±9.3	+1.6	-
5	136 ±12	13	78.3±10.5	4	-
6	140 ±16	9	80.3 ±7.9	2	-
7	142 ±14	y**	80.6 ± 9.7	1.7	-
8	136 ±7	13	79.6 ± 9.7	4	-
9	140 ±12	9	81.5 ±8.0	0.8	-
10	136 ±13	13	79.3 ± 9.6	3	0.04
11	137 ±12	12	80. ± 0.4	2.2	-
12	132 ±14	15	78 ±9.8	4.3	0.01
13	132 ±13	17	74.6 ± 9.9	7.7	0.01
14	134 ±12	15	77.1 ±9.9	5.2	0.002

The data from table № 6 show:

1. *Insignificant SBP lowering was shown only once after the 3-rd session at P=0.12, i.e. a statistically insignificant lowering was recorded.
2. ** significance level P=0.02. In other cases, it is less than 0.01. BP correction in 2 type diabetes mellitus did not have any effect on glucose level values. Daily fluctuations of glucose level in each patient were in common ranges.

Second part

The study on efficiency of increased BP correction compared to sham control and subsequent observation over BP dynamics in 28-day period in group of 49 persons, among which 10 persons were administered with sham devices.

The test of normal distributions PRIOR and AFTER correction showed compliance of parameters with gauss distribution, therefore they were compared using parametric Student's test including paired data.

Table №7 cl. 1,2 contained summarized results of 14-day BP correction PRIOR and AFTER course exposure with specified difference and its significance. Significant differences in SBP and DBP lowering on 14 and 5.4 mm Hg, correspondingly, were recorded.

Clauses 3 and 4 of table №7 provide asymmetry coefficients (AC) demonstrating directionality of correction process and Fig.1 - Fig. 4, distribution changes were observed in the sample. In clause 3, AC growth was recorded which was shown on Fig. 2. The growth of positive AC values showed the shift of distribution curve to the area of lower SBP values, and it was evident in comparison of Fig.1. and Fig.2. The correction led to the increase of values less than 132 mm Hg in the sample for over 2 times.

In clause 4 of table №7, AC change was recorded to negative values, and the values less than 80 mm Hg in DBP sample was increased approximately in 1.5 times. Visually, the growth of values was less evident on Fig 3. and Fig.4. It was again related with asymmetry – that the borders of values 80 were shifted to the right from the maximal value.

It followed from the foregoing that the analysis of exposure results only on the mean arithmetic value (mathematic expectation) did not give a full representation on nature of parameter change.

Table №7.

Efficiency of 14-day BP correction PRIOR and AFTER course exposure

№	Parameter	PRIOR correction	AFTER course	Difference PRIOR and AFTER	Significance
1	SBP mm Hg	154 ±17	140 ± 12.7	14	<0.01
2	DBP mm Hg	85.6 ±10.1	77.2 ± 8.8	5.4	<0.01
3	SBP asymmetry coefficient	0.432	0.563	-	-
4	DBP asymmetry coefficient	0.47	-0.27	-	-
5	SBP <132 mm Hg	28.2%	62%	33.8%	-
6	70< DBP < 80 mm Hg	41%	77%	36%	-

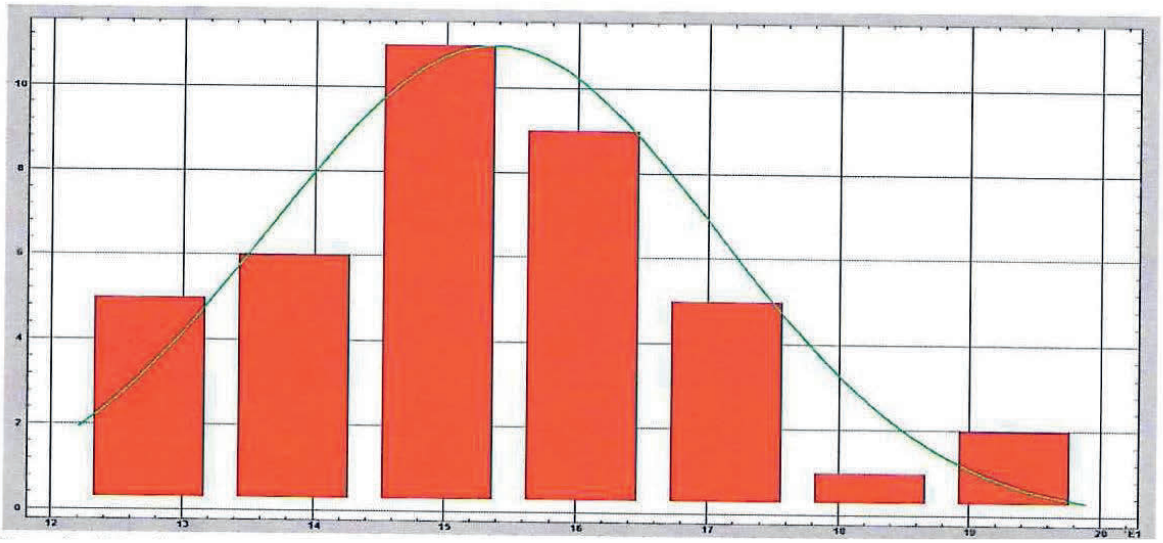


Fig.1. Asymmetry coefficient A=0.43

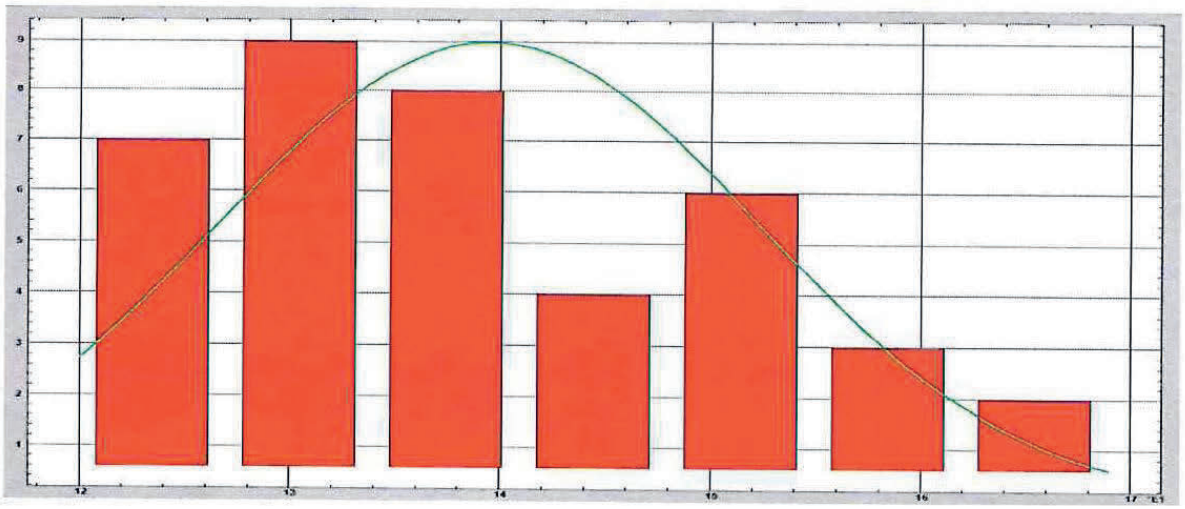


Fig. 2. Growth of asymmetry coefficient A = 0.56 – shift to low SBP

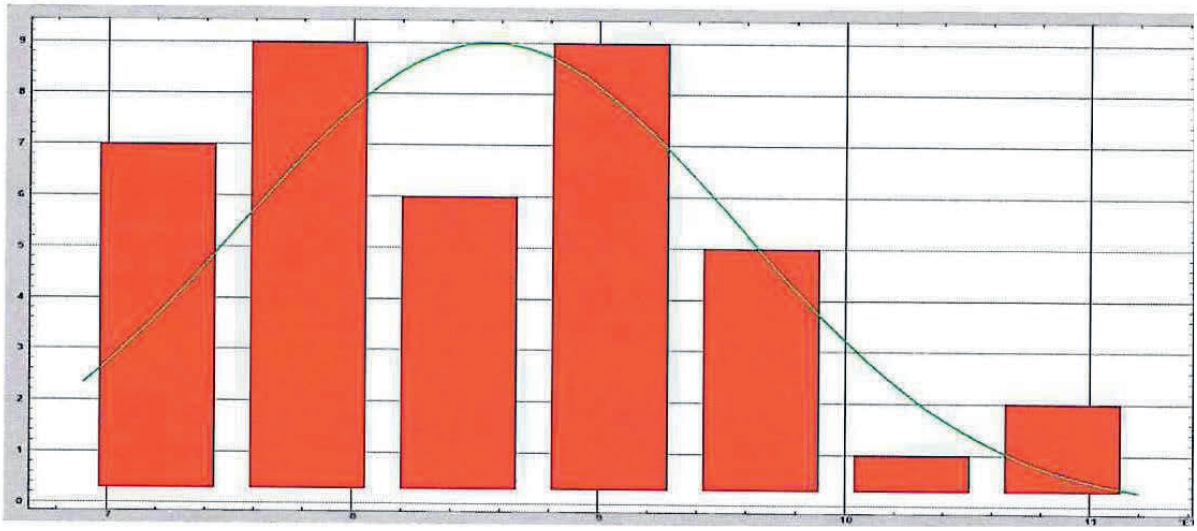


Fig. 3. Asymmetry coefficient A = 0.47

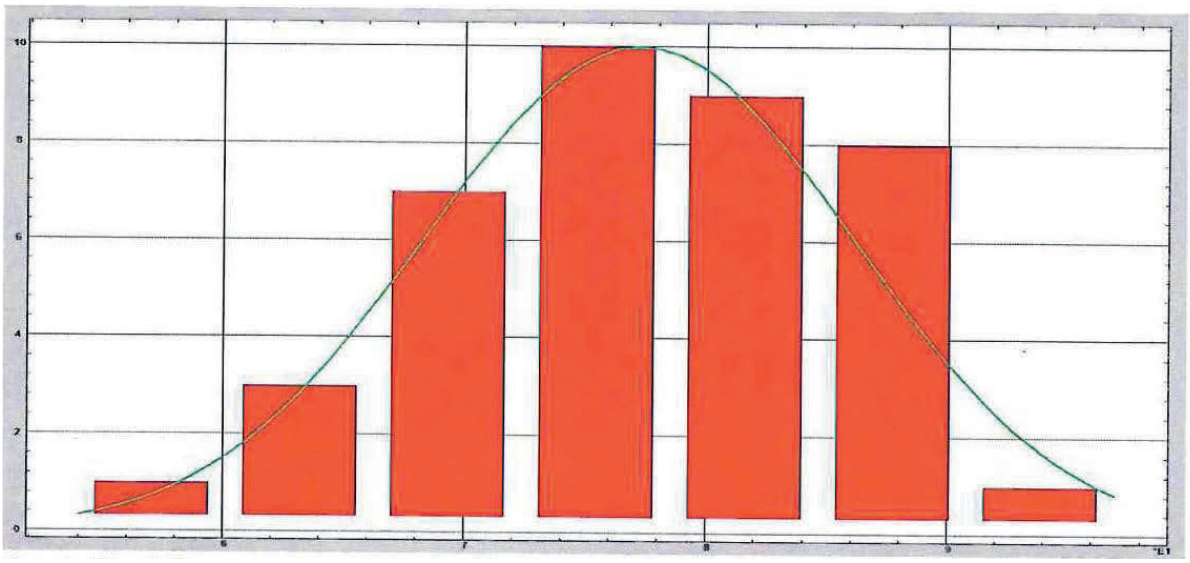


Fig.4. Asymmetry coefficient = - 0.27

Table № 8 provides results of heart rate observation both in correction period and observation period.

In period of BP correction, HR did not significantly changed, and in observation period, a significant HR decrease up to the normal was established.

Table №8.
Heart rate (beats/min) in two periods

№	Period	Start	End	Difference	Significance
1	Correction	78.6 ± 13.3	79.6 ± 26	1	-
2	Observation	78.3 ± 11.3	71.2 ± 8.58	7.1	<0.01

Table № 9 provides the results of assessment of sham treatment

During sham treatment, any statistical significance of differences in SBP and DBP changes was not recorded.

Table № 9.
Sham treatment

№	BP mm Hg	Start	End	Difference	Significance
1	SBP	145 ±23.6	141 ± 12.7	4	-
2	DBP	87.9 ± 9.34	81.5 ±8.37	6.4	-

Table № 10 provides results of assessment of sham observation

Table № 10.
Placebo observation for 28 days

№	BP mm Hg	Start	End	Difference	Significance
1	SBP	146 ± 15.5	144 ± 12.3	2	-
2	DBP	91 ± 5.4	80.9 ± 8.37	7.03	-

During the period of placebo treatment, statistical significance of differences in SBP and DBP change was not shown.

Table № 11 provides results of assessment of BP dynamics PRIOR correction, AFTER correction and in observation period of 28 days.

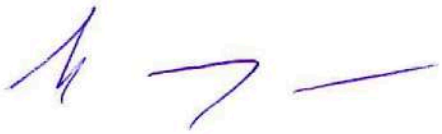
Table №11.
Treatment period 14 days and observations 28 days

	SBP mm Hg	DBP mm Hg
	Treatment period	
PRIOR correction	154 ±17	85.6 ± 10
AFTER a course	140 ±12 $p < 0.01$	77.2 ± 8.8 $p < 0.01$
	Observation period	
First 14 days	139 ± 1.24	79.1 ±8.9
Second 14 days	137 ± 1.73	78.4 ± 8.7
Total of 28 days	138 ± 1.88	77.5 ± 8.8
Average	138	78.3

During 28-day observation period, any statistically significant SBP and DBP differences were not reported. It was of interest that mean SBP value was 138 mm Hg, however, values below 130 mm Hg represented 71% in the sample, and with mean DBP value 78.3 mm Hg, proportion of values less than 80 mm Hg in the sample was 89%.

Based on the statistical analysis, cumulative conclusions can be made:

1. Administration of device "ABP -051" is safe – mean SBP was not lowered below 121 mm Hg, and mean DBP was not almost lowered below 70 mm Hg.
2. Efficiency of BP correction depended on DBP value, and the higher was SBP, the higher was correction efficiency.
3. Age-related limitations of the administration were absent in elderly people.
4. Treatment efficacy was confirmed in 14 days.
5. After 3 procedures, a short-term relative SBP increase about 3 mm Hg was observed, provided that initial SBP value is less than 140 mm Hg
6. ABP-051 administration is safe for persons with 2 type diabetes mellitus. During the treatment with device "ABP-051", glucose level was not changed.
7. With SBP value less than 140 mm Hg, efficiency of correction was on the level of 3 .... 7 mm Hg.
8. With SBP value above 150 mm Hg, efficiency of correction was on the level 23 mm Hg with significance level $p = 0.01$.
9. Placebo device in this case is not fully a sham device, as the fixation method leads to some compression of area MC6 and is an independent method in reflexotherapy, stimulating factor. The effect of mechanic pressure is not profound and does not bring a statistically significant hemodynamic result.

Study coordinator  I.V. Kirichok