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Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) in Inducing Weight Loss among Obese Filipino Patients: A Randomized Controlled Trial

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Abstract

Objective. To determine the efficacy of rTMS in decreasing body mass index (BMI) versus sham stimulation among obese Filipino patients.

Methodology. This was a single-center, randomized, sham-controlled, single-blind, parallel group trial. Participants were 15-65 years old with BMI ≥30 kg/m^2 and weight stable for 6 weeks. Participants were randomized to receive real rTMS or sham stimulation. Each underwent 4 sessions of stimulation over 2 weeks. Anthropometrics, total caloric intake (TCI), and VAS score for appetite were taken at baseline, 2, 4, 6, and 12 weeks.

Results. A total of 31 patients were randomized with 15 to the treatment and 14 to sham stimulation completing treatment, with 2 lost to follow-up. A significant decrease in BMI was noted after 4 weeks from the start of rTMS in the treatment group, (0.6±0.6, *p-value*=0.001), with weight change of -1.3±1.3 kg (*p-value*=0.009), but was no longer observed at 6 weeks onwards. No severe adverse effects were noted.

Conclusion. rTMS to the DLPFC effectively decreased BMI (0.6±0.6) and weight (-1.3±1.3 kg) from baseline to 4 weeks. At 6-12 weeks after rTMS however, there was no longer a significant difference, indicating that 4 sessions of rTMS may not be enough to produce a prolonged effect on weight loss.

Key words: obese, repetitive transcranial magnetic stimulation, weight loss

BACKGROUND

Obesity is characterized by excessive fat accumulation, causing adverse effects on health and well-being.[1,2] According to the Asia-Pacific guidelines, obesity is defined as a body mass index (BMI) of more than 25 kg/m^2. It is considered as a fast-growing epidemic which occurs in about 500 million adults, with its prevalence increasing in adolescents and children.[3] Obesity is linked to several disease entities that are leading causes of morbidity and mortality worldwide. These include type 2 diabetes mellitus, cardiovascular disease, cancer, and metabolic syndrome.[4]

Previously, non-pharmacologic treatment such as lifestyle modification was the first line of treatment in obesity. However, recent studies have shown that the success rate of lifestyle modification alone is low.[5]

Several studies have explored the link between food cravings and incidence of obesity. In patients who were obese, there is a lack of stimulation of the dorsolateral prefrontal cortex (DLPFC) in response to food, leading to increased food cravings.[6] Furthermore, stimulation of this area also reduced the neural activity in more remote areas like the orbitofrontal and anterior cingulate cortex,[7] and this further reduces food cravings. With less cravings, it is speculated that there will be decreased food consumption and overall weight loss.

rTMS is a non-invasive neuromodulation procedure that involves delivering magnetic waves at a high frequency. Research from animal studies have shown that activity in the prelimbic region (the homologous prefrontal cortex in rodents) is decreased by chronic cocaine use, and stimulation of the prelimbic cortex decreases compulsive cocaine seeking which is similar to addictive behavior in humans. Therefore, when the dorsolateral prefrontal cortex is stimulated by rTMS, it may decrease cortical activity and improve cognitive control. These studies were then applied to human behavior.[8]

rTMS delivered to the left DLPFC has been associated with reduction in cravings and subjective urge to smoke, both of which are associated with addictive behavior.[9] It is also currently accepted as a treatment option for several

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neuropsychiatric disease conditions like depression, bipolar disorder, Alzheimer's disease and Parkinson's disease.[2]

TMS is generally well tolerated and has been used for several years. Reported mild adverse effects of rTMS occur in about 5% of 1270 sessions among 113 patients who underwent rTMS according to a study by Maizey et al., in 2012.[10] Among these patients, 37% of reported mild adverse effects were related to anxieties and expectations regarding TMS.[10] These mild adverse effects included mild headache, stinging skin sensation, and nausea.

According to the Safety Guidelines on TMS published by Rossi et al., in 2009, the risk of rTMS to induce seizures is very low, at less than 1% of the population. In a review of accidental seizure events during TMS, 3 or 4 instances of seizures that occurred and have temporal relationship with receipt of TMS, 6 of 8 instances occurred in patients taking epileptogenic medications or have seizures already occurring as part of their disease, and 3 of 8 cases may represent non-epileptic events such as anxiety or syncope.[11]

Local pain and headache are also described and may occur in 28% and 39% respectively. The percentage of those who discontinued treatment due to pain is <2%, and was often relieved by oral pain relievers like NSAIDS.[11]

On review of existing literature, most studies explored the effect of rTMS on reducing food cravings after only 1 session of treatment. The assessment of impact on food cravings and appetite came immediately after the rTMS. These showed that rTMS did reduce food cravings, however this did not result in immediate reduction in food intake. One of the reasons cited was that the evaluation of treatment came after only one session, and thus its longer-term benefits were not explored.[9]

A study conducted by Se-Hong Kim in 2018[4] is a randomized, single-blind, sham-controlled trial conducted in Korea which enrolled 60 participants, divided equally and received either rTMS to the left DLPFC or sham stimulation over 2 weeks. Results showed that at the 4th week, participants who received rTMS showed a significant weight loss from baseline after 4 sessions (-1.35±2.31 kg vs 0.45±1.28 kg), reduction in BMI, fat mass and visceral adipose tissue compared to sham stimulation. These participants also had lesser appetite and consumed less kilocalories per day. This study is more beneficial to current clinical setting as it has significant influence in the management of obesity.

One of the limitations cited in the study was that the effect of rTMS was only studied up to 2 weeks after the last session. The long-term or permanent effect of rTMS even after the intervention has been discontinued has not yet been fully explored. Likewise, a similar study has not yet been conducted in the Filipino population.

OBJECTIVES

The general objective of the study was to compare the efficacy of rTMS in decreasing BMI versus sham stimulation among obese patients at St. Luke's Medical Center, Quezon City (SLMC QC). Specific objectives were: 1) To describe and compare the following parameters among obese Filipino patients who received rTMS versus sham stimulation over a period of 12 weeks: change in body mass index, change in appetite and food cravings and change in actual total caloric intake (TCI) 2) To describe the safety of rTMS, including serious adverse effects like seizures.

METHODOLOGY

Trial Design

This was a single-center, randomized, sham-controlled, single-blind, parallel group trial. Only the participants, and not the study staff, were blinded to the treatment given.

Participants

Participants included social service and private Filipino outpatients SLMC QC who were 15-65 years old with BMI ≥30 kg/m^2 who remained weight stable (±5%) for 6 weeks. Exclusion criteria were: history of prior rTMS, history of head injury or epilepsy/ seizure disorder, pacemaker, body metallic implants and other contraindications to MRI or rTMS, use of weight loss drugs within the past year or very low calorie diet, pregnancy or breastfeeding, eating disorder or substance dependence, current psychiatric illness or use of psychotropic medications, unstable cardiovascular disease (recent MI or stroke within 1 year, heart failure, acute limb ischemia, severe peripheral arterial occlusive disease), neurologic deficits based on initial physical exam, presence of other underlying causes of obesity (hypothyroidism, Cushing's syndrome, hypogonadism, insulinoma) noted on history or physical examination, and current use of cochlear implants.

Randomization/Allocation

Participants were randomized to receive either real rTMS plus standard of care non-pharmacologic therapy or sham stimulation plus standard of care non-pharmacologic therapy through sealed randomization envelopes, in a 1:1 ratio.

The primary investigator and the staff who performed rTMS were aware of the treatment allocation whereas participants were blinded.

Intervention

Baseline assessment included anthropometrics, laboratory results, Visual Analog Scale (VAS) score for appetite and average total daily caloric intake.

Anthropometric measurements included weight, height and body mass index. The height of each participant was measured up to the nearest 0.1 centimeter. The weight was measured using the same standing weight scale in the SLMC QC Weight Management Center, up to the nearest 0.1 kilogram. Body mass index was determined by dividing the weight of the participant in kilograms from the square of the height in meters. Waist circumference was measured to the nearest centimeter at the end of the normal expiration in a horizontal plane immediately superior to the left iliac crest (using the National Health and Nutrition Examination Survey protocols). Blood pressure was measured using an aneroid sphygmomanometer, and heart rate was obtained through palpation of radial pulse over 1 minute.

Each participant also underwent the following laboratory tests prior to initiation of the study: Thyroid stimulating

hormone, fasting blood sugar, glycohemoglobin, total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, 12-lead ECG, serum creatinine and complete blood count.

Appetite was measured using 10 cm visual analog scales measuring "urge to eat", "hunger," and "prospective food consumption." These were obtained at the start of the study, immediately after rTMS (week 2), 2 weeks after rTMS (week 4), 4 weeks after rTMS (week 6), and 10 weeks after rTMS (week 12). These scales are 10cm line scales with each end labeled with opposite attributes e.g., for hunger – "not hungry at all" and on the other end "extremely hungry," with different attributes of increasing intensity of hunger placed at 1 cm intervals. The participants were asked to encircle the category which best described his/her hunger state.

TCI was measured through a 3-day food diary, taken at baseline, at 2 weeks, at 4 weeks, at 6 weeks, and at 12 weeks of intervention. Food and beverage intake were recorded over 3 nonconsecutive days, including one weekend day. Average daily TCI was monitored and calculated by a nutritionist.

Study participants underwent either rTMS or sham stimulation according to the group to which they were randomized. There was a total of 4 rTMS sessions done at St. Luke's Medical Center Global City Institute of Neurosciences, provided over 2 non-consecutive days a week for 2 weeks. The TAMAS CR Technology device with either real or sham butterfly magnetic coil was used to administer rTMS. After mapping the abductor pollicis brevis site in the left motor cortex, the motor threshold for each participant was obtained as the minimum stimulus needed to induce contraction of the right thumb.[4]

For the treatment group, the site for stimulation of the left DLPFC was 5 cm anterior to and in the same parasagittal plane as the site of maximal abductor pollicis brevis stimulation. Twenty trains of 5 seconds with 55-second intertrain intervals were given at a frequency of 10 Hz and intensity of 110% of the participant's motor threshold, providing a total of 1000 pulses over 20 minutes.[4]

In the sham group, the sham-coil was placed over the interhemispheric fissure at the vertex, and stimulation is at low intensity (10% of resting motor threshold), enough to produce similar skin sensations as real rTMS.[4] Blinding was achieved in this way: both arms received a form of stimulation but the area and intensity are different. The staff and investigators were aware of their allocation but did not disclose such to the participants.

As part of standard of care, each participant in both treatment and sham groups was enrolled in a 6-week standard weight management clinic, which included nutrition counseling, 18 sessions of consultation (3-4 times a week), and guided exercise/use of gym. Prior to entry in the weight management program, each participant underwent cardiac clearance. The same physician also evaluated the patient at the end of the program. The rTMS sessions were done during the first 2 weeks of the 6-week weight management intervention. Figure 1 represents a schematic diagram of the study design.

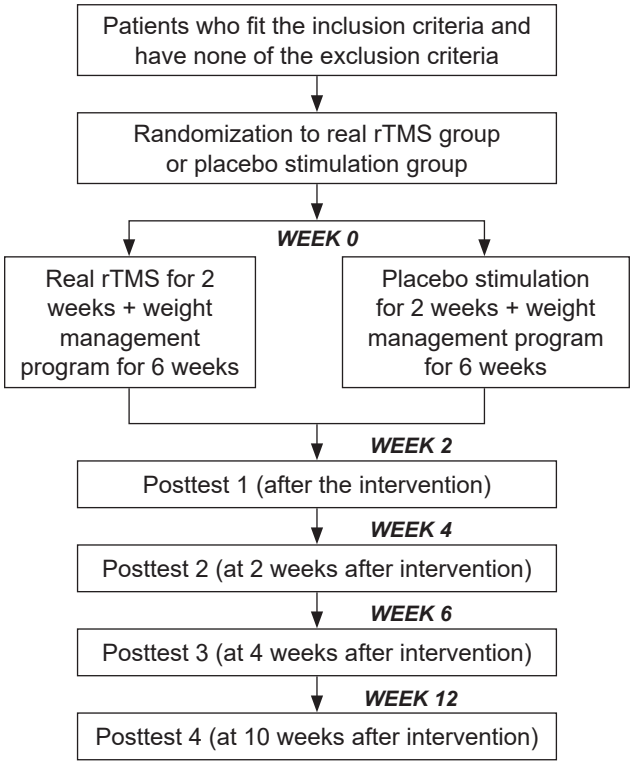

Figure 1. Schematic diagram of study design.

Outcomes

Primary outcome measure was a change in BMI from baseline to 4, 6, and 12 weeks. Secondary outcome measures were: weight change from baseline, change in average total daily caloric intake and change in VAS score for appetite. These were obtained at baseline, after the last session of transcranial stimulation, at week 4, week 6 and at week 12.

Sample Size

The sample size was calculated based on the comparison of change in BMI, the primary outcome of choice, before and after treatment for the TMS group versus sham group. Assuming that the change in BMI for the TMS group is -0.43±0.79 SD, and for the sham, 0.18±0.49, (Se-Hong Kim, et al., 2018), with an alpha error of 5% and power of 80%, and a 1-tailed alternative hypothesis, sample size deduced was 15 per group, for a total of 30 patients for 2 groups.

Statistical Methods

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Per-protocol analysis was done. In this analysis, only those who completed the treatment allocation and follow-up were included in the study. The results were expressed as the mean ± standard deviation (SD).

Between-group differences on outcome variables measured at baseline and at weeks 2, 4, 6, and 12 respectively were analyzed using ANCOVA with treatment group as factor and baseline values as covariates. Effect sizes were calculated for statistical differences between-group. Mixed linear model was used for within group differences for those that were measured at baseline, at week 2, at week 4, week 6, and at week 12.

For subjective appetite scores using VAS, the 2-way repeated measures ANOVA and multiple comparisons with Bonferroni corrections were used. A two-tailed *p-value* of <0.05 was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences version 21.[4]

Ethical Consideration

This clinical protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee. To ensure confidentiality, each patient was assigned a data generated code. The primary investigator was responsible for the integrity of the data. The manner of disseminating and communicating the study results guaranteed the protection of the patient's confidentiality.

RESULTS

Recruitment period was from July to August 2019 and all follow-up sessions were completed by February 2020. A total of 31 patients were randomized with 15 to the treatment and 14 to sham stimulation completing treatment, with 2 lost to follow-up. Figure 2 shows the participant flow of the study.

Table 1 summarizes the baseline characteristics of the study population. The two groups did not differ significantly at the start of the study. They were similar in terms of BMI, VAS scores, total daily caloric intake, and comorbid conditions like hypertension and diabetes. Baseline laboratory values were also similar, as seen in Table 2.

From baseline to 4 weeks after the start of intervention, there was a significant decrease in weight compared to baseline. There was significant difference in the change in weight at week 4 between the rTMS group and the sham group (*p-value*=0.0094). Patients in the rTMS group had a mean 1.3±1.3 kg decrease in weight while the sham group had a mean 0.1±1.5 kg increase in weight. Although there was a decrease in weight in the treatment group at weeks 6 and 12, this was not statistically significant as there was also some weight loss observed in the sham group.

There was a significant difference in the change in BMI compared to baseline at week 4 between the rTMS group and the sham group (*p-value*=0.0017). Patients in the rTMS group had a mean 0.6±0.6 decrease in BMI while the sham group had a mean 0.1±0.6 increase in BMI. Furthermore, large effect sizes were observed in change in body weight (0.786 to 0.996) and BMI (0.742 to 0.990) indicating a strong relationship between rTMS and these outcomes. At 6 weeks however, there was a plateau in BMI from baseline but the *p-value* was not significant. The plateau in BMI at 6 weeks posttest coincides with the weight plateau and may have accounted for this difference. At 12 weeks, there was likewise no significant BMI change between the two groups.

There was a continuous decrease in waist circumference with a difference of -5.3±7.3 cm at 6 weeks, however this was not statistically significant as there was also a slight decrease in the sham group (*p-value*=0.14). By 12 weeks, there was a slight regain/ increase in waist circumference when compared to that at 6 weeks, but these were not statistically significant.

There was a significant difference, from baseline to 2 weeks, in the change in TCI after intervention between the rTMS group and the sham group (*p-value*=0.0292). Patients in the rTMS group had a mean 281.8±41.0 kcal/day decrease while the sham group had a mean 75.6±228.2 kcal/day increase in total energy intake. However, from 4 weeks up to 12 weeks of the study, this effect is no longer observed.

VAS scores did not change significantly throughout the study in three aspects of appetite- hunger, desire to eat,

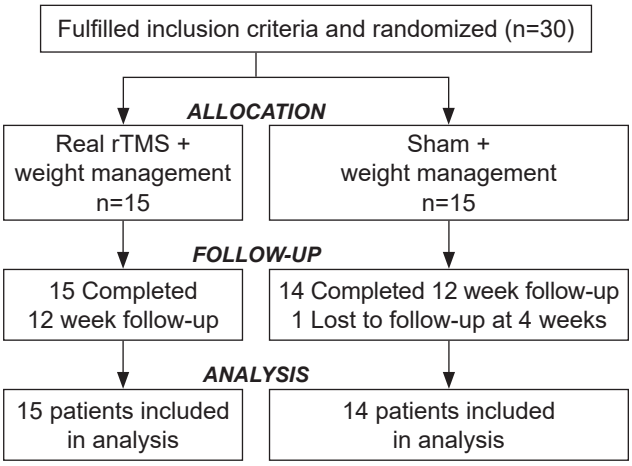

Figure 2. Participant flow of the study.

Table 1. Baseline characteristics of the participants

	rTMS group (n=15)	Placebo / Sham stimulation group (n=14)
Age (yrs)	41.3±10.4	41.2±7.6
Sex		
Male	7 (46.7%)	2 (14.3%)
Female	8 (53.3%)	12 (85.7%)
Waist circumference (cm)	110.6±9.9	107.4±10.8
Weight	89.9±12.0	85.9±15.3
Height	157.2±5.6	154.6±6.0
BMI	36.0±4.3	35.9±6.5
VAS for subjective appetite		
Hunger	4.1±2.7	3.6±2.4
Desire to eat	4.4±2.2	4.0±2.2
Food consumption	4.4±2.4	4.2±2.5
Total daily caloric intake	1851.3±605.5	1621.1±428.6
Hypertension	4 (26.7%)	3 (21.4%)
Diabetes Mellitus	4 (26.7%)	5 (35.7%)

Table 2. Baseline biochemical parameters of the participants

	rTMS group (n=16)	Placebo / Sham stimulation group (n=15)
Fasting blood sugar (mg/dl)	98.6±34.6	115.8±46.9
Glycohemoglobin (%)	6.0±1.2	6.5±1.7
Thyroid Stimulating Hormone	1.9±0.5	1.9±1.0
Total Cholesterol (mg/dl)	184.3±31.5	182.1±34.6
Triglycerides (mg/dl)	149.4±63.4	147.8±77.2
High density lipoprotein (mg/dl)	43.1±7.2	44.3±8.6
Low density lipoprotein (mg/dl)	109.2±34.6	105.9±38.5
Serum creatinine (mg/dl)	0.84±0.34	0.77±0.15

Table 3. Within-group differences in study outcomes assessed using mixed linear regression

	rTMS group (n=15)			Placebo/Sham Stimulation group (n=14)		
	Within Group Differences			Within Group Differences		
	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value
Weight						
After 2weeks	-0.66	1.33	0.623	0.09	0.48	0.847
After 4 weeks	-1.33	1.33	0.315	0.11	0.48	0.824
After 6 weeks	-1.36	1.33	0.305	-0.15	0.48	0.756
After 12 weeks	-2.87	1.33	0.030	-0.31	0.48	0.515
BMI						
After 2weeks	-1.16	0.65	0.076	0.09	0.23	0.682
After 4 weeks	-0.60	0.65	0.359	0.08	0.23	0.746
After 6 weeks	-0.56	0.65	0.387	-0.03	0.23	0.891
After 12 weeks	-1.21	0.65	0.064	-0.21	0.23	0.377
Waist Circumference						
After 2weeks	-1.8	1.45	0.216	-2.3	1.14	0.042
After 4 weeks	-3.7	1.45	0.011	-2.5	1.14	0.027
After 6 weeks	-5.3	1.45	0.000	-3.2	1.14	0.005
After 12 weeks	-4.1	1.45	0.005	-3.0	1.14	0.008
TCI						
After 2weeks	-281.1	124.3	0.024	75.6	87.3	0.387
After 4 weeks	-282.4	124.3	0.023	10	87.3	0.909
After 6 weeks	-236.8	124.3	0.057	-81.1	87.3	0.353
After 12 weeks	-153.8	124.3	0.216	-114.6	87.3	0.189
VAS Hunger						
After 2weeks	0.5	0.67	0.428	-0.9	0.61	0.129
After 4 weeks	-0.6	0.67	0.361	-0.4	0.61	0.498
After 6 weeks	-0.6	0.67	0.340	-0.4	0.61	0.476
After 12 weeks	-1.1	0.67	0.088	0.0	0.61	1.000
VAS Desire to Eat						
After 2weeks	-0.3	0.50	0.523	-1.1	0.55	0.046
After 4 weeks	-1.1	0.50	0.032	-0.9	0.55	0.090
After 6 weeks	-1.4	0.50	0.004	-0.9	0.55	0.118
After 12 weeks	-1.0	0.50	0.039	-0.4	0.55	0.482
VAS Food consumption						
After 2weeks	-0.4	0.56	0.511	-1.0	0.62	0.089
After 4 weeks	-1.2	0.56	0.039	-1.1	0.62	0.069
After 6 weeks	-1.1	0.56	0.045	-1.0	0.62	0.093
After 12 weeks	-1.4	0.56	0.012	-0.7	0.62	0.325

and prospective food consumption. There was a significant difference in hunger scores after intervention between the rTMS group and the sham group (*p-value*=0.023) at 2 weeks. Patients in the rTMS group had a mean 0.5±2.9 increase while the sham group had a mean 0.9±2.2 increase in hunger scores. At 4 up to 12 weeks however, there was no longer an observed difference between the two groups. There was no significant difference in desire to eat and prospective food consumption between the two groups from baseline up to 12 weeks of the study.

Within-group differences were analyzed through mixed linear regression model. These showed that within the rTMS group, there was a significant decrease in weight, waist circumference and VAS score for prospective food consumption when baseline values are compared to 12 weeks. However, when compared to the sham group (between-group difference) based on ANCOVA results reported above, the changes were not significant.

Safety

rTMS was well-tolerated by the participants. 2 patients in the treatment group reported transient mild headache (graded 3/10 post 1st session of rTMS for 1 patient, and graded 4/10 post 3rd and 4th session of rTMS for 1 patient). These occurred immediately after rTMS and were resolved within 24 hours. No other adverse event was reported and no participant dropped out of the study because of headache. No adverse effect was reported in the sham stimulation group.

Table 4. Correlation of change in VAS scores from baseline to 12 weeks with change in total caloric intake from baseline to 12 weeks

	Coefficient	P-value
VAS Hunger	0.13	0.3441
VAS Desire to Eat	-0.01	0.9398
VAS Food Consumption	-0.03	0.8356

Table 5. Correlation of change in weight, BMI, Waist Circumference from baseline to 12 weeks with change in total caloric intake from baseline to 12 weeks

	Coefficient	P-value
Weight	-0.17	0.3704
BMI	-0.17	0.3740
Waist Circumference	-0.27	0.1501

DISCUSSION

Efficacy of rTMS in Decreasing BMI

The weight loss in this study is comparable to that of the study by Kim et al., in 2018[4] which also showed a significant decrease in weight and BMI at 4 weeks after the rTMS. The weight loss in this study was -1.3±1.3 kg in the treatment group versus -1.35±2.31 kg in the study by Kim et al. Since Week 2 anthropometric values were not measured in their study, the researchers are unable to compare the 2-week data to that of other studies.

These results are also supported by 2 other studies conducted in 2019 (both published after our study protocol has been completed and subject recruitment was already ongoing). In the study by Kim et al., in 2019, 8 sessions of rTMS over 4 weeks were done and resulted in more weight loss of 2.75±2.3 kg.[12] Alvarado-Reynoso and Tututi's study employed a longer treatment period, with 5 rTMS sessions every week for 2 weeks, then once a week on weeks 3, 4, 6, 8, 12, 20 and 28 coupled with a low -carbohydrate diet. They also found a continuous decline in weight up to the last session at 28 weeks.[13]

The proposed explanation is that targeting the DLPFC helps decrease deranged eating behaviors and excessive food cravings. Decreased food cravings, in turn, decreases food intake and aids in weight loss.[4,12] The researchers did a correlation analysis and found that change in caloric intake was not significantly associated with change in BMI, waist circumference and weight. Although it is accepted in studies that less food intake leads to weight loss, several factors may have affected the results of this study. One may be that the sample size was not adequate for the correlation analysis done. Food intake through 3-day food diary may also be inaccurately collected by the subjects, thus a significant decrease in intake in relation to weight loss was also not observed.

There was no longer a significant change observed at weeks 6 and 12, however, indicating that although rTMS may be effective in decreasing body weight, the effects may not be permanent. The studies done by Kim and Alvarado-Reynoso employed assessment of weight immediately after the last session, and therefore were not able to explore the long-term effects of rTMS even if this intervention is no longer present. This current study may imply that regular sessions of rTMS may need to be given in order to maintain weight loss.

As to waist circumference, although there was a continuous decrease with a difference of -5.3±7.3 cm at 6 weeks, this was not statistically significant when compared to that of the sham group. It is possible that a steady decline in waist circumference may be observed if the study is further extended, or that there was inter-observer variability in measuring the waist circumference at each follow-up.

It is important to note that one of the subjects in the rTMS group displayed a significantly higher decrease in weight and BMI compared to the other subjects in both groups, and this may be a possible outlier in the study.

Effect of rTMS on TCI

In the first 2 weeks, the TCI was significantly lower in the treatment group. However, for the succeeding 2 weeks

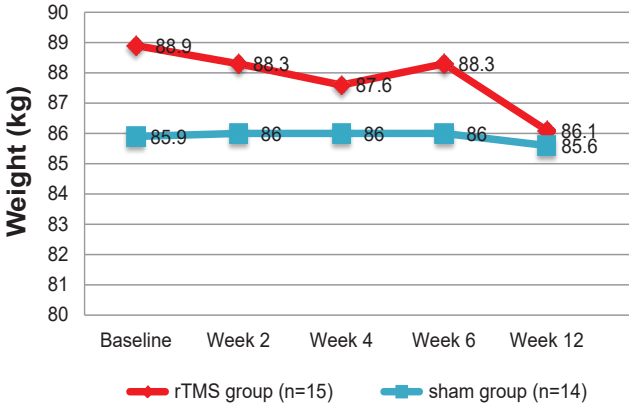

Figure 3. Comparison of weight from baseline between rTMS vs sham group.

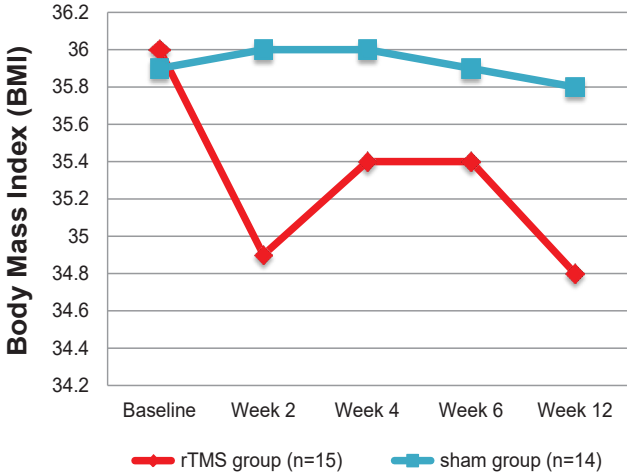

Figure 4. Comparison of BMI from baseline between rTMS vs sham group.

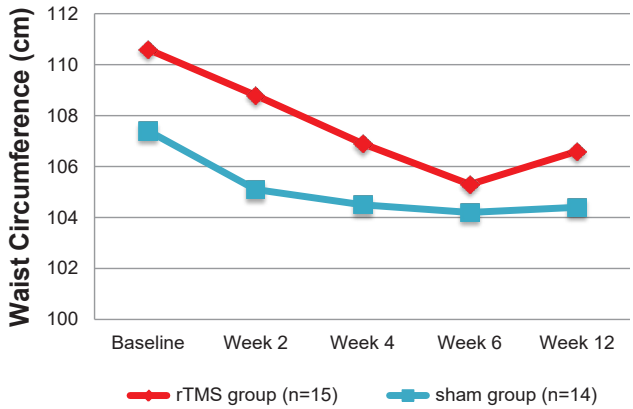

Figure 5. Comparison of waist circumference from baseline between rTMS vs sham group.

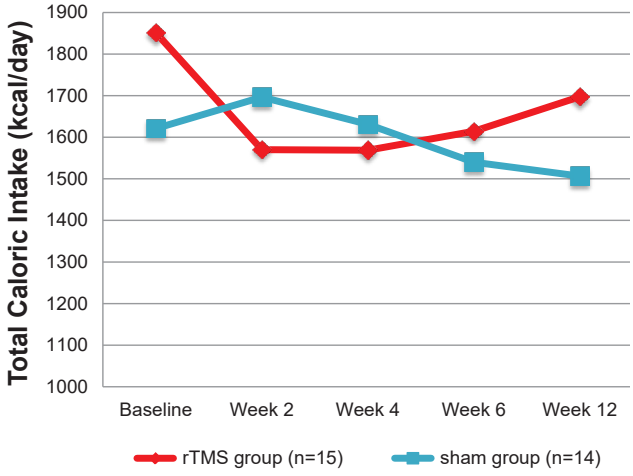

Figure 6. Change in total daily caloric intake from baseline between rTMS vs sham group.

onwards, there was no significant difference anymore between the two groups. This initial decrease coincided with the duration of rTMS procedure indicating that TCI may be decreased by rTMS but the effect is not permanent.

This may be reflective of the short-term impact of rTMS in decreasing appetite and food cravings. Thus, when the rTMS was no longer continued, there was a corresponding increase in intake in the treatment group. The permanency or reversibility of effects of rTMS on weight loss and food cravings in obese patients has not yet been studied, yet it is an area that needs to be explored. In a study by Mally et al., long-term effect of rTMS was studied in patients with Parkinson's disease. rTMS was given 2 times a day for 7 days (1 Hz, 100 stimuli per day) and was repeated at least twice a year for 3 years. There was significant decrease in progression of Parkinson's disease with the repeated stimulation over 3 years. They proposed that prolonged stimulation produced prolonged inhibition in intracortical connections which delayed progression of the disease.[14] Therefore, increasing the total number of rTMS to the DLPFC may potentially induce longer lasting effects on weight loss and caloric intake as well.

The result of this study is in contrast to the study by Kim et al., where there was a continued decrease in total caloric intake at Week 4.[4] However, since there was no Week 2 assessment in their study, a comparison of intake between Week 2 and Week 4, and therefore a possibility that there was lesser caloric intake at Week 2 than at Week 4, was not determined.

Change in VAS scores for appetite and change in total caloric intake showed no significant association when correlation analysis was done. A meta-analysis by Lowe et al., in 2017 supported this study's result, where they found that food cravings decreased after multiple stimulation however actual food consumption after both single and multiple sessions for rTMS was found to be inconsistent among different studies.[2] A study by Uher et al., showed that a decrease in subjective food craving did not necessarily translate to less food consumption between the two groups.[6] Differences in methodology i.e., specific brand of stimulation device, frequency and intensity of stimulation and higher BMI cutoffs in this study may account for the incongruent results.[2,6,12] It is also possible that the sample size in this study was not powered to observe a correlation between food cravings and food intake, as this study used change in BMI in computing for the sample size.

Another is the possible discrepancy in the method of collecting data for total caloric intake through the use of food diaries. Since it is subjective and based on recall, factors such as inaccurate recording of intake, writing down only of days with the least amount of oral intake, or inability to recall all food taken may have played a role in the inability to show significant results at week 4 onwards.

Effect of rTMS on appetite

Results showed that there was no significant difference in appetite between the treatment and sham groups from baseline to 12 weeks. This is comparable to the study by Kim et al., where there was no significant difference in the sham and treatment groups in terms of hunger and desire to eat; however, this study failed to show a significant

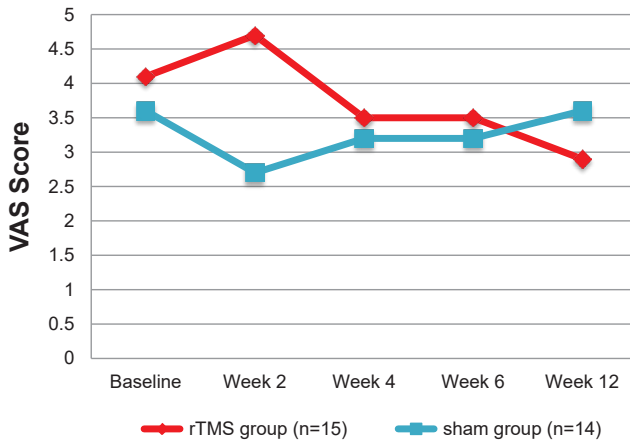

Figure 7. Change in hunger scores from baseline between rTMS vs sham group.

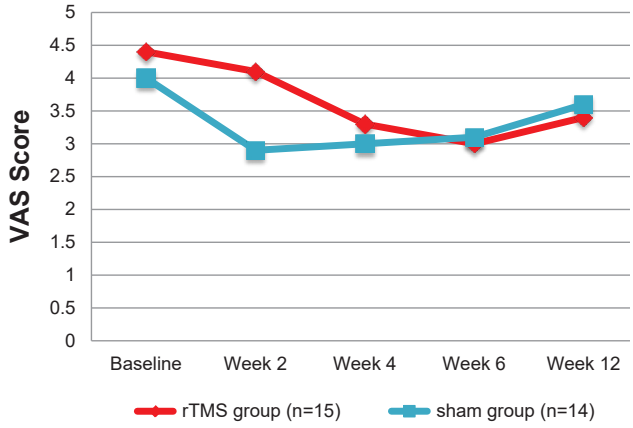

Figure 8. Change in desire to eat from baseline between rTMS vs sham group.

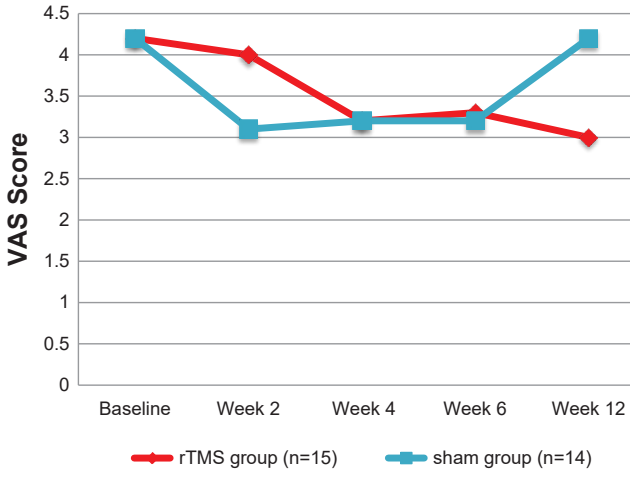

Figure 9. Change in prospective food consumption from baseline between rTMS vs sham group.

reduction in prospective food consumption as mentioned in the former study.[4] In their 2019 study, however there was no significant difference in prospective food consumption, but there was a significant reduction in hunger and desire to eat.[12]

There can be several reasons why there are contradicting results in the VAS scores for appetite. One reason may

be the differences in fasting time prior to taking the VAS scores. In the 2018 study by Kim et al., it was taken after 4 hours of fasting while in their 2019 study, it was after only 2 hours.[4,12] In this study, the fasting hours prior to testing were consistent for each participant, but was not uniform across all subjects, and these ranged from 2-5 hours of fasting (i.e., participant 1 fasted for 2 hours prior to each assessment, participant 2 fasted for 4 hours prior to assessment).

Another reason may be that caloric intake during the study was not standardized. Only the specific timing of last meal was consistent for each participant, however the actual intake/ meal prior to each assessment of appetite was not the same for all participants and therefore these may have affected their subjective scores.

Another reason is the possible placebo effect on the control group. Most of the patients in the sham group believed themselves to be in the treatment group and therefore these may have given lower ratings on perceived appetite.

Lastly, the differences in technique of rTMS application may also account for the different results in weight and appetite/ food cravings. In our study, we used 20 trains of 5 seconds at a frequency of 10 Hz and intensity of 110% of the participant's motor threshold. In the study by Kim et al., in 2019, 40 trains of 5 seconds with frequency of 10 Hz and intensity of 110% motor threshold was used.[12] Alvarado-Reynoso in 2019 used 10 trains of 100 pulses given at 10 Hz and 90% of motor threshold, with more sessions employed compared to the two studies.[13] While all these produced weight loss, the degree of weight loss and reduction in food cravings were different among the 3 studies.

Neuroendocrine effects of rTMS on food cravings have been studied. Ferrulli et al., in 2018, reported that orexigenic pathways have been altered as a result of TMS, producing an increase in norepinephrine and B-endorphins, while salivary cortisol is decreased. This suggests a potential role of TMS in inducing dopaminergic activation and modulation of the food-reward system.[15] With the advent of these biochemical tests that provide objective and measurable assessment of appetite, evaluation of food cravings no longer need to be purely subjective, thus increasing the accuracy of results. It still needs to be established, however, if alteration of the neuroendocrine pathways translates into actual reduction in food intake.

Limitations

There were only 4 sessions of rTMS done due to cost and inability to determine safety of the procedure. As this is the first study done among Filipinos, the researchers opted to use the same rTMS protocol that was used among obese patients in Korea, which employed 4 sessions of rTMS. Furthermore, fully accurate measurement of appetite and intake may not have been achieved due to the subjective nature of the VAS scores for appetite, as well as accounting for some inaccurately recorded food diaries. Another possible limitation may be that this did not have adequate sample size and power to declare statistical significance of the reported differences in changes in other outcomes (changes in desire to eat, hunger and total caloric intake between two groups) as the sample size in this study was computed based on BMI change from baseline.

CONCLUSION

rTMS to the DLPFC effectively decreases BMI and weight from baseline to 4 weeks in the treatment group compared to the sham group, with a decrease in weight by -1.3±1.3 kg and decrease in BMI by 0.6±0.6. At 6-12 weeks after rTMS however, there was no longer a significant difference, indicating that 4 sessions of rTMS are not enough to produce a permanent effect on weight loss. Although there was an initial significant decrease in total caloric intake in the first 2 weeks by about 200 kilocalories a day, it failed to show a consistent decline in total caloric intake after 2 weeks from the last session of rTMS. Furthermore, subjective scoring showed no difference as to hunger, desire to eat and prospective food consumption in the treatment group versus the sham group.

Recommendations

The researchers recommend a more controlled food intake and fasting time prior to testing for subjective appetite in order to have a better estimate of appetite/ hunger that is not related to quantity of food consumed prior to the testing. Body fat analysis may also help to determine if visceral adipose tissue decreases with rTMS, as this is an important risk factor for cardiovascular disease in obese patients. To eliminate bias and placebo effect, the researchers recommend exploring the usefulness of measuring neuroendocrine hormones like leptin, B-endorphins, cortisol and norepinephrine as objective markers of appetite in order to supplement the much more subjective food diaries and VAS scoring to measure hunger and appetite of the participants.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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