Combined rTMS To The Auditory cortex and Prefrontal Cortex For Tinnitus Control in Patients with depression.

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Directed by Professor Jae-Young Choi

The Master's Thesis

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ABSTRACT

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Objectives:

Recent studies suggest that the neuronal changes of the chronic tinnitus are beyond the auditory pathway. There is increasing evidence for repetitive transcranial magnetic stimulation (rTMS) on multiple brain cortex in addition to the auditory cortex for the treatment of tinnitus by various institution.We tried sequential treatment of rTMS on auditory cortex only and auditory area combined with prefrontal area in patient with both chronic tinnitus and depression.

Methods:

We recruited and enrolled patients who present chronic tinnitus more than one year with depressive symptom(4 male, 4 female, mean age 57). To select the site for the rTMS PET CT was performed. Patients received 1st rTMS on the primary auditory cortex for 5 days and on the primary auditory cortex and prefrontal cortex in the second treatment after relapse of tinnitus . THI(Tinnitus handicap inventory), VAS(Visual analog scale) and BDI were checked before and after rTMS.

Results:

The mean THI score of 8 patient changed 77.5 to 61.8 after 2nd TMS. There was statistical significance only in 2nd rTMS. The VAS score changed 8.6 to 6.2 after 1st rTMS and 7.6 to 4.6 after 2nd rTMS which means statistically significant changes on both time on VAS score. The changes of THI after 2nd TMS was bigger than 1st and the changes of VAS score shows similar pattern. The changes of BDI score, which indicates the severity of depression shows variable pattern

after rTMS. Patients with mild depression(BDI score < 10, n=4) showed much improvement of THI with 2nd combined rTMS (delta THI 24.5) than with the 1st rTMS on auditory area (delta THI 5.5). In contrast, combined rTMS showed no better effect on THI improvement(delta THI 6.5) than 1st rTMS on auditory cortex (delta THI 9) in patients with moderate to severe depression (BDI > 10, n=4)

Conclusions:
Our study showed that combined rTMS on auditory cortex and prefrontal area has more benefit than rTMS on auditory area only on tinnitus control in patients with depression. Further studies for the most optimal combination of the stimulation on both area in needed.

Key words : tinnitus, depression, repetitive transcranial magnetic stimulation, brain

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I. INTRODUCTION

Chronic tinnitus is defined as a perception of sound in the absence of sound stimuli. About 10 to 15% of the adult population affected by tinnitus.[1] Various treatment modalities such as medication, retraining and electrical stimulation has been proposed for tinnitus therapy. However, these modialities are effect only a partial group of patients.

There are various hypothesis to explain the development and aggravation of the tinnitus. However, the exact mechanism underlying the tinnitus is still unknown. Recent studies suggest that the neuronal changes of the chronic tinnitus are beyond the auditory pathway. According to the neurophysiological model suggested by Jastreboff, the development and perception of the tinnitus connected with not only auditory area but subcortical and prefrontal area where control the autonomic nerve system and mood.[2-6] The development and aggravation of tinnitus is also related to the depression.[7] The prevalence rates of depressive disorders in patients with tinnitus fall between 14% and 80%.[8-9] Recent neuroimaging study showed prefrontal area where the integration of cognitive and emotional precessing occurs are involved in the development of chronic tinnitus. Based on these relationship, antidepressive medication such as tricyclic nortriptyline and serotonin reuptake inhibitor improve tinnitus as well as depression.[10-11]
.

Repetitive magnetic stimulation(rTMS) which can noninvasively stimulates specific area of brain cortex is widely used for the treatment of various psychological disease. Especially, stimulation of prefrontal area with rTMS has been proved to be effective in

patients with depression.[12-15]rTMS of the auditory cortex has shown beneficial effect for the treatment of chronic tinnitus[16-17] . Nevertheless, stimulation related issues, such as duration, intensity as well as predictors of response. Recently, rTMS on multiple brain cortex in addition to the auditory cortex has been tried for the treatment of tinnitus.[18] Regensburg et al. showed that combined rTMS on frontal and temporal brain cortex were more effective than rTMS on temporal area only. [19] However, low-frequency left temporal rTMS with low-frequency right dorsolateral prefrontal cortex did not showed more benefit.[20]

We tried sequential treatment of rTMS on auditory cortex only and auditory area combined with prefrontal area in patient with both chronic tinnitus and depression. In our comparision, combined rTMS on autitory cortex and prefrontal area has more effect on tinnitus suppression in patients group with mild depression than the effect of rTMS on auditory cortex only.

II. MATERIALS AND METHODS

1. Patients

Eight patients(4 male, 4 female, mean age 57) with chronic subjective tinnitus more than 1 year were included in this study. All the patient have depressive symptom more than 10 BDI(Beck Depression Inventory) score.[21] The patients received various medical therapy for tinnitus such as gingko extract but did not take any medication for depression. This study has been approved by the local ethics committee. Table 1 showed the detailed profile of the patients.

Table 1. Patient data

No.	Sex	Age	History	Site	PTA*	BDI
1	M	61	None	L	13 27	14
2	M	46	None	B(L>R)	13 33	11
3	M	65	COM(B)	L	25/10 S.O.	24
4	F	44	SSNHL(R)	B(R>L)	15 12	13
5	F	70	SSNHL(R)	B	25 20	14

6	F	67	SSNHL(R)	R	53	17	36
7	F	52	Behcet's disease	R	13	13	17
8	M	52	None	B(L>R)	63	73	26

B both , *R* right, *L* left
COM chronic otitis media
*SSNHL*sudden sensory-neural hearing loss
*average of pure tone audiometry over 500, 1000, 2000 hertz
S.O. scaled out

2. Treatment protocol

Before rTMS history taking and systemic physical examination were performed. Pure tone audiometry showed mild hearing loss in 3 patients and moderate hearing loss in 2 patients. One patient (No. 3) have unilateral deafness who suffered from chronic otitis media. THI(Tinnitus handicap inventory),[22] VAS(Visual analog scale)[23] and BDI were checked before and after rTMS. To select the site for the rTMS PET CT was performed. 1st rTMS was applied on the primary auditory cortex for 5 days and 2nd rTMS was performed on the primary auditory cortex and prefrontal cortex. Figure 1 shows the flow of the treatment.

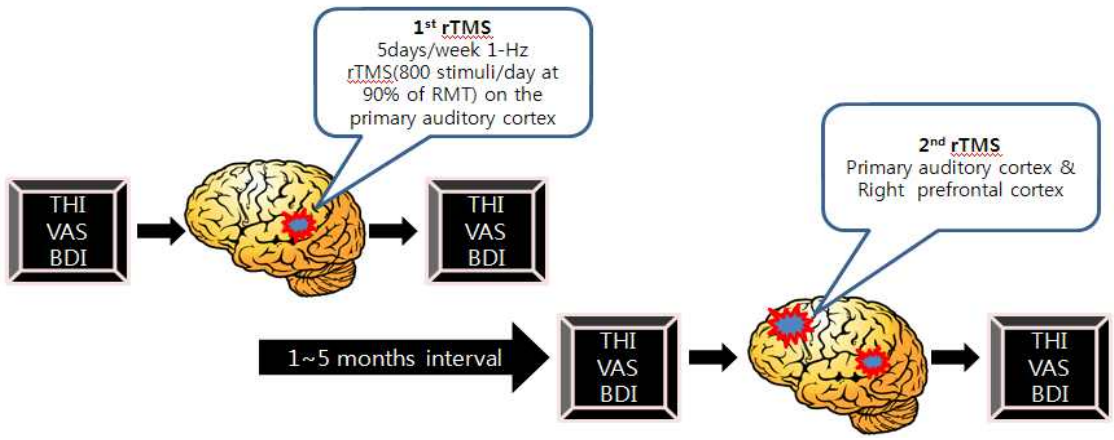


Figure 1. Flow chart

3. Imaging

A baseline FDG-PET/CT scan before rTMS treatment FDG-PET scan were performed using a Biograph 6 PET CT scanner(Siemens Medical Systems,

Malvern, PA). The CT portion was a six-Siemens Sensation helical CT scanner, and the PET portion had ‘‘Hi-Rez’’VR LSO (lutetium silicate oxime) 4-mm crystals arranged in a full-ring gantry with high-speed Pico Electronics TM. Images were acquired 30 minutes after the intravenous administration of 12mCi (444 MBq) FDG (fluorodeoxyglucose). Automated analysis of the PET brain studies was performed by the NeuroQTM Display and Analysis Program Version 2.0 (Cardinal Health,Dublin, OH). This system expresses activity within predefined regions of the participant’s brain image as standard deviations of the mean activity, in the same predefined regions, obtained from a normal PET brain database of 50 patients. The registration algorithm for fitting the patient’s brain scans to the normal template was a robust spatial transformation method.[24-25]

4. rTMS and delivering stimulation

A MagPro TMS unit connected to a Medtronic C-B65 figure-of-8 shaped coil were used to deliver stimulation (Magstim Company, Whitland, Wales, UK). Medtronic (Medtronic Corporation, New York, USA) A targeting algorithm was developed as follows: 1) the temporal lobe PET asymmetry was targeted when it was both clear and accessible to rTMS, 2) the posterior one third portion of the superior temporal gyrus that lies opposite to the ear with loudest tinnitus was targeted if PET asymmetry was not accessible to rTMS, and 3) the same location in the left hemisphere was targeted when no PET asymmetry was accessible and when tinnitus perception could not be lateralized.[26] The right temporal lobe was targeted for treatment in 3 subjects, and the left temporal lobe was targeted in 5. During the first treatment, rTMS was applied all 8 patients one time per day at an intensity of 110% of the motor threshold (MT) measured that day and at a rate of 1 Hz for 800 pulses per Session (8 seconds on, 2 seconds off, over 16 minutes) on the auditory cortex only. Treatment was delivered for five consecutive days (4,000 pulses total). After one to five months 2nd rTMS was applied on both auditory and prefrontal areas. Stimulation was administered over the right prefrontal cortex by the same intensity to the 1st stimulation(4000 pulses, 1Hz, 110% RMT) and stimulation of auditory cortex was done in the same way. According to International 10-20 electrode position T3 (left) or T4(right) overlie primary auditory cortex on each side of the head, and F4 overlies right prefrontal cortex.[27-30]

5. Statistical analysis

The statistical analysis was performed on T-test, Wilcoxon test using SPSS. Factors were considered to be significant at the 5% level.

This study was approved by the Institutional Review Board at Yonsei University College of Medicine.

III. RESULTS

1. The acitivation of Auditory cortex

The PET imaging befroe rTMS showed hyperactivities on the auditory cortex in all the 8 patients. Rt auditory cotex 3, Lt autitory cortex 3 and Both 2). Of these, the direction of PET hyperactivity opposite to the direction of tinnitus was not found.

2. Effets of rTMS on tinnitus

All the patients were tolerable during the rTMS and there was no reported side effects after rTMS. The 1st rTMS on the primary auditory cortex improved THI score in6 out of 8 patients after rTMS and the THI score get worse 4-8 weeks after 1stTMS except one patient (Number 8). The rest 2 out of 8 patients did not response to the 1stTMS. The response to 2nd rTMS on both prefrontal and temporal area is also variable. 6 out of 8 patients showed good response to 2nd TMS but 1 patient did not respond. The THI socre got worse in a patent 1. (Figure 2)

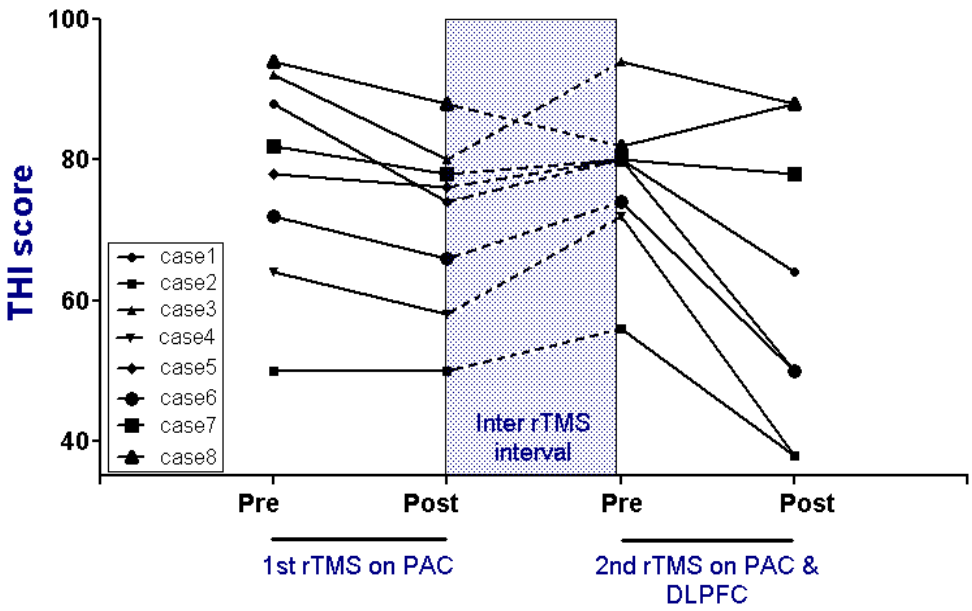
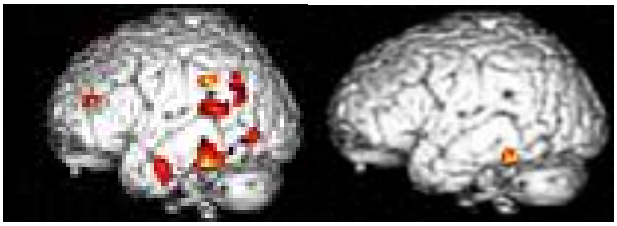


Figure 2

Figure 2. The changes of THI score with serial TMS on auditor

cortex only (1st rTMS) and combined auditory cortex and prefronal area(2nd rTMS) 2 patients out of 8, symptoms after first treatment did not chage, but has responded to the second treatment.



Figuer 3. PET CT shows the changes of FDG uptake after rTMS. Hot spots on both temporal and prefrontal areawere disappeared after serial rTMS.(Patient 1)

3. Comparison of the effect on tinnitus of rTMS ; temporal v.s temporal + prefrontal

We compared the effect of 1st and 2nd rTMS on tinnitus. The mean THI score of 8 patient changed 77.5 to 61.8 after 2ndTMS. There was statistical significance only in 2nd rTMS. The VAS score changed 8.6 to 6.2 after 1st rTMS and 7.6 to 4.6 after 2ndrTMS which means statisticallysignificant changes on both time on VAS score(Figure 4). The changes of THI after 2nd TMS was bigger than 1st(Figure 5) and the changes of VAS score shows similar pattern(Figure 6).

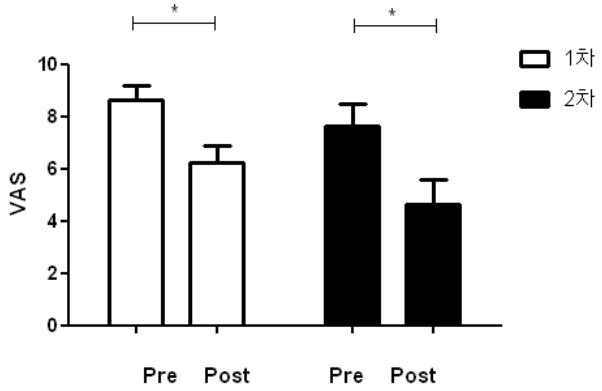


Figure 4. Changes on VAS score

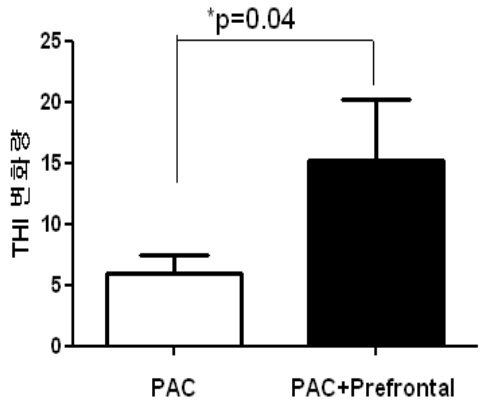


Figure 5. Variance of THI

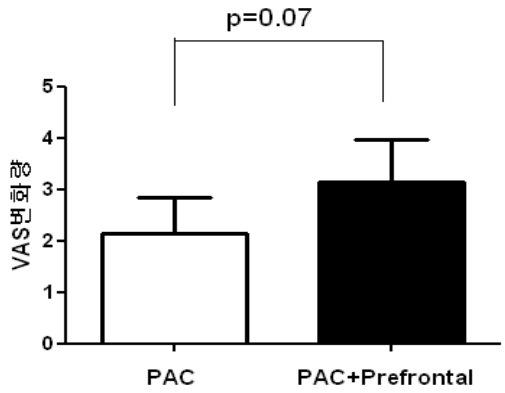


Figure 6. Variance of VAS

4. Effects of rTMS on depression

The changes of BDI score, which indicates the severity of depression shows variable pattern after rTMS. The 1st rTMS on auditory cortex improved BDI score in 5 out of 8 patient but the BDI socre got worse in 3 patients. Only 2 patients showed mild improved in BDI score after 2nd rTMS on both prefrontal and temporal area is also variable. The BDI scoreshowed no changes or worse in the rest 6 patients. The mean BDI score of 8 patients did not change significantly after both 1st and 2nd rTMS. (Figure 7, 8)

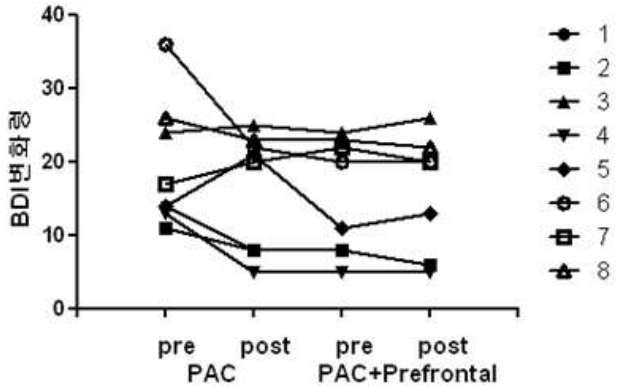


Figure 7. The changes of BDI score

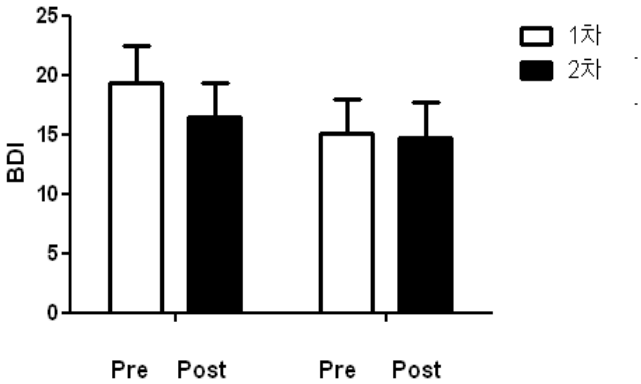


Figure 8. Variance of BDI

5. The effect of rTMS accoriding to the BDI socre

We divided the patients into two groups according to the severity of depression. Patients with mild depression(BDI score< 10, n=4) showed much improvement of THI with 2nd combined rTMS(delta THI 24.5) than with the 1st rTMS on auditory area(delta THI 5.5).In contrast, combined rTMS showed no better effect on THI improvement(delta THI 6.5) of combined treatment than 1st rTMS on auditory cortex(delta THI 9) in patients with moderate to severe depression(BDI> 10, n=4)(Figure 9). This result shows that combined rTMS has more effect on tinnitus suppression in patients with mild depression than patients with moderate to severe depression.

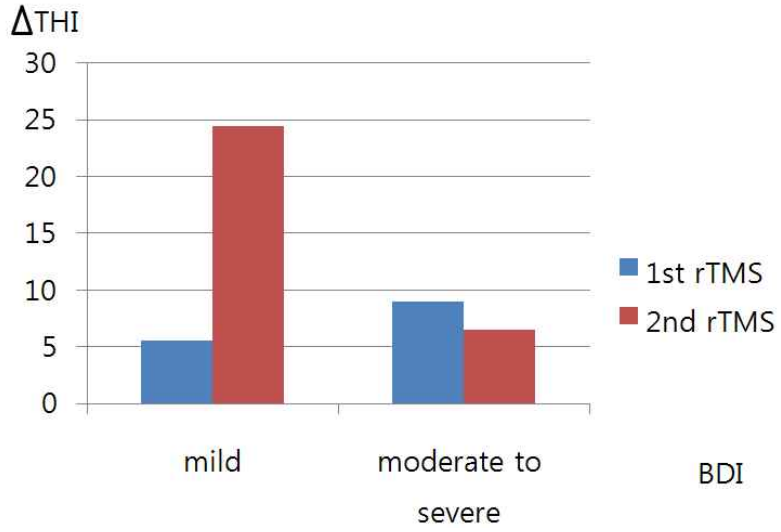


Figure 9. The effect of rTMS accoriding to the BDI socre

IV. DISCUSSION

Because rTMS is effective on both depression and tinnitus, rTMS on both prefrontal area and auditory cortex applied on the same time in several previous studies. Kreuzer et al. enhanced the effect of low-frequency left temporal rTMS on tinntus with the low-frequency right dorsolateral prefrontal cortex [20]. Regensburg et al. recently reported that combination of high-frequency rTMS on prefrontal area and low-frequency tempora rTMS on auditory cortexshowed a trend toward more pronounced effects on tinnitus control than low frequency temporal rTMS alone. However, the inter-individual variability has been high in both treatment groups which indicates that more individualized treatment approach is needed. Therefore, we tried serial rTMS on auditory cortex alone and combination auditory and prefrontal area in the same patients. We expected that the combination rTMS has better effect on tinnitus in patients with severe depression. However, our study showedthat combination rTMS has much better effect in the tinnitus patient with mild depression. We interpretate this result that the network between auditory area and prefrontal area is not fixed in these group of patients, so the combination rTMS showed more effect.

The effect of rTMS on depression was variable among patients, and the mean BDI score was not changed after 1st or 2nd rTMS, which would be expected if rTMS had not directly resulted in mood changes. As in our result, the anti-depressive effect ofrTMS on prefrontal area is not consistent. Moreover, Kreuzer PM et al. also did not observe statistically significant change in the BDI scores after combined rTMS on both

auditory cortex and prefrontal area.[20] These results indicates that the tinnitus suppression effects is not due to the result of a potential antidepressant effect of frontal rTMS. Because the DLPFC is part of the temporal-prefrontal network, which is considered critical for transient storage of auditory stimuli. Therefore, an rTMS of the DLPFC can disrupt neuronal activity involved in tinnitus maintenance. One interesting aspect of our data is that the BDI score improved after 1st rTMS on auditory area alone. These data suggest that the depressive mood comes from the tinnitus in some patients.

V. CONCLUSION

Although limited number of the patients, our study showed that combined rTMS on auditory cortex and prefrontal area has more benefit than rTMS on auditory area only on tinnitus control in patients with depression. Further studies for the most optimal combination of the stimulation on both area in needed.

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ABSTRACT(IN KOREAN)

우울감을 동반한 이명 환자에서 청각 피질과 전전두 피질에 대한combined rTMS 의 효과

<지도교수 최재영 >

연세대학교 대학원 의학과

박세라

목적:
최근의 연구에 따르면 만성 이명에서의 신경학적인 변화는 청각 전달로 이후의 것으로 제시되고 있으며, 여러 기관의 연구를
통해 청각 피질 뿐 아니라 뇌의 여러 군데의 피질을 자극하는 것이 이명의 치료에 도움이 된다는 증거들이 제시되고 있다. 본 연구에서는 우울감을 동반한 만성 이명 환자에서 청각 피질만을 자극하여 치료 후 청각 피질과 전전두 피질을 복합 자극 하는 순차적 rTMS의 효과를 보고자 하였다.

방법:
본 연구에서는 우울감을 동반하며 1년 이상의 만성 이명을 호소하는 8명의 환자를 대상으로 하였다. (남자 4명, 여자 4명, 평균 연령 57세) rTMS 자극 방향을 정하기 위하여 PET CT를 시행하였으며 환자는 5일간의 1차 치료로서 일차 청각 피질에 rTMS를 받았으며, 증상 재발 후의 2차 치료로 일차 청각 피질과 전전두 피질에 복합 rTMS를 받았다.

결과:
8명의 환자의 평균 THI는 2차 치료 후 77.5에서 61.8로 감소하였으며, 이차 치료 후에만 통계학적인 유의성이 관찰 되었다. VAS 점수는 1차 치료 후 8.6에서 6.2로, 이차 치료 후 7.6에서 4.6으로 감소하였으며 2번의 치료 모두에서 통계학적 유의성을 보였다. THI와 VAS 모두 1차 치료 보다 2차 치료 시 변화량이 더 큰 경향을 보였다. 우울감의 정도를 나타내는 BDI 변화량은 다양한 패턴을 보였으며, BDI 10미만의 경한 그룹(4명)에서 1차 치료(THI 변화량 5.5)보다 2차 치료(THI 변화량 24.5)이 훨씬 큰 결과를 보였다. 반대로, BDI 10이상의 중고도 그룹에서는 1차 치료와 2차 치료 간의

THI 변화량에 유의한 차이를 보이지 않았다.

결론:
본 연구를 통해 우울감을 동반한 이명에서 청각 피질과 전전두 피질에 대한 combined rTMS가 청각 피질만을 자극했을 때보다 효과적이었으며 이와 같은 양 측 영역의 치료에 대한 향후 연구가 더욱 필요할 것으로 생각된다.

핵심되는 말 : 이명, 우울증, 반복적 경두개 자기 자극술, 뇌