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Experience Of One-Electrode Symplicity Flex Catheter And Multi-Electrode Symplicity Spyral Catheter In Kazakhstan.

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ABSTRACT

The purpose of research is to compare the efficacy and safety of applying one-electrode Symplicity Flex catheter and multi-electrode Symplicity Spyral catheter. Materials and methods. Inclusion criteria: age 30-70, diagnosed with essential arterial hypertension (AH), arterial pressure (AP) > 160/100 mm Hg. resulted while taking three or more drugs with written informed consent. Exclusion criteria: average daily systolic AP <135 mm Hg., glomerular filtration rate < 45 ml/min/1.73 m2), symptomatic AH. In both groups there was performed renal artery radiofrequency denervation (RDN) with radiofrequency power 5-8 watt with constantly controlled temperature and impedance. In the I-st group, the duration of each application was 2 minutes, in the II-nd group duration of each application made up 1 min. Results. At the time of this analysis the renal artery radiofrequency denervation was performed with 44 patients in the I-st group and 14 patients in the II-nd group. 6 months later after renal artery RDN 25 patients of the I-st group and 4 of them in the II-nd group were examined once more. In no case there were revealed long-term complications, significant deterioration of renal blood flow and renal function. It was found a marked reduction of office AP 6 months later after the application of renal artery RDN, there was a decrease of systolic AP/diastolic AP indexes at the office measurement for 39/28 mm Hg. (p <0,01) in the I-group and for 58/46 mm Hg. in the II-group, respectively. The average duration of renal artery RDN procedure in the I-group was 63,3 ± 27,01 min., while in the II-group - 36,4 ± 15,63 min. Conclusion. Application of multi-electrode catheter in clinical practice helps to significantly reduce the total duration of intervention and improve efficiency.

Keywords: resistant arterial hypertension, renal artery radiofrequency denervation, multi-electrode catheter

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INTRODUCTION

WHO defines arterial hypertension (AH), as "a leading global risk of increased mortality from cardiovascular diseases in the world" (The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), 2013). Throughout the world 7 million people die and 1 billion people suffer due to high arterial pressure or hypertension every year (Zhunuspekova, 2014).

Also AH ranks the third place in the world as a cause of population disablement (Cicala et al., 2010). There is a linear relationship between blood pressure level and the likelihood of these events. Each increase of systolic arterial pressure (SAP) for 20 mm Hg, and diastolic - for 10 mm Hg. increases the possibility of severe, including lethal complications twice (Bruno, 2012, Egan et al., 2010). AH becomes the cause of death from a stroke in 51% of cases, 45% of deaths of coronary heart disease (CHD), also due to existing of HD in patients (Dias et al., 2011).

Resistant arterial hypertension (RAH) is a form of arterial hypertension, which entails a high level of morbidity and mortality, as well as an increase in additional costs for diagnosis and treatment. According to the definition of the European Society of Cardiology (2013) RAH is a clinical situation in which, while prescribing 3 or more antihypertensive drugs of different classes (one of which is a diuretic) it fails to reach target arterial pressure (<140/90 mmHg) . It is estimated that in patients with hypertension RAH prevalence is 10% -15% (Calhoun et al., 2008, Daugherty et al., 2012), and in some subgroups of patients with hypertension, such as patients with obesity, diabetes mellitus, chronic renal failure RAH incidence is twice higher compared with general population (Erdine et al., 2011).

The study is based on the analysis of > 600 thousand persons with hypertension is indicative of RAH prevalence at the level with 14.8% of treated patients and 12.5% - among the total number of patients with hypertension (Judd and Calhone, 2014).

In recent years, a great interest is excited with the development of a new non-drug treatments for resistant arterial hypertension (RAH) of renal artery radiofrequency denervation (renal artery RDN) that gave a hope to improve treatment outcomes. Renal artery RDN is based on two-way RF catheter ablation of renal nerves located in the adventitia of the renal arteries.

After a series of experimental and initial clinical work (Schlaich et al., 2009), indicating the persistent antihypertensive effect of renal artery RDN, in late 2011, there were presented the results of two multicenter trials to confirm the safety of this method and its long-term clinical efficacy.

In Kazakhstan, the first reports on the work in this direction occur in 2012, when in the "National Scientific Cardiac Surgery Center" there were performed 77 renal artery RDN (Musayev et al., 2015). Widespread use in the practice of the mentioned technology began in 2013 after the presentation of Symplicity Catheter System ™ by Medtronic company at the III Congress of Physicians and V Congress of Cardiologists in the Republic of Kazakhstan. According to our research, the same positive results were obtained when using renal arteries RDN in patients with RAH (Stanbul et al., 2014).

Some of the main criteria for introduction of new treatment method are safety, effectiveness and duration of impact. It should be emphasized that in assessing the long-term results of Symplicity HTN-1 research, there was not observed the reduction in the antihypertensive effect during the 24 month period (Flaa et al., 2011, Kovalenko, 2012).

The most long-term outcomes of Simplicity HTN-2 research are the data obtained from when inspecting patients at the period of 36-month observation, indicating preservation of a significant antihypertensive effect of reducing AP by -33/-19 mm Hg. from baseline (n=4). Among the identified undesirable side effects, as well as in the previous Simplicity HTN-1 study, there were no significant events due to device or intervention (Lichikami, 2015).

However, obtained results of Symplicity HTN-3 research on failure of primary efficacy endpoint, which were published in the press release from January 9, 2014, and then in the «New England Journal of Medicine»,

caused a heated debate in the medical community about the future use of renal arteries RDN in clinical practice (Persu et al., 2015, Shaw and Warren, 2015).

Nevertheless, the researchers indicate the use of non-effective technologies as the first and likely cause of the failure of this study. HTN-3 researchers themselves have published data supporting the use of non-optimal technology in this study, where only 6% of patients were applied the recommended method of bilateral retrograde spiral (Kandzari et al., 2015).

Currently clinical practice has been already implemented multi-electrode catheters with spiral arrangement of electrodes, which should eliminate the shortcomings of previous devices for renal arteries RDN and increase the effectiveness of the procedure.

In this study, we set the task to compare the efficacy and safety of Symplicity Catheter technology and Symplicity Spyral multi-electrode catheter to identify the optimal option in RAH treatment.

MATERIALS AND METHODS

The study was conducted in accordance with national and international regulations governing clinical trials of new treatments: the Declaration of Helsinki of the World Medical Association, in acting release of 2004. Research report was approved by Ethics committee of Scientific - Clinical Center of Cardiac Surgery and Transplantation of Kazakhstan. All members gave informed consent in written form on the treatment procedure and possible complications. Clinical section of the work was carried out on the base of Scientific - Clinical Center of Cardiac Surgery and Transplantation, Taraz, Kazakhstan.

Patients with average daily AP below 135 mm Hg., patients with symptomatic AH, patients with widespread lesions of renal artery (RA) and with severe comorbidities were not considered as candidates for RDN. Also patients with renal insufficiency (glomerular filtration rate (GFR) <45 ml/min/1.73 m2) and pregnant were excluded. Prerequisites for carrying out renal artery RDN were a diameter of renal arteries of at least 4 mm and a length of the section to the first bifurcation of at least 20 mm.

The study included 58 patients with RAH at the age from 30 to 70 years old (average age - 54,9 ± 10,07). 34 (58%) of them were women, 3 of them had diabetes, 4 of them had obesity and 5 suffered acute cerebrovascular event (ACE) (Table).

Indicators measuring AP in the office were more than 180 mm Hg. while continuous accepting 3 or more drugs (one of them is diuretic).

Table. Clinical and demographic characteristics of patients

Rate	I – st group (n=44)	II – nd group (n=14)
Average age, years	54,9	55,0
Women, abs. (%)	26 (59%)	8 (57%)
Type 2 diabetes, abs. (%)	3 (6,8%)	-
Obesity, abs. (%)	1(2,2%)	3 (21,4%)
With a history of ACE, abs. (%)	3 (6,8%)	2 (14,2%)
GFR >60 ml/min/1,73 m2 (by CKD-EPI formula), abs. (%)	41 (93%)	14 (100%)
Office AP, mm.Hg		
SAP	185±16	195±15
DAP	114±11	119±6
Key: ACE - acute cerebrovascular accident, GFR - glomerular filtration rate, SAP - systolic arterial pressure, DAP - diastolic arterial pressure.		

Procedure of renal artery RDN was performed under conditions with X-ray operation room, femoral access by the system to Symplicity renal arteries denervation (Medtronic, USA), which consists of a radiofrequency wave generator and a disposable catheter. In the I-st group (n = 44) renal denervation was performed using one-electrode Symplicity Flex catheter, and in the II - nd group (n = 14) using multi-electrode Symplicity Spyral catheter. The patients underwent diurnal AP monitoring, cardiac and renal arteries

ultrasound examination. Research was carried out by conventional procedures using highly informative expert class devices.

In both groups, renal artery RDN was performed with radiofrequency waves with power of 5-8 watt with constantly controlled temperature and impedance at the catheter tip. In the I-st group, the duration of each application was 2 min, criteria for efficacy were to achieve optimal temperature and impedance parameters being automatically registered from the tip of catheter. In case of automatic interruption of radiofrequency exposure due to poor contact of the probe-electrode with the wall of artery, re-application was carried out. In the II - nd group the duration of each application was 1 min, criteria for efficacy were also achieving optimal temperature and impedance parameters being automatically registered from the tip of catheter. In the II - nd group there was an opportunity to disable one, two or three of the four electrodes as required.

Immediately after the treatment in both groups catheters and introducers were removed, and hemostasis was performed by manual method for 15-20 min and then a pressure aseptic bandage was applied.

During the procedure there were used non-ionic X-ray contrast specimen (Visipaque 320, GE Healthcare Ireland, Ireland, and Ultravist, Schering AG, Germany), diluted with physiologic saline in the ratio of 1: 1. All patients were determined for creatinine concentration in blood and creatinine clearance on the 2nd day after the procedure and before discharge. 6 months later after the procedure there were monitored indicators of office AP measurement, diurnal AP monitoring - DAPM, the degree of daytime and nighttime reduction in systolic and diastolic AP (SAP and DAP), variability of daytime and nighttime AP), GFR (glomerular filtration rate) according to the formula for CKD-EPI , the level of blood plasma aldosterone were evaluated.

Premedication and management of the patient after the procedure. Before transfer to X-ray operation room the premedication with 10 mg of bruzepam and 0.005% mg 4.0 of fentanyl was carried out. Directly in the operation room before the first application for the purpose of analgesia 1% 1.0 of morphine or 0.1 mg of fentanyl were injected intravenously slowly by stream infusion. If necessary during a procedure additional 5-10 mg of diazepam was injected.

Statistical data analysis was performed using STATISTICA 6.0 software methods of parametric statistics, in comparative analysis the Student's t-test was applied, also there was performed correlation and frequency analysis. In the presence of data insubmission to the law of normal distribution the comparison of two different groups on quantitative traits was performed by Mann-Whitney U-criterion. Differences were considered significant at $p = 0.05$.

RESULTS

The average duration of renal artery RDN procedure in the I-group was 63,3 ± 27,01 min., while in the II-group 36,4 ± 15,63 min. The average amount of contrast substance used is 150 ± 23 ml. In the I-st group there were performed 9±2 RF manipulations on every renal artery, and in the II–nd group there were performed 8±3 radiofrequency manipulations on every renal artery. 5 patients in the I-group and 2 patients in the II-group were additionally injected narcotic analgesics due to severe pain in the lumbar region during an operation. There were no complications from the kidneys and at the puncture.

In the I-group the vessel diameter when having renal artery RDH was 4 mm. and above, whereas in the II-group in all cases, without exception, the vessel diameter was 3 mm, which allows ablation in the distal end of the vessel, where the greatest number of nerve fibers are concentrated.

According to the office measurement baseline average value of SAP and DAP in the I-group made up 185/115 ± 16/11 mm Hg. and in the II-group it was 194/115 ± 14/5 mm Hg. After applying renal artery RDN (after 6 months observation) there was noted a decline in SAP/DAP when office measuring for 39/28 mm Hg. ($p < 0,01$) in the I-group and for 58/46 mm Hg. in the II-group, respectively (Figure). Percentage wise in the I-group the reduction in SAP/DAP accounted for 21% / 24%, and in the II-group 30%/39%, respectively.

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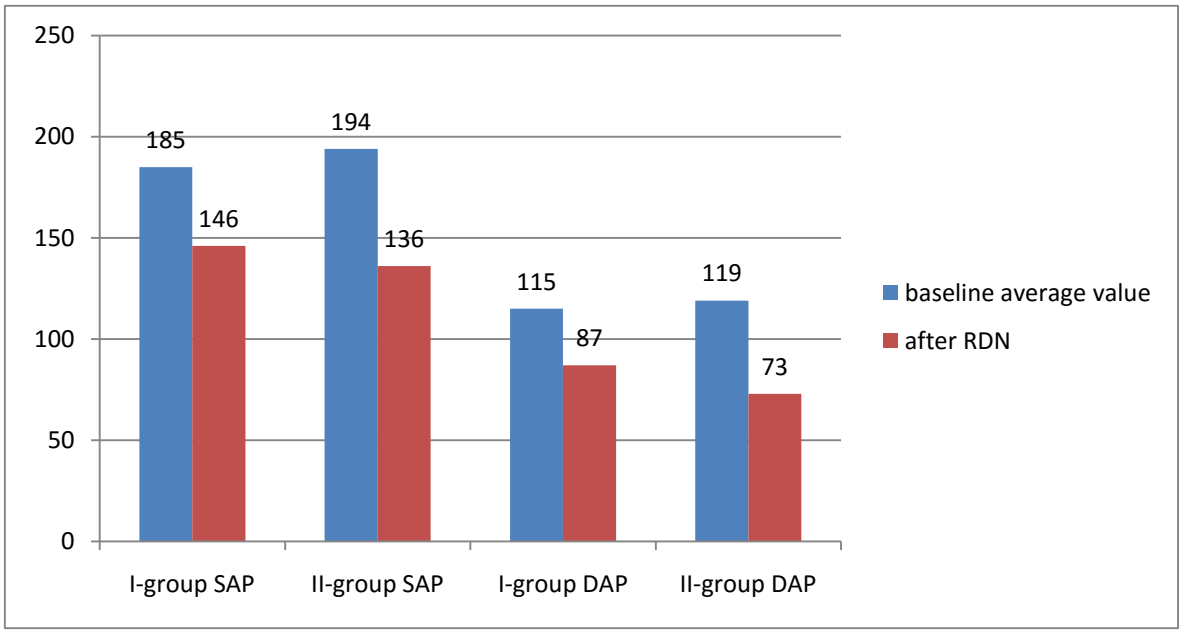

Figure. The level of SAP and DAP reduction in I and II- groups in 6 months

According to 24-hour blood pressure monitoring there was a decrease for 49/30 mm Hg. in the I-group and for 55/34 mm Hg. in the II-group, respectively (difference is unreliable). After 6 months a frequency exceeding the target levels of SAP and DAP during the night made up 30 and 28%, respectively (p ≤0,05). 7 patients in the I-group and 4 patients in the II-group after 6 months subjectively showed life quality improvement in the form of lower intensity and reduce the number of episodes of headache and dizziness, as well as the improvement of sleep. Mean rates of creatinine at baseline and after 6 months remained within the normal range without significant change in both groups - 85.3 and 87,5 ± 15/15 mcmol/l, respectively (difference is unreliable). Mean GFR (by CKD-EPI) also did not change significantly - 77 and 80 ± 21/16 ml/min /1.73 m 2 at baseline and after 6 months, respectively. The levels of renin and aldosterone blood plasma compared to baseline values have not changed as well.

DISCUSSION

Since the publication of the first results on the efficacy and safety studies, Simplicity HTN-1 and - 2 radiofrequency ablation of renal sympathetic nerves (renal denervation) was considered to be as one of the most promising directions in the region of arterial hypertension treatment, especially resistant to therapy. Subsequent results of Simplicity HTN-1 and 2, and numerous studies around the world left no doubt about its effectiveness. More modern data of pilot studies on the effectiveness of treatments in cases of other diseases - chronic heart failure, diabetes, atrial fibrillation, obstructive sleep apnea syndrome, appeared.

However, negative results of blind, randomized, controlled clinical trial to evaluate the safety and effectiveness of Simplicity HTN-3 renal denervation were quite unexpected and disappointing in the USA, although it confirmed the safety of the procedure (Zvartu et al., 2014).

Researchers at most centers of the European Society Arterial Hypertension, having experience in performing this procedure, have one thing in common - the results of the study do not outweigh the accumulated vast array of data indicative on the procedure effectiveness, but merely indicate the need for further analysis and a more reasonable approach.

According to the data of our study, RDH procedure is an effective non-drug treatment for patients with RAH. And the use of multi-electrode Symplicity Spyral catheter allowed to reach the maximum hypertensive effect compared with the results of Symplicity Flex.

According to the office measurement baseline average value of SAP and DAP in the I-group were 185/115 ± 16/11 mm Hg. and in the II-group - 194/115 ± 14/5 mm Hg. After applying renal artery RDN (after 6 months observation) there was a decline in SAP/DAP in office measuring for 39/28 mm Hg. (P <0,01) in the I-group and for 58/46 mm Hg. in the II-group, respectively. The best results in the II-group we associate with using Symplicity Spyral catheter in renal arteries with a diameter of 3 mm, which allowed having ablation in concentrated distal vessel end of the largest number of nerve fibers.

These results are consistent with Symplicity HTN-2 studies data, where after 30 months observation, 37 patients had a decrease in SAP and DAP for 35 and 13 mm Hg. respectively (Esler et al., 2013). For adherence to the developed algorithm of patients selection for RDN performance, currently it requires a multidisciplinary approach involving an endocrinologist, nephrologist, neurologist, cardiologist (Esler et al., 2010, Verloop et al., 2013).

Application of multi-electrode catheter in clinical practice reduces the exposure time to 2 minutes on each renal artery and significantly reduces the total duration of intervention. In our study, operating time decreased twice, where the average length of renal artery RDN procedure in the I-group was 63,3 ± 27,01 min. and in the II-group - 36,4 ± 15,63 min.

Despite the encouraging results obtained in ongoing research, there is a group of patients who fail in achieving target levels of AP. Thus, according to Symplicity HTN-1 study, the proportion of these patients was 7%, according to Symplicity HTN-2 study it is 10%, according to the Heidelberg register - 24% (Blessing et al, 2013.). Whereby, the effectiveness of the procedure was defined as a decrease in SAP ≥10 mmHg. 6 months later after RDN. In our work, the effectiveness of the procedure is outlined in all cases.

Currently there are considered pathophysiologic, anatomic, and iatrogenic causes of unsatisfactory RDN results in this group of patients. One of the factors that can affect the effectiveness of the procedure is the fullness of the artery denervation on its entire length, a sufficient number of effective applications, which is not always possible, especially in patients with complex anatomy of renal arteries. Application of multi-electrode Symplicity Spyral catheter in the II-group made it possible to solve this problem. In this group, ablation was performed in vessels with a diameter of 3 mm. and complex anatomical renal arteries, where the effectiveness of multi-electrode Symplicity Spyral catheter compared with one-electrode Symplicity Flex catheter was obvious.

Today there is a problem of renal arteries re-innervation, which can eventually prevent or reduce long-term renal artery RDN effect. In our study, we plan to continue the study to assess the long-term results and procedure safety. In addition, during three-year observation of patients after renal artery RDN Symplicity HTN-1 study demonstrated marked steady decline in AP (Sobotka, 2012).

FINDINGS

Renal arteries RDN is a safe and effective treatment for patients with GRA. Application of multi-electrode Symplicity Spyral catheter in clinical practice helps to improve efficiency and significantly reduce the overall duration of intervention.

RESEARCH RESTRICTIONS

The present study has some limitations due to uneven distribution of the number of patients in the groups studied, which is insufficient to produce statistically significant laws for a number of endpoints. To achieve the objectives, further controlled studies with greater power are required.

CONFLICT OF INTERESTS

All authors declare on no potential conflict of interest requiring disclosure in this article.

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