Acta Neurologica Indonesia
Department of Neurology, Faculty of Medicine Universitas Indonesia
ISSN 3032-6303

Case Report

Transcranial Pulse Stimulation as a New Navigated Focal Brain Therapy for Vascular Cognitive Impairment: Case Report

Andrie Gunawan[1], Amanda Tiksnadi[1], Dyah Tunjungsari[1], Christine Kathy Putri Sari[1]

[1]Department of Neurology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; E-mail: andriegunawandr@gmail.com

ABSTRACT

Introduction: To evaluate the cognitive function of vascular cognitive impairment (VCI) after transcranial pulse stimulation (TPS) sessions.
Case Report: TPS is a non-invasive brain stimulation method. Stimulation was administered using NEUROLITH TPS generator (Storz Medical AG) with 3 Hz ultrashort pulses at 0.25 mJ mm-2 energy density over 12 sessions (6000 pulses per session), three times a week. Target areas included the bilateral DLPFC (1600 pulses per hemisphere), parietal regions (P3, P4) (800 pulses per hemisphere), and precuneus (PCu) (1200 pulses). Cognitive function tests were conducted before the first and after the last TPS session, including MMSE, MoCA-Ina, 15 Boston Naming Test Patient, Digit Span, CERAD (Visuoconstruction, Delayed Memory, Recognition, Verbal Fluency), and Trail Making Test A & B.
Discussion: Case 1 was a 48-year-old man with VCI and dysphasia post-stroke infarct (10 months prior), affecting the left caudate nucleus, left lentiform nucleus, and left internal capsule. The patient presented memory and executive function issues but preserved recognition. Case 2 was a 62-year-old man with VCI and anomic aphasia, following a cerebral infarction 5 months prior affected the left putamen, corona radiata, internal capsule, and globus pallidus. After 12 sessions, Case 1 showed amplification in working memory but had executive function challenges. Case 2 demonstrated improvement in immediate memory, recognition, and visuoconstruction, but had lingering issues with delayed verbal, visual memory, and executive function.
Conclusion: TPS stimulation of areas related to cognitive function appears to enhance memory, recognition, and other cognitive function. TPS may be a novel add-on therapy for VCI post-stroke patients.

Keywords: aphasia; noninvasive brain stimulation; stroke; transcranial pulse stimulation; vascular cognitive impairment

INTRODUCTION

Vascular Cognitive Impairment (VCI) is a spectrum of cognitive impairment due to cerebrovascular injury, which encompassing mild CVI, vascular dementia, and mixed dementia. Mild VCI is a decline in cognitive function that is not fully the diagnostic criteria for dementia. Vascular dementia refers to cognitively impairment which cause functional dependency due to vascular lesions, such as poststroke dementia, multi-infarct dementia, strategic infarct dementia, and

subcortical ischemic dementia. Meanwhile, mixed dementia is the result of both vascular and degenerative etiology.[1] Epidemiology of VCI is difficult to calculate because of the heterogeneity and limitation of current diagnostic criteria. However, the population-based Rotterdam study estimated the incidence of VCI was 0.1 per 1000 person-years in 60-64 years old population. The estimates increased to 7 per 1000 person-years in 90-94 years old population.[2] Knopman *et al* found that vascular disease accounts for 25% of dementia cases which showed significant vascular contribution to the pathophysiology of dementia.[3] Moreover, Schneider *et al* also found that 38% cases of dementia caused by infarct suggesting a significant role for vascular disease in dementia cases.[4]

VCI affects cognitive domains, such as attention, processing speed, executive function, but also affects neuropsychiatric aspects, such as behavioral and mood disturbance, sleep difficulty. Behavioral disturbance includes apathy, disinhibition, irritability, and psychomotor retardation. Meanwhile, depression is the most common mood disorder in VCI. Neuropsychiatric changes in VCI correlate associated with worsening cognitive function and functional status which significantly reduce patients' quality of life on social and healthcare aspects as well as their caregivers.[1,5] Therefore, the diagnosis and management of VCI should be addressed correctly to improve patients' quality of life.

The management of VCI required multidiscipline approach that involves pharmacological therapy, brain stimulation therapy, and other non-pharmacological modalities which focus on improving patients' and caregivers' quality of life. Nowadays, Non-Invasive Brain Stimulation (NIBS), such as Transcranial Magnetic Stimulation (TMS) has been shown to improve brain functions in neuropsychiatric diseases.[6] Cantone *et al* found that systematic TMS sessions in VCI patients can aid the diagnostic and therapeutic process, also predict the prognosis. After TMS sessions, affected cognitive domain and neuropsychiatric symptoms was improved in patients with VCI.[5] However, TMS has some limitations,

such as the limitation of spatial resolution from electrical conductivity which also affect other brain areas outer than the actual stimulation site, also it cannot access deep brain structure without affect the superficial layers.[6] In recent years, Transcranial Pulse Stimulation (TPS), a novel NIBS techniques that use single ultrashort ultrasound pulses, has emerged to overcome current limitations. Transcranial Pulse Stimulation (TPS) enables targeted brain stimulation in specific locations with a lateral resolution. It also can reach up to 8 cm into the brain, effectively targeting deep brain regions such as the thalamus, which is typically lying around 5 to 6.5 cm beneath the scalp.[7] There are several studies about the safety and efficacy of TPS in Alzheimer's disease and depression.[8–12] However, the study about the safety and efficacy of TPS in VCI management is still limited. Therefore, we reported our case of VCI that underwent TPS sessions to evaluate the cognitive function of Vascular Cognitive Impairment (VCI) after Transcranial Pulse Stimulation (TPS) sessions.

CASE ILLUSTRATION

Case 1 (Mr. A)

A 41 years old male was brought by family members due to incoherent speech for the past 15 hours since the last medical review. When engaged in communication, the patient's responses became slower, occasionally answering questions inaccurately. Upon examination, the patient could spontaneously open their eyes, but could not correctly answer the names of their children, although they could respond with the correct names of their spouse and themselves. Spatial orientation was limited to acknowledging the hospital, but when asked again, the patient mentioned the laboratory. There was a mistake in identifying the month, although they could still state the year. The patient reported a complaint of headache. One month prior to the current state, there were complaints of left-sided headaches with unknown characteristics, rated as Numeric Rating Scale (NRS) 2, and no analgesic medication was taken. Three days prior to hospital, the headache increased to NRS 4, and no medication was taken for one day. According to the wife, the patient's

habits have changed from usual. The behavior has become abnormal. There is no weakness on one side, slurred speech, facial asymmetry, fever, weight loss, or cough for more than two weeks.

From neurologic examination, patient had slight central type paresis of right facial nerve and right hemiparesis. From head CT scan, there was infarct affecting left caudate nucleus, left lentiform nucleus, and left internal capsule. There were no remarkable findings from blood test results. Aphasia concluded through evaluation using Indonesian aphasia test called TADIR (Tes Afasia untuk Diagnosis Informasi Rehabilitasi). Patient's neurobehavior state examination was found in Table 1.

The patient was diagnosed with post ischemic stroke, vascular cognitive impairment, stage 2 hypertension, and type 2 diabetes mellitus. Patient was given pharmacotherapy, including clopidogrel, aspirin, simvastatin, vitamin B, vitamin B12, folic acid, amlodipine, candesartan, and methylphenidate. Patient also had TMS and tDCS, then continued with TPS therapy for a total of 8 sessions and speech therapy.

Two months post TMS and tDCS therapy, the patient is more expressive than before. Seven months post TMS and tDCS therapy, the patient's memory has improved. However, the patient still sleeps a lot and lacks motivation or initiative. Ten months post TMS therapy, complaints have improved, but the patient sleeps more during the day and is still reluctant to perform routine activities such as the dawn prayer. Patient had tDCS on several locations such as, F3 and F4 areas with 2000 mA and 1200 s, left DLPFC area, left and right Broca area with 2000 mA and 1200 s, also with virtual reality daily for 2 weeks. Patient also had initial TMS sessions daily for 2 weeks on F3 area with 20 Hz and 1600 pulse, F4 with CTBS once, and right B with 4 Hz and 2000 pulse. Then, for maintenance TMS sessions, patient had stimulus on left D area with 20 Hz and 1600 pulse, right D area with CTBS three times, and PCU.

Three months after the last TMS session, the patient underwent TPS therapy for a total of 8 sessions. According to the family, a week later, the patient became more active, less drowsy, and started showing initiative

to wake up early for other activities. For TPS sessions, patient stimulated on left DLPFC area with a total of 1800 pulses for three times a week. Then, patient stimulated on both sides of DLPFC area with 1600 pulse, P3 and P4 area with 800 pulse, and PCU with 1200 pulse with a total of 6000 pulse for three times a week.

Case 2 (Mr. S)

A 62 years old male was brought by family members due to difficulty pronouncing words and pronouns for the past 3 days prior to admission. Patient seemed to be silent a lot with mood disorders, mispronounced children's names, and names of objects. Patient still understood the function of an object but could not say its name. Patient still able to spoke in a few words, but often struggle and mispronounces names, also had difficulty stringing sentences. Facial expressions were said to be flatter. There was no double vision. Patient still could follow commands. Patient had stroke 5 months prior to admission with right hemiparesis and speech impairment. However, patient already went to work and had a meeting. According to patient's wife, patient was able to drive a car several times.

From neurologic examination, patient was fully alert, but had dysphasia. Also, patient had central type paresis of left facial nerve and right hemiparesis. Patient's neurobehavior state examination was found in Table 1. Patient had cerebral infarction affected the left putamen, corona radiata, internal capsule, and globus pallidus 5 months prior to admission.

The patient was diagnosed with aphasia post ischemic stroke with vascular cognitive impairment. Patient was given pharmacotherapy, including citicoline, donepezil, clopidogrel, aspirin, atorvastatin, vitamin B complex, folic acid, amlodipine, vitamin D, and probiotic.

Patient had TPS therapy for a total of 8 sessions and speech therapy. The TPS protocol was three times a week with 6000 pulse each session with energy density 0,2-0,25 mJ/mm^2 and 3-4 Hz. TPS was given to both sides of DLPFC, P3, P4, and PCU areas. After each TPS sessions, patient was given speech therapy for 45-60 minutes. On fifth day of TPS sessions, patient said there was improvement on right hand sensory. On eighth day

of TPS sessions, patient said that his mood was better, but still had insomnia. On eleventh day of TPS sessions, patient had no complaints.

Table 1. Cognitive functions test results for each patient before the first and after the last TPS sessions

	CASE 1		CASE 2	
	Pre-assessment	Post-assessment	Pre-assessment	Post-assessment
MMSE (/30)	27	26	28	28
MoCA-Ina (/30)	20	24	23	25
Forward digit span	5	5	5	5
Backward digit span	0	4	3	3
CERAD: Trial I-III	2/3/4	2/4/4	2/5/4	4/6/6
15 Boston Naming Test (/15)	11	13	15	15
Verbal Fluency Test	7/min	6/ min	7/ min	13/ min
Visuoconstruction (/11)	11	11	7	11
Delayed Memory (/10)	0	1	0	4
Recognition (/10)	8	9.5	9	7.5
Trail Making Test A	1 min 21 sec	1 min 30 sec	54 sec	1 min 7 sec
Trail Making Test B	5 min 0 sec	4 min 19 sec	1 min 46 sec	2 min 59 sec

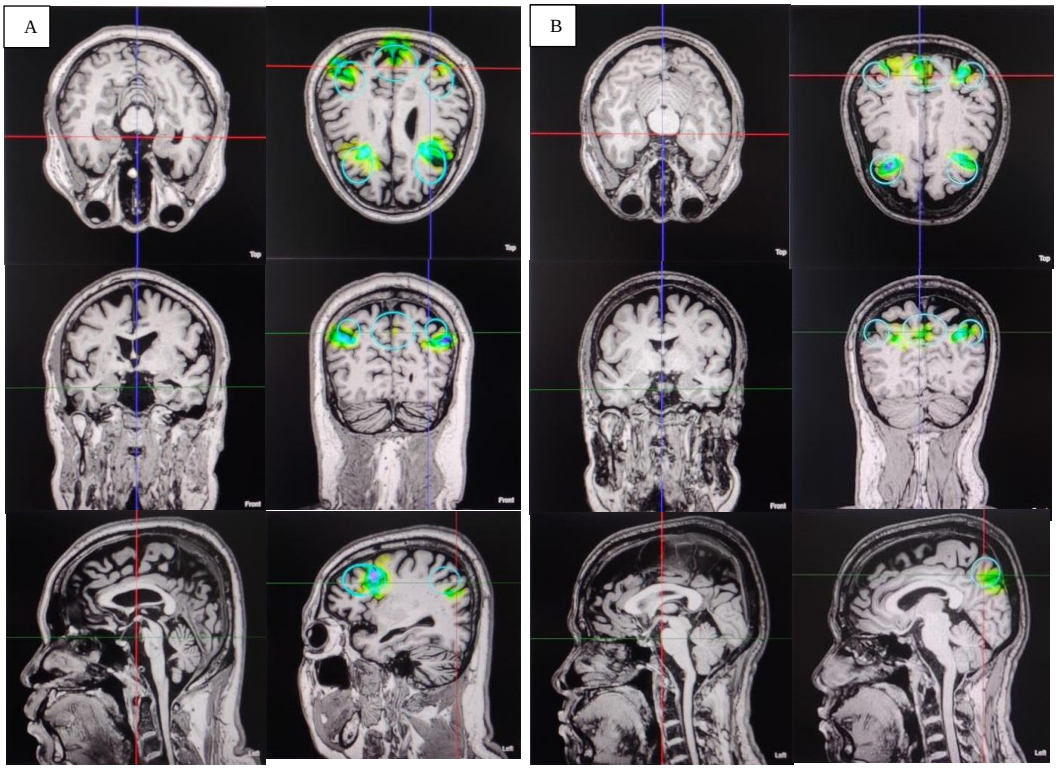

Figure 1. Head CT scan after TPS stimulation; (A) Patient of Case 1, (B) Patient of Case 2

DISCUSSION

We reported two cases of VCI post-stroke that underwent transcranial pulse stimulation in our center. We evaluated cognitive function tests before the first and after the last TPS session, including MMSE, MoCA-Ina, 15 Boston Naming Test Patient, Digit Span, CERAD (Visuoconstruction, Delayed Memory, Recognition, Verbal Fluency), and Trail Making Test A & B.

Case 1 was a 48-year-old man with VCI and dysphasia post-stroke infarct (10 months prior), affecting the left caudate nucleus, left lentiform nucleus, and left internal capsule. Case 2 was a 62-year-old man with VCI and anomic aphasia, following a cerebral infarction 5 months prior affected the left putamen, corona radiata, internal capsule, and globus pallidus. The definition of VCI was first described in 2006 by the NINDS in collaboration with the Canadian Stroke Network. In 2011, AHA/ASA scientific defines VCI as "a syndrome with evidence of clinical stroke or subclinical brain injury and cognitive impairment affecting at least one cognitive domain".[13] From this definition, both cases were diagnosed with VCI post-stroke. Our first case presented memory and executive function issues but preserved recognition. Meanwhile, our second case presented an anomic aphasia and depressive mood.

Both cases underwent a TPS session three times a week. TPS is a non-invasive brain stimulation method. Stimulation was administered using NEUROLITH TPS generator (Storz Medical AG) with 3 Hz ultrashort pulses at 0.25 mJ mm-2 energy density over 12 sessions (6000 pulses per session), three times a week. Target areas included the bilateral DLPFC (1600 pulses per hemisphere), parietal regions (P3, P4) (800 pulses per hemisphere), and precuneus (PCu) (1200 pulses).

Efficacy of Transcranial Pulse Stimulation for Vascular Cognitive Impairment

After 12 sessions, Case 1 showed amplification in working memory but had executive function challenges. Case 2 demonstrated improvement in immediate memory, recognition, and visuoconstruction, but had lingering

issues with delayed verbal, visual memory, and executive function. These showed that there was some improvement after the TPS session. We found no other studies investigate the effect and efficacy of TPS for VCI. However, Fong *et al* assessed the effectiveness of TPS in mild neurocognitive patients in old-age adults, not only limited to cerebrovascular etiology. The subject received neuro-navigated TPS intervention for two weeks with three sessions per week. In this study, TPS system used was consisting of mobile single transducer and infrared camera system for MRI based neuro-navigation. TPS generates single ultrashort (3 μs) ultrasound pulses with energy levels at 0.2-0.25 mJ/mm^2 and pulse frequencies at 4-5 Hz. This study used global brain stimulation where the total energy of 6000 pulses per sessions was distributed to all accessible brain areas homogenously. Fong *et al* assessed detailed cognitive assessment, APOE genotype, and brain-derived neurotrophic factor (BDNF). They found statistically significant effects of time on HK-MoCA (p=0.004), 30-sec interval of Verbal Fluency Test (p=0.041), Stroop interference (p=0.023), and Chinese IADL (p=0.05) after completed the whole TPS sessions. However, they found no significant difference in serum BDNF level.[14]

We also found similar studies that investigate the effect and efficacy of TPS for Alzheimer's disease. In Beisteiner *et al*, it is found that TPS improved significantly neurophysiological score after the whole sessions, and last up to three months.[8] Therefore, TPS has the potential to notably enhance cognitive function immediately following the procedure, with this improvement sustained over time.

Transcranial Pulse Stimulation (TPS) employs repetitive, single, ultrashort pulses within the ultrasound frequency to stimulate the brain. With a neuro-navigation device, TPS can precisely target specific areas of the human brain with high accuracy. This method differs from transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS), which utilize direct or induced electrical currents. The use of electrical current for brain stimulation may encounter limitations due to conductivity issues and difficulties in reaching deep brain

regions. In contrast, TPS utilizes low-intensity, focused ultrasound, offering excellent spatial precision and resolution for noninvasive modulation of subcortical areas. Despite the problem of skull penetration, TPS effectively enhances skull penetration in the human brain using lower ultrasound frequencies.[8,15]

Transcranial pulse stimulation uses the process of mechanotransduction which stimulate Vascular Growth Factors (VEGF) and Brain-Derived Neurotrophic Factors (BDNF) to improve cerebral blood flow, promote angiogenesis and nerve regeneration. The mechanical stimulus from TPS will stimulate the biochemical responses within the cells which influence some essential cells functions, such as migration, proliferation, apoptosis, and differentiation.[16,17] Therefore, it play an important role in the healing process of central-venous-system-based diseases. Besides, TPS also affect neuron and induce neuroplasticity through increased cell permeability, stimulation of mechanosensitive cells receptors, the release of nitric oxide which stimulate vasodilation, increased metabolic activity, and angiogenesis.[18]

In addition to neurocognitive impairment, patients in our case also experienced depressive mood. After the whole TPS sessions, patient had no complaint, his mood was getting better. Fong *et al* also evaluated depressive symptoms in VCI after the completion of TPS sessions using HAM-D-17. However, the improvement could not be explained. The HAM-D total score decrease from 12 weeks as usual treatment to 2 weeks post TPS sessions. Then, the HAM-D total score increase from 2 weeks post TPS sessions to 12 weeks follow up. Other studies also studied about the effect of TPS in patient with depression. Cheung *et al* studied about the effect of TPS in adult with depression. It showed a significant improvement, and the effect was sustainable at the 3-month follow up. It is concluded that TPS is effective in reducing depression among adults with major depressive disorder.[11]

Other study conducted by Matt *et al* also found similar results, but the population were patient Alzheimer's disease with depressive symptoms. It found a significant improvement changes in Beck Depression

Inventory (BDI-II) after TPS sessions.[12] In both studies, the area that was stimulated was an area related to depression, namely the extended Dorsolateral Prefrontal Cortex (DLPFC).[11,12] This area was selected because previous studies found that there is an imbalance between both sides of DLPFC in patients with major depression disorder.[19] Besides, previous study also found that the stimulated DLPFC by TMS or tDCS, can effectively improve the depressive mood.[20] Both studies showed that stimulation of this area showed progressive improvement to alleviate depressive symptoms in patients with major depressive disorder. In our cases, we also stimulated DLPFC area, and we found improved depressive mood, but unfortunately, we did not use quantitative instruments to evaluate the change in depressive symptoms. This suggests that TPS can also be used as a modality for diagnosis and treatment of depression or other neuropsychiatric disorders.

Safety of Transcranial Pulse Stimulation for Vascular Cognitive Impairment

In our case report, both cases did not complain any serious adverse effects after completed the whole TPS intervention. This is in line with Fong *et al* study which showed all participants (n=19) showed no serious adverse effects after completed the whole TPS intervention.[14] In systematic review conducted by Castano *et al*, 93% of subjects of included studies did not experience any adverse effect. Only 7% of the subject reported adverse events, including headache, dizziness, and paresthesia in the application area. These symptoms were reported with spontaneous resolution.[9] In other systematic review conducted by Chen *et al*, only 2 studies reported the side effects of TPS. The side effects were painless pressure sensation, pain, headache, mood deterioration, nausea, and drowsiness. However, the side effects lasted no longer than 1 day.[10] Therefore, TPS may be safe for the patient, but large-scale randomized trial are needed to confirm these findings.

CONCLUSION

TPS stimulation of areas related to cognitive function appears to

enhance memory, recognition, and other cognitive function as well as alleviate the depressive symptoms. TPS may be a novel add-on therapy for VCI post-stroke patients. We suggest further large-scale, randomized, controlled trials to study about the effect and safety of transcranial pulse stimulation on vascular cognitive impairment.

ACKNOWLEDGEMENT

All parties acknowledged must have been consented, do not put any identity of patients in the case report article here.

REFERENCE

1. Graff-Radford J. Vascular Cognitive Impairment. Continuum (Minneap Minn). 2019;25(1):147-64.
2. Ruitenberg A, Ott A, Van Swieten JC. Incidence of dementia: does gender make a difference?. Neurobiol Aging. 2001;22:575-80.
3. Knopman DS, Parisi JE, Boeve BF, et al. Vascular Dementia in a Population-Based Autopsy Study. Arch Neurol. 2003;60:569-75.
4. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69(24):2197–204.
5. Cantone M, Lanza G, Fisicaro F, et al. Evaluation and treatment of vascular cognitive impairment by transcranial magnetic stimulation. Vol. 2020, Neural Plasticity. Hindawi Limited; 2020.
6. Matt E, Kaindl L, Tenk S, et al. First evidence of long-term effects of transcranial pulse stimulation (TPS) on the human brain. J Transl Med. 2022 Dec 1;20(1).
7. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. Hum Brain Mapp. 2018 May 1;39(5):1995–2006.
8. Beisteiner R, Matt E, Fan C, et al. Transcranial Pulse Stimulation with Ultrasound in Alzheimer's Disease—A New Navigated Focal Brain Therapy. Advanced Science. 2020 Feb 1;7(3).
9. Fernández-Castaño R, Fernández-Blázquez MÁ, Echevarría Fernández I, Cabrera-Freitag M, Freitag K. Effect of Transcranial Pulse Stimulation for the Treatment of Alzheimer´s Disease and its Related Symptoms. Curr Alzheimer Res. 2023 Jul 27;20(4):244–9.
10. Chen X, You J, Ma H, Zhou M, Huang C. Transcranial pulse stimulation in Alzheimer's disease. CNS Neurosci Ther. 2024 Feb 1;30(2).
11. Cheung T, Li TMH, Ho YS, Kranz G, Fong KNK, Leung SF, et al. Effects of Transcranial Pulse Stimulation (TPS) on Adults with Symptoms of Depression—A Pilot Randomized Controlled Trial. Int J Environ Res Public Health. 2023 Feb 1;20(3).
12. Matt E, Dörl G, Beisteiner R. Transcranial pulse stimulation (TPS) improves depression in AD patients on state-of-the-art treatment. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2022;8(1).
13. Rundek T, Tolea M, Ariko T, Fagerli EA, Camargo CJ. Vascular Cognitive Impairment (VCI). Vol. 19, Neurotherapeutics. Springer Science and Business Media Deutschland GmbH; 2022. p. 68–88.
14. Fong TKH, Cheung T, Ngan STJ, Tong K, Lui WYV, Chan WC, et al. Transcranial pulse stimulation in the treatment of mild neurocognitive disorders. Ann Clin Transl Neurol. 2023 Oct 1;10(10):1885–90.
15. Minjoli S, Saturnino GB, Blicher JU, Stagg CJ, Siebner HR, Antunes A, et al. The impact of large structural brain changes in chronic stroke patients on the electric field caused by transcranial brain stimulation. Neuroimage Clin. 2017;15:106–17.
16. d'Agostino MC, Craig K, Tibalt E, Respizzi S. Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction. Vol. 24, International Journal of Surgery. Elsevier Ltd; 2015. p. 147–53.
17. Zhang J, Kang N, Yu X, Ma Y, Pang X. Radial Extracorporeal Shock Wave Therapy Enhances the Proliferation and Differentiation of Neural Stem Cells by Notch, PI3K/AKT, and Wnt/β-catenin Signaling. Sci Rep. 2017 Dec 1;7(1).
18. Mariotto S, Cavalieri E, Amelio E, Ciampa AR, De Prati AC, Marlinghaus E, et al. Extracorporeal shock waves: From lithotripsy to anti-inflammatory action by NO production. Nitric Oxide. 2005;12(2):89–96.
19. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. Biol Psychiatry. 2008 Feb 15;63(4):369–76.
20. Liu S, Sheng J, Li B, Zhang X. Recent advances in non-invasive brain stimulation for major depressive disorder. Vol. 11, Frontiers in Human Neuroscience. Frontiers Media S. A; 2017.