Transcranial Magnetic Stimulation for Treatment Resistant Depression: Six Case Reports and Review†

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Background: *Depressive disorder is a common, recurrent, and chronic disorder that is a leading cause of functional impairment and disability. An estimated 20-40% of patients do not benefit sufficiently from existing therapies. Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for psychiatric illness. Evidences support its use in depression, either alone or combined with antidepressants. During rTMS, a time-varying current is discharged in an insulated coil attached to the scalp surface, generated a brief dynamic magnetic field that can freely, non-invasively penetrate the skull and induce the eddy current in the neural tissue. The rTMS works as a neuro-stimulator and neuro-modulator at the same time, which can modify the functionality of the brain circuits involved in the pathophysiology of mental illness especially in depressive disorder.*

Material and Method: *The authors reported six cases of various types of depressive disorder, double depression, borderline personality disorder with depression, psychotic depression with nihilistic delusion, post-schizophrenic depression, and treatment resistant depression non-respond to electroconvulsive therapy (ECT).*

Results: *Four in six cases responded well with 10 daily sessions of rTMS. However, a patient with psychotic depression yielded no response. Five patients with moderate depression reached the remission criteria of Hamilton Depression Rating Scale-17 items (HAM-D-17). The means HAM-D-17 of rTMS responders were decreased from 22.4 (SD = 4.1) to 5.2 (SD = 2.9). A patient with psychotic depression did not show any benefit from rTMS and got subsequent modified ECT.*

Conclusion: *This is the first cases report of using rTMS for the treatment of depression in Thailand. The rTMS gave promising results in various forms of depression. Due to its safety, needing no anesthesia, suitable for out-patient care, rTMS might be a treatment alternative in the acute phase of moderate non-psychotic depression. The authors also reviewed the current evidence.*

Keywords: *Repetitive transcranial magnetic stimulation, rTMS, treatment resistant depression*

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Depressive disorders afflict one out of five women and one out of ten men at some time during their lives[1]. The World Health Organization has ranked depression fourth in a list of the most urgent health problems worldwide. Due to the recurrent and chronicity of the disorders, depression is a leading cause of functional impairment and disability. Moreover, depressive co-morbidity increases the morbidity and mortality of many physical diseases *i.e.* coronary artery disease, stroke, and hypertension. Despite the availability of effective treatments, the rate of suicide occurs in approximately 15% of depressive patients. An estimated 20-40% of patients do not benefit sufficiently from existing therapies[2].

Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for psychiatric illnesses[3]. The technique, originally introduced in 1985, is non-invasive and safe, and can easily be applied to the scalp in a relatively painless manner, not requiring anesthesia, avoiding transient memory loss[4], and not induced seizure as in electroconvulsive therapy (ECT). During rTMS, a time-varying current is discharged in an insulated coil attached to the scalp surface, generating a time-pulse magnetic field that

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can freely, non-invasively penetrate the skull and induce the eddy current in the cortical neural tissue, which subsequently depolarized underlying nerve cells tangentially oriented to the magnetic field[5]. Repeated stimulation in an attempt to locally enhance neural activity works as a neuro-stimulator and neuro-modulator in the same time and can modify the functionality of the brain circuits involved in the pathophysiology of mental illnesses[6]. The high frequency rTMS (repetitive rate > 1 Hz) yielded the stimulation effect, which was proposed to be the therapeutic mechanism for functional imbalance of prefrontal cortex in depression[7,8]. Most recent meta-analysis showed high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) is superior to sham in the treatment of depression[9]. This is the report of the experience of using rTMS in Thailand.

Material and Method

The authors aimed to do the preliminary case studies of using rTMS in a routine clinical setting as an additional strategy to antidepressant medication and standard usual care. Between January and December 2007 in the Department of Psychiatry, Faculty of Medicine, Khon Kaen University, six patients of various types of depressive disorder underwent the rTMS. All patients gave written informed consent. The authors used rTMS treatment parameters according to the reported clinical trials[10,11] and safety guidelines described by the International Federation of Clinical Neurophysiology[12]. The stimulation site was at the left dorsolateral prefrontal cortex (LDLPFC). A Magstim Rapid 2 Magnetic Stimulator (Magstim Company Ltd, Whitland, UK) with two 70-mm figure-eight coils were used. At the first treatment session, resting motor threshold (MT) was determined by delivering single TMS pulses to the motor cortex for the right abductor pollicis brevis muscle. Motor threshold was defined as the visible contractions in 5 of 10 single stimulations. The MT estimation was repeated weekly. The scalp location at 5 cm anterior to the motor cortex in a parasaggital line was used to represent the DLPFC. The coil was placed flat against the scalp with the handle of the coil oriented in parallel to the vertex-preauricular line. A swimming cap for each patient was worn to mark the site of stimulation and help to keep the placement of the TMS coil constant during and across each session.

Repetitive TMS was delivered at a frequency of 10 Hz in 5-second trains at 80% of the estimated motor threshold. Thirty-two trains were given in each session (1,600 pulses per session) with a 15 to 30 second inter-train interval. Ten sessions (16,000 total pulses) were given within a 2-week period.

Concomitant treatment

All patients received antidepressants or other psychotropic medications directed at treating depression and related symptoms by the attending physicians. The medication regimens remained the same throughout the rTMS period. The treatment as usual was given to all and one got weekly family therapy.

Measurements

Prior to the first TMS session, independent raters administered the HAM-D 17-items. This measure was repeated after the tenth session by the same rater. Response was defined as a 50% decrease in HAM-D-17 score from baseline, remission was defined as HAM-D-17 < 8. The adverse effects were collected at each session by interviewing the patients. The case record form was used to record all the session details (date, treatment parameter, medication used, and adverse effects).

Results

There were five females and one male. Five were Thais and one was Turk, age range was 24-60 years. Three out of six were treated as outpatients while another three were admitted in the psychiatric ward during the course of treatment. They were diagnosed by the attending psychiatrists as one double depression, two borderline personality disorder with depression, one psychotic depression with nihilistic delusion, one post-schizophrenic depression, and one recurrent depression with a history of non-responding to electroconvulsive therapy (ECT) and all the patients had a history of resistance to various antidepressants treatment.

Five of six cases responded well with 10 daily sessions of rTMS, a patient who had psychotic depression did not respond (Table 1). The five patients who responded to rTMS, had moderate depression at the beginning of the treatment, four patients reached the remission status. The means HAM-D-17 of rTMS responders decreased from 22.0 (SD = 4.1) to 5.2 (SD = 2.9), which reached the statistical significant difference at $p = 0.01$ (Fig. 1).

A patient with double depression requested for an additional 10 rTMS sessions. The HAM-D-17 score was 5 at the end of tenth session then reduced to 0 at the end of twentieth session. She returned to her

Table 1. Clinical characteristics of 6 patients and treatment response

Patient No.	Age/Sex	Diagnosis	Medications (mg)	HAM-D-17 before	HAM-D-17 after 10th	HAM-D-17 after 20th	Remark
1	28/F	BPD with depression	Fluoxetine 80 Valproate 600 Perphenzine 8	17	3	-	
2	27/F	BPD with depression	Haloperidol 8 Fluoxetine 40 Lithium 200 Trihexyphenidyl 10	23	2	-	
3	44/F	Double depression	Paroxetine 40	22	5	0	Plus family therapy
4	24/F	Post-schizophrenic depression-social phobia	Perphenazine 16 Trihexyphenidyl 4 Fluoxetine 40 Chlorpromazine 200	28	7	-	BPRS score 30 ≥ 20
5	38/M	Recurrent depressive disorder	Amisulpride 50 T3 40 Lithium 300	20	9	-	Non responder and intolerance to antidepressants
6	60/F	Psychotic depression with nihilistic delusion	Risperidone 6 Fluoxetine 40	38	36	-	Follow with modified ECT

BPD = borderline personality disorder; BPRS = brief psychiatric rating score

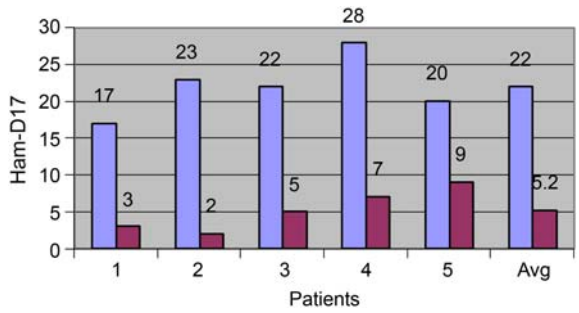

Fig. 1 HAM-D-17 score after 10th session rTMS at left dorsolateral prefrontal cortex in 5 non-psychotic depression

normal mood and activities, which she had not experienced after many years of depression. However, this patient received concomitant family therapy.

One Turkish patient had more than 20 years of chronic depression and never got a satisfactory response from antidepressant treatment and two courses of ECT in Germany. He reported that he got much improvement (HAM-D-17 = 9) and subsequently responded to previously unresponsive antidepressant. He could go back to Germany and worked efficiently there for six months before the depression recurred and he asked for another course of rTMS.

A patient with psychotic depression had two previous episodes of severe depression with psychotic features with response to ECT. The current episode was also severe and had marked nihilistic delusion that her head and limbs had disappeared. She thought that she had already died and asked the physician to inform her relatives about her death. She did not get any benefit from 10 sessions of rTMS and got subsequent modified ECT, which yielded marked improvement.

The adverse effects were only mild and transient. The most common was pain at the stimulation site in three of six subjects. Two patients experienced headache after TMS for a few hours but did not need analgesics. There were no seizure like experiences and treatment-emergence mania in the presented patients during and after TMS treatment.

Discussion

This is the first experience of using rTMS in Thailand. At first, it was quite difficult to initiate patients into treatment due to its novelty, unfamiliarity, and the feeling of being unsure to the effectiveness and safety. The authors included the heterogenous

form of depression in this series. However, the results favored rTMS no matter what their diagnosis. This might be due to all the patients with depression shared common biological abnormalities, which presented as common depressive symptomatology. For example, increasing regional cerebral blood flow from rTMS at the left prefrontal cortex may be responsible for the symptom improvement no matter what type of depression they had[13].

The efficacy trials of using rTMS in depression began in 1993. From that time, there has been growing evidence of the randomized controlled trial, multi-centered trials, systematic review, and meta-analysis. Two recent multi-centered studies have been done, one from a European country[14] and another one from the United States of America[2]. In the study of O'Reardon et al (2007) 301 medication-free treatment resistant depression underwent rTMS alone at 10 Hz, 120%. The motor threshold was set at 3000 pulses/session on the working days for four weeks. In the study of Herwig et al (2007), 127 patients with moderate to severe depressive episodes and varied in antidepressants treatment-resistant status were included. The stimulation parameters were 10 Hz at 110% MT, 2000 pulse per day for 15 working days. All participants concomitantly received mirtazapine or venlafaxine along with rTMS. Both studies were considered to be adequate rTMS treatment trials (stimulation 2000-3000 pulse/day for more than 2 weeks). While the study of O'Reardon et al showed the marked rTMS remission, response rate and significant symptoms improvement at four weeks, the study of Herwig et al, did not show significant response when compared to sham stimulation and medications. These might be due to concomitant use of drugs might have potent treatment effect and obscure the rTMS effect. In addition, the patients were not antidepressant resistant as in the study of O'Reardon et al. In the presented case series, the patients were treatment resistant and got stable drug regimens throughout the course. From these data, it might interpret that rTMS would have much benefit when applied to antidepressant resistant patients either alone or as an augmentation to antidepressant drugs.

Many reviews and meta-analyses have been carried out since 2001[15]. From the most recent meta-analysis[9], thirty double-blind sham-controlled studies with 1,164 patients with major depressive episode without psychotic features according to DSM-IV criteria were included. The majority of participants in the real (n = 451) and sham rTMS treatment condition (n = 399) were resistant to medication. The findings showed that high-frequency rTMS over the left DLPFC is superior to sham in the treatment of depression. The effect size is robust [d = 0.39 (95% CI: 0.25-0.54)] and comparable to at least a subset of commercially available antidepressant drug agents. Most of the recent evidence favored the use of rTMS in acute treatment of depression. There are only a few open studies using rTMS for long-term relapse/recurrent prevention[16]. Some refractory MDD patients who received maintenance rTMS alone could continue their medication-free period for 26 to 43 months[17]. The role of rTMS in maintenance treatment of depression needs to be elucidated. Some conflicting evidence also exists and should be considered carefully before accepting rTMS as a standard treatment[18,19]. The heterogeneity of the results might come from the difference in stimulation parameter, site of stimulation, concomitant use of medications and other treatment, and difference in diagnosis/psychopathology. However, the later trial tended to use a higher stimulation parameter, increased number of pulses, and longer course of treatment, which proved to increase the effectiveness too. It might be proposed that rTMS treatment has a dose-response characteristic as many medication therapies do.

When considering the adverse effects reported in meta-analyses by Schutter (2008), the most commonly observed adverse effects associated with rTMS were headaches, dizziness, nausea, and painful local sensation. These side-effects are typically considered to be mild and respond promptly to analgesics. In the presented case series, the adverse effects were only mild symptoms and needed no treatment. The most common side effects in the present study were pain at the stimulation site, due to local contraction of the underlying muscles. The pain was only of short duration until the stimulation ended. The severity of pain depended on the power of the stimulation, one of the presented patients could not tolerate the pain when stimulated at the 80% MT, and therefore the power was decreased to 75% MT. In the past, there were two case-reports of self-limited seizure induction from the stimulation at motor cortex and frontal lobe using 110-120% MT[20,21], there were reports of treatment-emergence mania[22-24]. However in large multi-center trials, no such report occurred. It appeared to be safe when following the treatment guideline proposed by Wassermann[12]. When balancing the risk-benefit of rTMS and ECT in the treatment of non-psychotic depression, rTMS appeared to be safer

especially for some risk groups *i.e.* depression in pregnant women[25] and adolescent depression[26].

In conclusion, the rTMS gave promising results in this preliminary case series of various forms of depression. Due to its safety, needless anesthesia, and suitable for out-patient care, rTMS might be a treatment alternative in acute phase of moderate non-psychotic depression. However, to generalize the results, further well-controlled studies are required.

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การใช้สนามแม่เหล็กกระตุ้นสมองเฉพาะที่เพื่อรักษาโรคซึมเศร้าที่ไม่ตอบสนองต่อการรักษา: รายงานผู้ป่วย 6 ราย พร้อมทบทวนวารสาร

ธวัชชัย กฤษณะประกรกิจ, สุชาติ พหลภาคย์, กนิดา ทัศนิยม, วิจิตรา พิมพะนิตย์

ภูมิหลัง: *โรคซึมเศร้าเป็นโรคที่พบบ่อยมักกลับเป็นซ้ำ และเรื้อรังเป็นสาเหตุสำคัญที่ทำให้สูญเสียความสามารถในชีวิตประจำวันและการทำงานบกพร่องไป มีผู้ป่วยโรคซึมเศร้าประมาณร้อยละ 20-40 ที่ไม่ตอบสนองต่อการรักษาด้วยยารวมทั้งวิธีการที่มีอยู่ในปัจจุบันการกระตุ้นสมองเฉพาะที่ด้วยสนามแม่เหล็ก (Repetitive Transcranial Magnetic Stimulation [rTMS]) เป็นนวัตกรรมการรักษาโรคทางจิตเวช และระบบประสาทเริ่มมีหลักฐานสนับสนุนในการรักษาโรคซึมเศร้าทั้งใช้เพียงอย่างเดียวหรือใช้ร่วมกับยารักษาซึมเศร้า โดยการผ่านกระแสไฟฟ้าเข้าสู่ขดลวดจะก่อให้เกิดสนามแม่เหล็กที่พุ่งตรงเข้าสู่สมองเฉพาะแห่งได้อย่างอิสระแล้วกระตุ้น ให้เกิดการเปลี่ยนแปลงกระแสไฟฟ้าในสมองอีกทอดหนึ่ง rTMS นี้จะมีผลทั้งในการกระตุ้นสมอง และปรับเปลี่ยนการทำงานของวงจรประสาทที่เกี่ยวกับโรคทางจิตเวชโดยเฉพาะโรคซึมเศร้า*

วัสดุและวิธีการ: *นำเสนอผู้ป่วยโรคซึมเศร้าชนิดต่าง ๆ 6 ราย ได้แก่ double depression, borderline personality disorder with depression, psychotic depression with nihilistic delusion, post-schizophrenic depression และ treatment-resistant major depression ที่ไม่ตอบสนองต่อการรักษาด้วย electroconvulsive therapy (ECT)*

ผลการศึกษา: *ผู้ป่วย 5 ใน 6 ราย มีการตอบสนองต่อการรักษาด้วย rTMS ในระดับดีมาก คือ จากอารมณ์เศร้าระดับปานกลาง ที่มีความคิดฆ่าตัวตายเป็นระยะ ๆ เมื่อรักษาแล้ว 4 ราย มีอาการดีขึ้นมากจนหาย (remission) ค่าคะแนน Hamilton Depression Rating Scale-17 จาก 22.4 (SD = 4.1) ลดลงมาเป็น 5.2 (SD = 2.9) มีเพียงผู้ป่วย 1 ราย ที่เป็น psychotic depression ไม่ตอบสนองต่อ rTMS และต้องได้รับการรักษาด้วย ECT ต่อ*

สรุป: *รายงานนี้เป็นประสบการณ์การรักษาโรคซึมเศร้าด้วย rTMS ครั้งแรกในประเทศไทยพบว่า rTMS ให้ผลการรักษาที่ดีในผู้ป่วยโรคซึมเศร้าหลายแบบจากที่มีความปลอดภัย ไม่ต้องใช้การดมยาสลบทำได้ในคลินิกผู้ป่วยนอก จึงอาจสามารถใช้เป็นทางเลือกหนึ่ง ในการรักษาโรคซึมเศร้าระดับปานกลาง และไม่มีอาการโรคจิตที่ไม่ตอบสนองต่อการรักษาได้ ผู้นิพนธ์ได้ทบทวนวรรณกรรมผลการรักษาด้วย rTMS ในปัจจุบัน*