Japanese journal of complementary and Alternative medicine Sep. 2015 Vol.12 No.2 : 73-78

Changes of Cerebral Blood Flow by the Weak Trans-Cranial Ultrasound Irradiation in Healthy Adult Volunteers

Shukan Okano[1], Kazuo Uebaba[2], Yuta Manabe[3], Kazuhiro Shibata[4], Yoshio Shimotori[5]
[1]Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University,
[2]Faculty of Health Science, Teikyo Heisei University,
[3]Dementia Diagnosis Center, Yokohama Shintoshi Neurosurgical Hospital,
[4]Image Diagnosis Region, Yokohama Shintoshi Neurosurgical Hospital,
[5]Research and Development Center, Kamiyama Mfg. Co., Ltd.

Abstract

In the recent aging society, many strategies against cerebral diseases including dementia are needed. As hand massage treatments promote blood flow for muscle fatigue and other disorders, ultrasound vibration may promote cerebral blood flow. A novel, long wavelength ultrasound vibration device with high permeation (less than 30 kHz, 2 mW / cm²) was applied to investigate cerebral blood flow before and after the frontal or occipital trans-cranial irradiation. In this study, the frontal or a mixture of the frontal and the occipital irradiation were conducted respectively on Xenon (Xe) gas X-ray Computed Tomography (CT), and Single Photon Emission Computed Tomography (SPECT) experiments in healthy adults who did not have any excluding criteria. From the results, we confirmed that the low milliwatt ultrasound vibration emitted by the device promoted cerebral blood flow.

Key words : trans-cranial ultrasound vibration, cerebral circulation, Xe gas X-ray CT, SPECT

Introduction

Aging has progressed and one in four persons is 65 years old or older in Japan. Moreover, reportedly, the number of dementia patients and persons likely to develop dementia has reached about eight million. Regarding the brain function, the motor function, intellectual activity, and circulatory function decline with aging and dementia in the elderly is considered due to these conditions. For treatment of brain disease including dementia, various drug therapies have been investigated, but highly safe non-drug therapy is also needed.

Electroconvulsive therapy in which electricity is transcranially applied to improve depression, schizophrenia, and Parkinson's disease and percutaneous intracranial magnetic stimulation therapy have been established and clinically applied as non-drug physiological treatment methods for the central nervous system. Although the action mechanisms of these treatment methods have not been elucidated, it has been reported that the clinical effect is exhibited through correction of maldistribution of neurotransmitters in the brain by improving cerebral blood flow[1]. Especially, correlation between improvements of cerebral blood flow and clinical symptoms has been demonstrated by evaluation of cerebral blood flow using SPECT[2]. However, of transcranial stimulations of intracranial tissue, ultrasound stimulation has not previously been investigated.

In this study, the cerebral blood flow promoting the effect of a weak massage of the entire head by long-wave ultrasound vibration was investigated in healthy subjects. Generally, anatomical physiological changes in the brain are examined by tomography using Magnetic Resonance Image (MRI), X-ray CT, SPECT, and Positron Emission Tomography (PET). These examinations visualize small blood vessels, promoting rapid advance in medical diagnosis. Of these, we considered the use of Xenon (Xe) gas X-ray CT and SPECT, which are employed to diagnose dementia. Generally, disease is likely to develop when blood flow is unfavorable. Therefore, we decided to investigate whether cerebral blood flow is improved.

In previous studies on the influence of this device on the human body, the health promotion effect of a sound massager for the head[3] and the effect of ultrasound vibration on human brain waves and blood flow[4] were investigated. The safety and measurement method of ultrasound intensity data of this device have been presented by sound field measurement in an intracranial model treated with an ultrasound massager[5].

Based on the main specifications of ultrasound therapeutic devices in the Japanese Industrial Standards (JIS) standard: frequency, 500 kHz - 5 MHz; and maximum intensity, 3 W / cm^2 or lower[6], these conditions of this device were set at 30 kHz and 2 mW / cm^2 or lower, respectively, emitting a very weak ultrasound, to secure the safety and low-invasiveness (name of the device: Mu-Ma Pro).

In this study, changes in cerebral blood flow after head stimulation using Mu-Ma Pro were measured. Firstly, changes in cerebral blood flow were confirmed in healthy subjects using Xe gas X-ray CT and then measured in different healthy subjects using SPECT.

Materials and Methods

Healthy individuals who did not conflict with the following exclusion criteria 1) - 3) were selected for the subjects.

Exclusion criteria:

1) Past medical history of or being treated for head injury
2) Judged as ineligible by a physician
3) Aging-related changes and ischemic and tumorous lesions clearly observed on head by MRI

Study 1

Subjects: After obtaining consent, the massage hair band of Mu-Ma Pro (Kamiyama Manufacturing Company Limited, Chiba) (Photo1) was attached to the forehead in two healthy adults (Subject1: 52-year-old male, Subject 2: 68-year-old female), and the distribution of cerebral blood flow was measured before and after stimulation with transcranial ultrasound vibration for 20 minutes using Xe gas X-ray CT. The image data were analyzed using ImageJ of the US National Institutes of Health (NIH),and the mean relative luminance of the image was compared.

The measurement protocol is presented in Fig. 1. One ultrasound vibrator each was attached to the bilateral sides of the forehead (two vibrators in total) and pulses were applied alternately at 1.5 second intervals. The specifications of the device (Mu-Ma Pro) are shown in Table 1.

Study 2

Subjects: One ultrasound vibrator each was attached to the bilateral sides of the forehead and occipital region (four vibrators in total) in two healthy adults (Subject 3: 68-year-old male, Subject 4: 62-year-old female), and pulses were applied alternately at 1.5 second intervals for 20 minutes.

The physiological influence of stimulation of the head with 30 kHz ultrasound vibration using Mu-Ma Pro on the intracranial structures was evaluated using SPECT. For the nucleus for SPECT, 111 MBq ^{123}I-IMP (IMP) was selected. To investigate changes in cerebral blood flow after stimulation, pharmacokinetics of the agent were investigated in several compartments based on the compartment model in which behavior of the agent was clarified using schematized quantitative values for convenience employing the autoradiography

Correspondence: Shukan Okano, s_o_ohjitokyo@yahoo.co.jp

(ARG) method. SPECT images were acquired by ARG twice before and after stimulation using Mu-Ma Pro. To eliminate the influence of IMP administered before stimulation, stimulation was applied two days after the first test and SPECT was performed.

Table 1 Basic specifications of transcranial weak ultrasound vibration stimulation device (Mu-Ma Pro)

1	Rated voltage. rated current	AC100 V, 0.3 A or lower
2	Ultrasound frequency	30 kHz ± 5% or lower
3	Ultrasound intensity	Max of 2 mW / cm^2
4	Mean max ultrasound output / vibrator	1.6 mW / sec
5	Number of ultrasound vibrators	4 (2 on the forehead. 2 on the occipital region)
6	Modulated pulse ratio / vibrator	10 % ±1 %

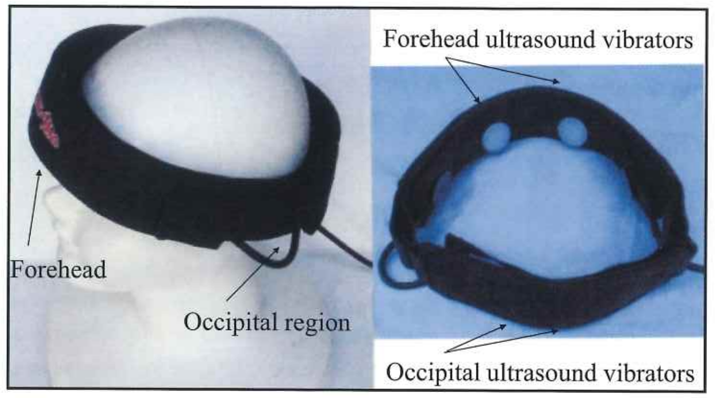

Photo 1 Attachment of the transcranial weak ultrasound vibration stimulation device (Mu-Ma Pro) and vibrator attachment sites on the inner surface of the band

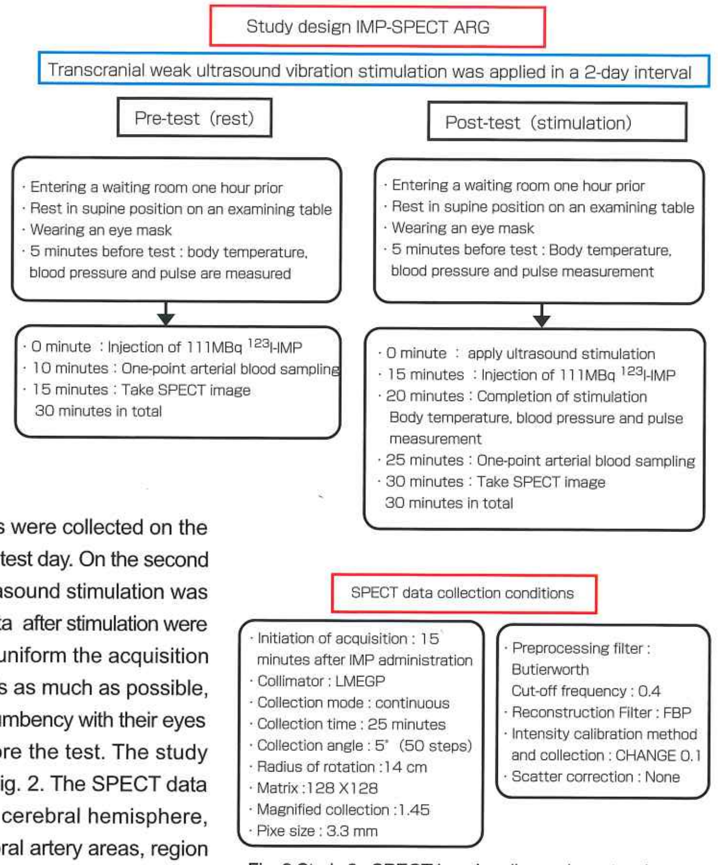

Fig. 2 Study 2 : SPECT imaging diagnosis protocol measuring changes in cerebral blood flow after stimulation

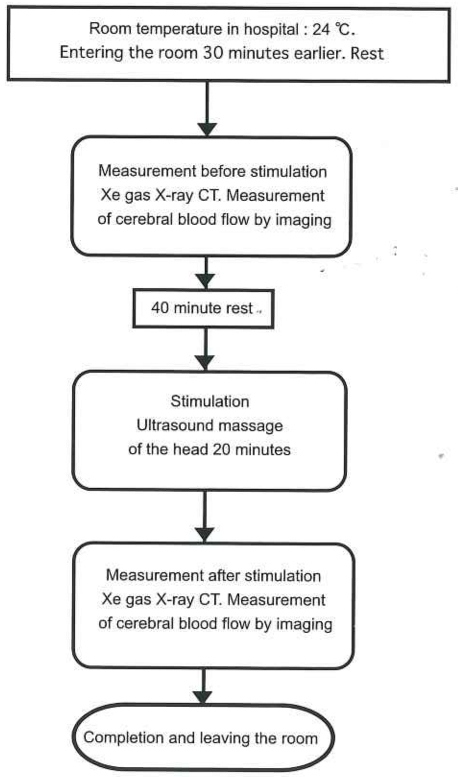

Fig. 1 Study 1: Xe gas X-ray CT diagnosis protocol of measuring changes in intracranial blood flow after stimulation

Basic data of the subjects were collected on the first acquisition on the first test day. On the second test day, transcranial ultrasound stimulation was applied and changes in data after stimulation were collected by SPECT. To uniform the acquisition conditions of the two tests as much as possible, the subjects waited in recumbency with their eyes closed for one hour before the test. The study protocol is presented in Fig. 2. The SPECT data were collected from the cerebral hemisphere, anterior and middle cerebral artery areas, region anterior to the anterior cerebral artery area, region posterior to the middle cerebral artery area, posterior cerebral artery area, putamen area, and hypothalamus.The mean cerebral blood flow was measured in all these regions in each hemisphere before and after stimulation and compared. Then, the percent increase in combined cerebral blood flow of the bilateral hemispheres was compared to those before and after stimulation.

Study 1 was approved by the Ethics Committee of Sanai Hospital and Study 2 was approved by the Ethics Committee of Yokohama Shintoshi Neurosurgical Hospital.

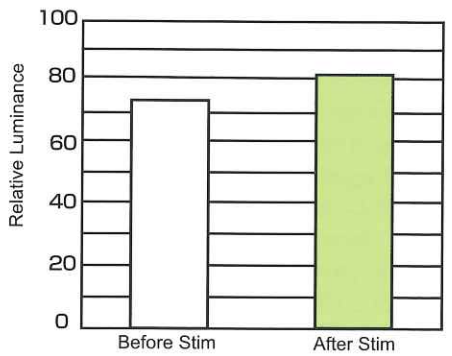

Fig. 3 Changes in relative luminance of cerebral blood flow (Xe gas X-ray CT)

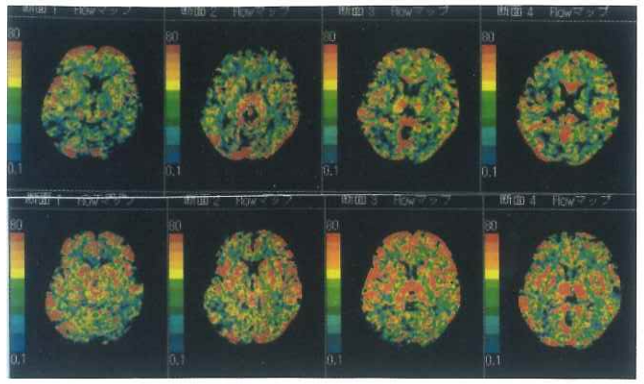

Photo 2 Subject 1 (52-year-old male)
Upper row: Before stimulation, Lower row: Blood flow after stimulation

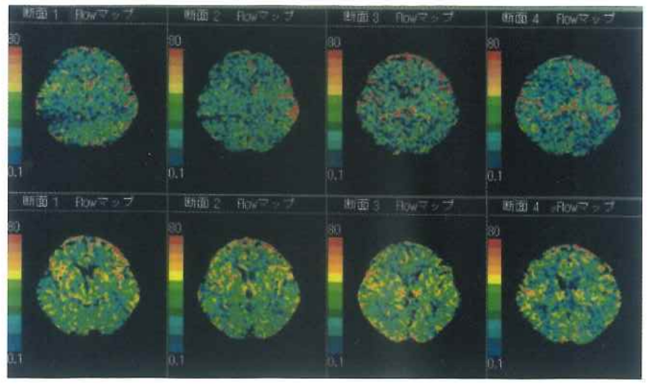

Photo 3 Subject 2 (68-year-old female)
Upper row: Before stimulation, Lower row: Blood flow after stimulation

Results

Study 1

The measurement results on Xe gas X-ray CT are shown as Photos 2 (Subject 1) and photos 3 (Subject 2).

Four tomograms of the brain before stimulation are shown in the upper row and tomograms after 20-minute stimulation are shown in the lower row, representing quantitative blood flow images. Low, high, and middle blood flow are presented in blue, red, and yellow, respectively. The contour of the brain was not clear before stimulation, but it became clear due to an increase in blood flow after stimulation. The mean relative luminance of the brain of the two subjects analyzed using Image J was 74.62 units before stimulation, but increased to 82.09 units after stimulation, as shown in Fig.3.

Study 2

The measurement results on SPECT are shown in Photos 4 (Subject 3) and photos 5 (Subject 4). Quantitative images before and after stimulation are presented on the left and middle, respectively. The right image represents the difference between before and after stimulation.

The numerical data on changes in cerebral blood flow after stimulation using Mu-Ma Pro are shown in Table 2. As shown in Fig. 4, the mean cerebral blood flow of the eight regions in the entire right hemisphere was 36.50 mL before stimulation and increased to 42.23 mL after stimulation in Subject 3. In the entire left hemisphere, it was 35.55 mL before stimulation and increased to 41.84 mL after stimulation. In Subject 4, the mean cerebral blood flow in the entire right hemisphere increased from 40.54 mL before stimulation to 45.13 mL after stimulation. The entire left hemisphere increased from 40.56 mL before stimulation to 45.78 mL after stimulation. No laterality was noted in either subject. The rate of increase in the total cerebral blood flow combining the sixteen regions of the bilateral hemispheres was 116.68 % in Subject 3 and 112.12 % in Subject 4, regarding that before stimulation as 100 % (Fig. 5).

No adverse effects in the cardiovascular system including changes in blood pressure or burns in contact regions were noted.

Discussion

According to our previous study[5], the underwater intensity of 30 kHz ultrasound vibration used for ultrasound stimulation to the head was a maximum of 1.6 mW / cm^2 at the center of the vibrating surface.The maximum output intensity of commercial ultrasound therapeutic devices for heat treatment for the trunk is specified to 3 W / cm^2 by JIS. Low frequency ultrasound has been reported to have strong penetration ability. Regarding the intensity of this device, the head was stimulated with a very weak output, being less than 1 / 1,875 of the upper limit of the JIS standard.

Cerebral blood flow generally increased in both Study 1 (Xe gas X-ray CT) and Study 2 (SPECT). Anatomically, activation of cerebral blood flow in the regions related to emotion and memory, such as the brainstem extension, the limbic system including the amygdala and hippocampus, and lower medial region of the temporal lobe, is considered. Since weak massage by long-wave ultrasound vibration of this device may have promoted blood flow based on the SPECT images of cerebral blood flow before and after stimulation, it may have an influence on emotion and memory in humans.

It is unclear whether this device influences diseases because the number of subjects was small and the subjects were healthy adults, however, safety has been confirmed. Ultrasound physical therapy capable of complementing drug therapy may be established in the future by performing a study involving patients with brain disease.

Conclusion

Although the intensity of the ultrasound vibrator set at 30 kHz and 2 mW / cm^2 or lower is 1 / 1,875 of the maximum output (3 W / cm^2) of commercially available ultrasound devices for heat treatment

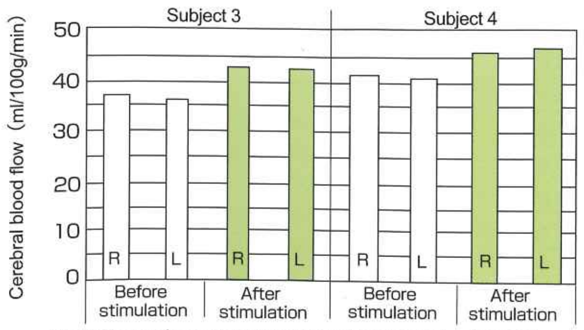

Fig. 4 Change in cerebral blood flow after stimulation (SPECT)

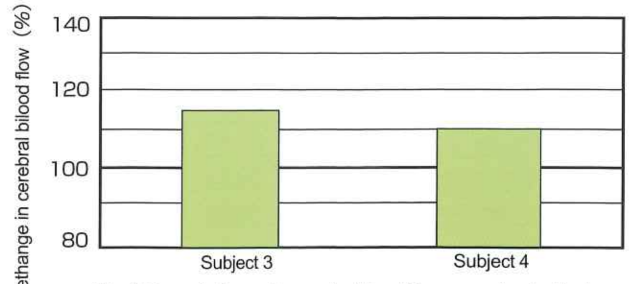

Fig. 5 Percent change in cerebral blood flow regarding that before stimulation as 100% (SPECT)

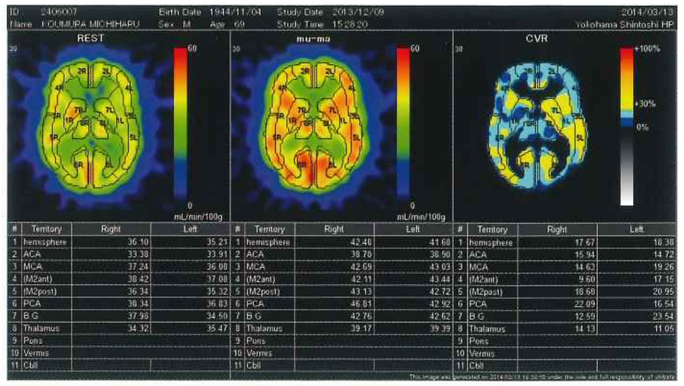

Photo 4 Subject 3 (68-year-old male)
Before stimulation, After stimulation, Change after stimulation

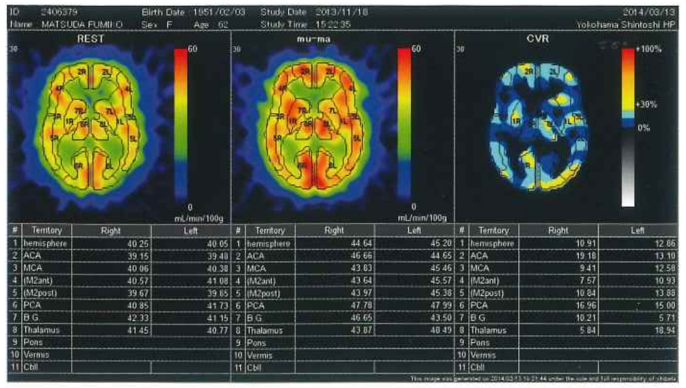

Photo 5 Subject 4 (62-year-old female)
Before stimulation, After stimulation, Change after stimulation

for the trunk, transcranial radiation through the forehead alone increased blood flow throughout the brain on Xe gas X-ray CT. In addition, combined stimulation through the forehead and occipital region promoted cerebral blood flow on SPECT.

Although the number of subjects was small limiting the study, low-frequency transcranial weak ultrasound vibration stimulation increases cerebral blood flow as an intracranial influence.

Table 2 Changes in cerebral blood flow (SPECT) after stimulation using the transcranial weak ultrasound vibration stimulation device

Suject 3

Brain region	Before stimulation (ml/100g/min)		After stimulation (ml/100g/min)		Increase (%)	
	Right	Left	Right	Left	Right	Left
hemisphere (Cerebral hemisphere)	36.10	35.21	42.48	41.68	17.67	18.38
ACA (Anterior cerebral artery area)	33.38	33.91	38.70	38.90	15.94	14.72
MCA (Middle cerebral artery area)	37.24	36.08	42.69	43.03	14.63	19.26
M2ant (Anterior to the middle cerebral artery area)	38.42	37.08	42.11	43.44	9.60	17.15
M2post (Posterir to the middle cerebral artery area)	36.34	35.32	43.13	41.72	18.68	20.95
PCA (Posterir cerebral artery area)	38.34	36.83	46.81	42.92	22.09	16.54
B.G (Putamen area)	37.98	34.50	42.76	42.62	12.59	23.54
Thalamus	34.20	35.47	39.17	39.39	14.13	11.05

mlL/ min / 100 g : Blood flow (mL) per minute per 100 g brain tissue

Suject 4

Brain region	Before stimulation (ml/100g/min)		After stimulation (ml/100g/min)		Increase (%)	
	Right	Left	Right	Left	Right	Left
hemisphere (Cerebral hemisphere)	40.25	40.05	44.64	45.20	10.91	12.86
ACA (Anterior cerebral artery area)	39.15	39.48	46.66	44.65	19.18	13.10
MCA (Middle cerebral artery area)	40.06	40.38	43.83	45.46	9.41	12.58
M2ant (Anterior to the middle cerebral artery area)	40.57	41.08	43.64	45.57	7.57	10.93
M2post (Posterir to the middle cerebral artery area)	39.67	39.85	43.97	45.38	10.84	13.88
PCA (Posterir cerebral artery area)	40.85	41.73	47.78	47.99	16.96	15.00
B.G (Putamen area)	42.33	41.15	46.65	43.50	10.21	5.71
Thalamus	41.45	40.77	43.87	48.49	5.84	18.94

mlL/ min / 100 g : Blood flow (mL) per minute per 100 g brain tissue

Funding

This study was conducted with research and development expense of Kamiyama Manufacturing Company Limited.

Acknowledgement

We are grateful to the subjects who kindly cooperated for measurement in this study and the staff of the testing facilities, Sanai Hospital and Yokohama Shintoshi Neurosurgical Hospital. We are also grateful to Drs. Hiroshi Toyama and Yoshitaka Inui, Department of Radiology, Fujita Health University, for ultrasound and nuclear medical measurements, and Mr. Kiyotaka Watanabe, Planning Department (central nervous system field) of Nihon Med-Physics Co., Ltd., for instruction in technical documents of SPECT. We deeply appreciate Dr. Teruhisa Watayo, Sanai Hospital, for understanding and encouragement for the unprecedented tests and Dr. Kenji Kosaka for giving us information concerning dementia and opinions regarding device development.

References

1. Kuji K. Diagnostically helpful clinical test. SPECT on dementia diagnosis. Current Dementia Practice. 2012; 2(1): 16-24.
2. Kuji K. Compaints which vary the cerebral blood flow. Handbook of Diagnostic Imaging of Nuclear Medicine. Elsevier Japan Co. Ltd.
3. Uebaba K, Xu F, Yatsuka S, Kim J. Double blind RCT test of ultrasound head massage on autonomic nerve function. Thirty third Annual Meeting of Japan Ayurveda Society. 2011.
4. Shimotori Y, Watayo T, Okano S. Health promoting effects of head sound wave massager. Health Science. 2007; 23(4): 274.
5. Okano S, Shimotori Y, Watayo T. Effects of ultrasound vibration on human EEG and blood circulation. J Physiol Sci. 2008; 58 (Suppl.): S98.
6. List of the requirements for the safety of ultrasound physical medicine. JIS t0601-205 / IEC 61102.
7. Okano S, Shimotori Y. Measurement of sound field of ultrasound massager for the head in skull model. Med Device. 2015; 85(1): 14-21.