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ORIGINAL ARTICLE

Clinical effects on semi-structured suicidal thinking with two intermittent Theta-Burst stimulation intervention protocols in depressive disorder

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Abstract

Objective: *To analyze the clinical outcomes of two intermittent theta burst protocols applied to depressed patients with semi-structured suicidal thinking.* **Methods:** *23 participants with Depression according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria, were accepted via informant consent and randomized in Group A: 1 session and Group B: 3 sessions, during 4 weeks, using clinical Scales for depression and suicidal behavior to assess each participant.* **Results:** *Wilcoxon rank test analysis showed statistically significant post-treatment reduction on suicidal thoughts for Group B ($p < 0.01$) with also a larger effect-size (> 0.80) which it was measured with Hedges' g. Hazard Ratio analysis showed a major probability for Group B to decrease suicide-related thinking.* **Conclusions:** *A decrease in suicidal thinking was more observed in the group that received three sessions daily for 4 weeks, indicating more sessions during the day could offer a quicker response to suicidal thinking, especially for prevention of this type of behavior in areas where no hospitalization is available. These results support the feasibility of creating new preventive methods to improve the efficacy in the early eradication of suicidal thoughts.*

Keywords: *Depression. Intermittent Theta Burst. Suicide behavior. Suicidal thinking. Transcranial magnetic stimulation.*

Efectos clínicos sobre el pensamiento suicida semiestructurado con dos protocolos de intervención de estimulación intermitente Theta-Burst en el trastorno depresivo

Resumen

Objetivo: *Analizar los resultados clínicos de dos protocolos de estimulación Theta Burst intermitente aplicados en pacientes deprimidos con ideación suicida semiestructurada.* **Métodos:** *23 participantes con Depresión según los criterios del Manual*

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Diagnóstico y Estadístico de los Trastornos Mentales 5ª edición, fueron aceptados mediante consentimiento informado y aleatorizados en Grupo A: 1-sesión y Grupo B: 3-sesiones, durante 4 semanas, utilizando escalas clínicas de depresión y conducta suicida para evaluar a cada participante. **Resultados:** *El análisis con la prueba de suma de rangos de Wilcoxon mostró una reducción estadísticamente significativa de los pensamientos suicidas después del tratamiento para el Grupo B ($p < 0,01$) con también un mayor tamaño del efecto (> 0,80) que se midió con la g de Hedges. El análisis de Riesgo Relativo mostró una mayor probabilidad de que el Grupo B disminuyera los pensamientos suicidas.* **Conclusiones:** *La disminución de la ideación suicida fue más observada en el grupo que recibió tres sesiones diarias durante cuatro semanas, indicando que más sesiones durante el día podrían ofrecer una respuesta más rápida en la ideación suicida, especialmente para la prevención de este tipo de comportamiento en áreas donde no se dispone de hospitalización. Estos resultados apoyan la viabilidad de crear nuevos métodos preventivos para mejorar la eficacia en la erradicación precoz de los pensamientos suicidas.*

Palabras clave: *Depresión. Estimulación Theta Burst Intermitente. Conducta suicida. Pensamiento suicida. Estimulación magnética transcraneal.*

Introduction

Major depressive disorder (MDD) affects 380 million people worldwide, with 60% linked to suicidal behavior rates, and 25.5% growth rate due to severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). In suicide-related behavior rates, there is a limited pharmacological treatment efficacy, with discomforting side effects in patients. Repetitive transcranial magnetic stimulation (rTMS) and its variant, intermittent theta burst stimulation (iTBS), are a non-invasive, Food and Drug Administration-approved treatment for MDD, the latter applies burst triplets at 50 Hz and a 200-ms interval, helping induce greater changes in synaptic plasticity than rTMS; with some clinical evidence on accelerated protocols (more sessions per-day and less days of treatment)[1]. Some clinical evidence of changes in suicidal thinking using iTBS was found by Desmyter et al. in a Sham/active-iTBS, suggesting 39% (n = 50) remission rates[2]; other studies with a minor sample showed similar outcomes[3]. Recently, Mehta et al., 2022, obtained remission rates of up to 49% (n = 159) in an iTBS/10Hz-rTMS intervention[4]. Based on the latter, we hypothesized that more sessions per day could reduce more effectively the presence of suicide-like thinking.

Our objective was to compare the clinical effectiveness and hazard reduction of two iTBS interventions (once-daily sessions and thrice-daily sessions) on semi-structured suicidal thinking in clinically depressed adult patients.

Materials and methods

The study was conducted from October 2021 to March 2023 at the "Dr. Moisés López González" Neurodiagnostics and Rehabilitation Unit by trained professionals at the Autonomous University of Queretaro, Mexico. The trial was performed according to the Declaration of Helsinki and approved by the Bioethics Committee of the Faculty of Medicine of the Autonomous University of Queretaro. The study was registered in ClinicalTrials.Gov. (NCT05694754). Patients were recruited from private and public health institutions and online surveys.

A total of 149 participants recruited from various clinical private or public centers and online surveys were initially assessed; where 23 patients of both sexes between 18 and 45 years of age met the criteria for major depression and semi-structured suicidal thinking and were accepted (Fig. 1A). Inclusion criteria within the study included DSM-5 clinical based diagnostic for MDD (Table 1). Patients must have had stable pharmacological treatment at least for the last 30 days with adequate adherence to it; electroencephalogram (EEG) with no contraindications to receive iTBS treatment (paroxysmal or epileptic activity). Exclusion criteria included patients with seizure activity or the presence of suicidal attempts in the last 30 days or have structured suicidal ideation, as well as a significant risk of suicide attempts of moderate-to-high lethality during treatment. Participants with intracranial metallic objects, intracranial or metallic plates in the skull, pacemaker, cochlear implant, neuro-stimulation device and/or shunt valves, cochlear implant, neuro-stimulation device, and/or shunt valves were also excluded. Patients with assessment sessions and/or stimulation sessions with at least 3 consecutive absences were excluded. Exclusion criteria took into consideration reports of SARS-CoV-2 Covid-19 symptoms during treatment. All participants signed

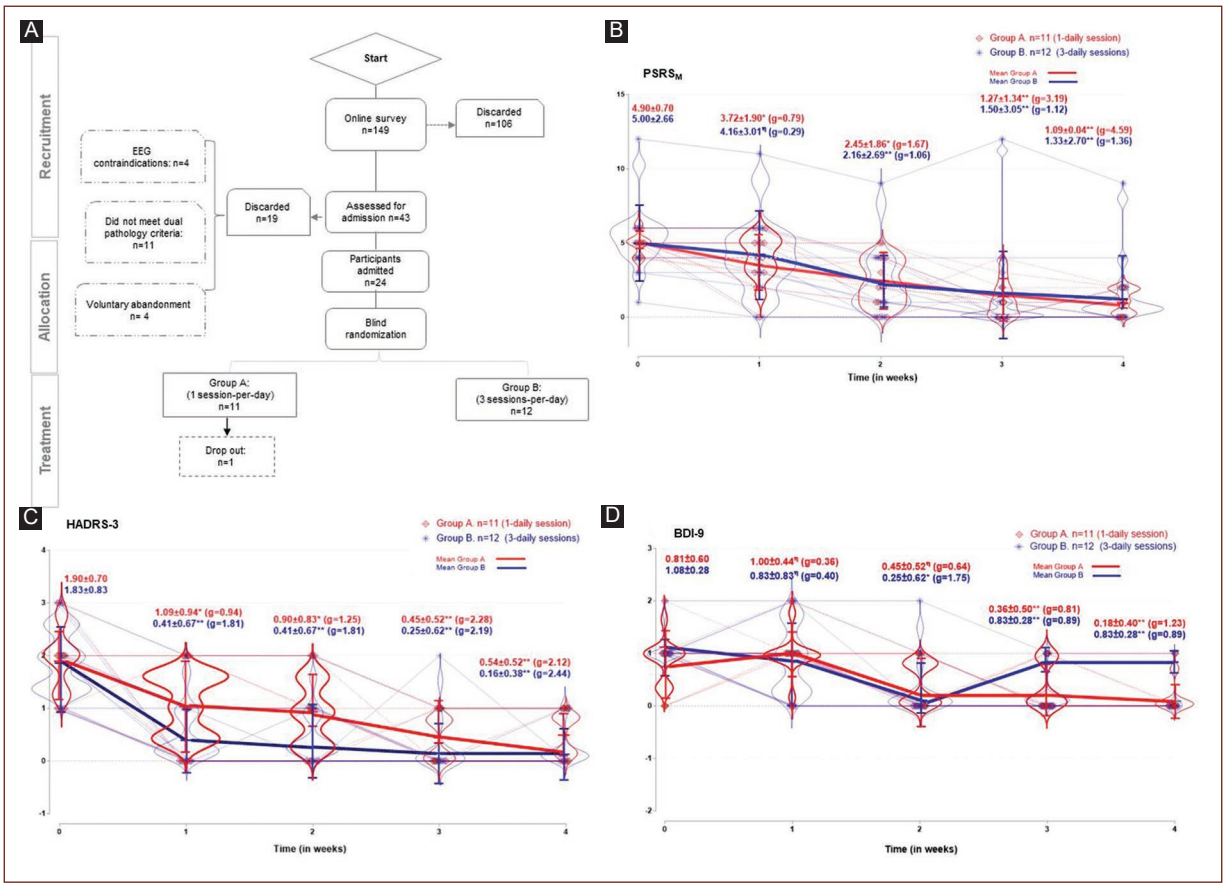

Figure 1. A: the flow diagram illustrates the stages (recruitment, allocation and treatment) of the iTBS protocol: 1 session (Group-A) and 3 sessions (Group-B). Only one drop out occurred during the treatment process. **B:** plutchik Suicide Risk Scale with the modifiable items (PSRS$_M$). Suicidal ideation structure can be assessed with **C:** rating depression scale item-3. **D:** beck depression inventory item-9. The X axis shows the evaluation time in terms of weeks: 0 (baseline), 4 (post treatment). The red (Group-A) and blue (Group-B) violin plots represents the distribution of the subjects throughout time. The Y axis shows the clinical scale scores; p-value ($p < 0.05$*; $p < 0.01$**; $p < 0.001$***; h = non-significant) Group A (n = 11), Group B (n = 12); g = Size Effect with Hedges g.

informed consent and were able to leave the study at their own free will at any time they wanted to.

A controlled triple-masked trial design with a non-probabilistic sample was used. Patients were randomized: Group A: bursts of 3 pulses at 50Hz, repeated at 5Hz for a 2-second period (10-bursts), followed by an 8-s intertrain interval, for a total of 600 pulses.

Group-B: Same parameters with a daily 3-time application and 10-min rest intervals in between each session.

Each patient chose an envelope with a randomization code which placed them in Group A (n = 11) or Group B (n = 12). To reduce bias, we masked the protocol to patients, iTBS provider and rater. The motor threshold was set at 80% (visual method). The treatment intensity consisted in the application of the minimum amount of single-pulse energy for the induction of cortical excitability.

Both groups received 4 weeks of iTBS (5-days per on week days), using a Magventure-Pro-R30 stimulation equipment, and an MCF-B70 stimulation coil.

The coil was positioned on the left dorsolateral prefrontal cortex ($_L$DLPFC). Positioning was determined by the 10-20 EEG system over F3, by means of location software (BA9, BA8, BA43 William-Beam and Jeff Borckardt), using vertex as reference, by marking the nasion-inion and tragus-tragus midpoints.

Primary outcome measures were changes on (A) presence/severity of symptomatology of depression, measured with the Hamilton depression rating scale (HADRS): 21-item version instrument to assess/follow-up severity of symptomatology and response to

Table 1. Mentions the clinical criteria for the diagnose of major depressive disorder according to DSM-5

Assessment scores on two treatment groups. Mean ± SD/(Hedges g)										
	HADRS		MADRS		BDI		HAM-A			
	Baseline	Post treatment	Baseline	Post treatment	Baseline	Post treatment	Baseline	Post treatment		
A	31.36 ± 6.03	8.72 ± 6.97** (2.92)	31.18 ± 5.70	9.09 ± 7.24** (3.29)	34.90 ± 8.43	5.45 ± 7.50** (4.30)	27.27 ± 6.18	9.45 ± 8.11** (2.37)		
B	29.36 ± 3.85	6.20 ± 4.80** (4.63)	31.90 ± 6.67	4.70 ± 3.94** (3.75)	34.36 ± 16.62	6.60 ± 6.85** (2.07)	24.36 ± 4.94	9 ± 6.63* (2.52)		
Weekly assessment scores on suicide risk behavior scales. Mean ± SD/(Hedges g)										
	PSRS					$PSRS_M$				
	Baseline	W1	W2	W3	W4	Baseline	W1	W2	W3	W4
A	10.54 ± 2.33	6.90 ± 2.21** (1.54)	4.45 ± 2.80** (2.27)	3.00 ± 2.75** (2.84)	2.18 ± 2.75** (2.84)	4.90 ± 0.70	3.72 ± 1.90* (0.79)	2.45 ± 1.86* (1.67)	1.27 ± 1.38** (3.19)	0.90 ± 0.94** (4.64)
B	9.81 ± 2.60	6.81 ± 3.54** (0.92)	3.90 ± 3.78** (1.75)	3.00 ± 3.94** (1.96)	3.37 ± 3.40** (2.04)	5.36 ± 2.46	4.54 ± 2.84 (0.29)	2.36 ± 2.73** (1.11)	1.63 ± 3.64** (1.15)	1.60 ± 2.91** (1.34)
Weekly assessment scores on suicide risk behavior scales. Mean ± SD/(Hedges g)										
	BHS									
	Baseline	W1	W2	W3	W4					
A	12.54 ± 4.94	8.27 ± 3.55* (0.95)	4.72 ± 3.03** (1.83)	3.81 ± 3.5* (1.9)	2.36 ± 2.01** (2.59)					
B	10.33 ± 6.47	7.72 ± 4.38 (0.46)	4.63 ± 3.44* (1.06)	3.09 ± 2.7* (1.4)	2.22 ± 2.44** (1.60)					
Weekly assessment on items related to suicide risk behavior on clinical depression scales. Mean ± SD/(Hedges g)										
	HADRS (3)					MADRS (10)				
	Baseline	W1	W2	W3	W4	Baseline	W1	W2	W3	W4
A	1.90 ± 0.70	1.09 ± 0.94 * (0.94)	0.90 ± 0.83* (1.25)	0.45 ± 0.52** (2.26)	0.54 ± 0.52** (2.12)	2.18 ± 0.75	1.63 ± 1.12* (0.55)	1.18 ± 1.07* (1.04)	0.63 ± 0.92* (1.77)	0.90 ± 0.30* (2.15)
B	1.90 ± 0.83	0.63 ± 0.67** (1.61)	0.45 ± 0.68** (1.83)	0.25 ± 0.62** (2.19)	0.20 ± 0.42** (2.48)	1.90 ± 1.04	1 ± 0.89 (0.89)	0.33 ± 0.50* (1.81)	0.08 ± 0.28* (2.48)	0.10 ± 0.28* (2.48)

(*Continues*)

Table 1. Mentions the clinical criteria for the diagnose of major depressive disorder according to DSM-5 (*continued*)

Weekly assessment on items related to suicide risk behavior on clinical depression scales. Mean ± SD/(Hedges g)												
	BDI (9)											
	Baseline	W1	W2	W3	W4							
A	0.81 ± 0.60	1.00 ± 0.44 (0.36)	0.45 ± 0.52 (0.64)	0.36 ± 0.50* (0.81)	0.18 ± 0.40* (1.23)							
B	1.08 ± 0.28	0.83 ± 0.83 (0.40)	0.25 ± 0.62* (1.75)	0.83 ± 0.28** (0.89)	0.83 ± 0.28** (0.89)							
Weekly assessment on absence of suicidal thinking structure with the depression items related to suicide. Percentage (%), n, Hazard Ratio (HR). Without presence of suicidal thinking (1)/ Presence of suicidal thinking (2)												
	HADRS (3)								MADRS (10)			
	W1		W2		W3		W4		W1		W2	
	36.3 (4)	50 (6)	36.7 (4)	50 (6)	54.5 (7)	83.310)	45.5 (5)	75 (9)	9.09 (1)	41.7 (5)	36.4 (4)	58.3 (7)
1	63.64 (7)	50 (6)	63.7 (7)	50 (6)	45.5 (4)	17.7 (2)	54.5 (6)	25 (3)	90.9 (10)	58.3 (7)	63.6 (7)	41.7 (5)
2	0.7272	1.37	0.5	1.37	0.84	1.17	0.555	1.8	0.215	4.58	0.624	1.60
HR=	36.3 (4)	50 (6)	36.7 (4)	50 (6)	54.5 (7)	83.3 (10)	45.5 (5)	75 (9)	9.09 (1)	41.7 (5)	36.4 (4)	58.3 (7)
Weekly assessment on absence of suicidal thinking structure with the depression items related to suicide. Percentage (%), n, Hazard Ratio (HR). Without presence of suicidal thinking (1)/ Presence of suicidal thinking (2)												
	MADRS (10)				BDI (9)							
	W3		W4		W1		W2		W3		W4	
	63.6 (7)	100 (12)	90.9 (10)	91.7 (11)	9.09 (1)	36.7 (4)	63.6 (7)	75 (9)	72.3 (8)	83.3 (10)	90.9 (10)	91.7 (11)
1	36.4 (4)	0 (0)	9.09 (1)	8.3 (1)	90.9 (10)	63.7 (7)	36.4 (4)	25 (3)	27.3 (3)	16.7 (2)	9.09 (1)	8.3 (1)
2	0.636	1.57	0.991	1	0.2476	4.03	0.848	1.17	0.8679	1.15	0.991	1
HR=	63.6 (7)	100 (12)	90.9 (10)	91.7 (11)	9.09 (1)	36.7 (4)	63.6 (7)	75 (9)	72.3 (8)	83.3 (10)	90.9 (10)	91.7 (11)

Data are presented as percentages (%), means, and standard deviations (SD). Effect size: Hedges' g. Clinical scales: HAM-D – Hamilton Depression Rating Scale (cut-off: non-depressive 0–7; mild 8–16; moderate 17–23; severe ≥24); HAM-A – Hamilton Anxiety Rating Scale; MADRS – Montgomery–Åsberg Depression Rating Scale (cut-off: non-depressive 0–6; mild 7–19; moderate 20–34; severe ≥ 35); BDI – Beck Depression Inventory (cut-off: minimal 0–9; mild 10–18; moderate 19–29; severe 30–63); PRS – Plutchik Suicide Risk Scale; PRSM – Modifiable items of PRS; BHS – Beck Hopelessness Scale; HAM-D (3), MADRS (10), BDI (9) – suicide-related items. L-DLPFC: left dorsolateral prefrontal cortex. p-values: ***p < 0.001, **p < 0.01, *p < 0.05. Timepoints: baseline, week 1 (W1), week 2 (W2), week 3 (W3), week 4 (W4), and post-treatment. Wilcoxon rank-sum test revealed statistically significant post-treatment differences between groups.

treatment[5]; the Montgomery–Asberg depression rating-scale (MADRS): 10-item interview to assess symptom severity. Items evaluate sadness, internal tension, sleep alterations, lack of concentration, laxity, anhedonia, pessimistic thoughts[6], and suicidal ideation; the Beck depression inventory (BDI): Self-report of symptomatology composed by 21 Likert-type items[7]. Anxiety symptoms were assessed with the Hamilton rating scale for anxiety (HAM-A)[8:] 14-item questionnaire to evaluate the severity of anxiety symptoms. Bias/response set on clinical scales was performed with the 33-item Marlowe Crowne social desirability scale (MCSD). (B) Suicide risk thoughts: beck hopelessness scale (BHS): 20 items with dichotomous answers (true/false), referring own well-being and attitude toward the future. Plutchik suicide risk scale (PSRS): a self-applied 26-item instrument with dichotomous response (Yes/No), which enables the identification of suicide attempts, impulsivity, plans related to self-destruction, hopelessness, depression, and use of sleep-inducing drugs[9].

An evaluation with PSRS, as well as with the items that quantify changes throughout the treatment ($PSRS_M$), was performed and the total score of the scale was obtained. An observation of changes in the structure of suicidal thinking over time was carried out using item 3 of the HADRS-3, and item 9 of the beck depression scale (BDI-9). BHS and item 10 of the MADRS-10 were used as a backup tool to assess the same symptomatology (Figs. 2A and B).

Statistical analysis

We used GraphPad Prism v.6, and the Statistical Package for the Social Sciences v.22. The analysis included the Mann–Whitney *U*-test for intergroup analysis; Friedman and Wilcoxon tests were used for intragroup assessment; effect size was calculated with Hedges' g and hazard ratio (HR) with a 95% confidence interval (CI) to observe risk reduction on suicidal thinking (HR ≥ 1: is considered statistically significant). $p \leq 0.05$ was considered statistically significant[10].

Results

Demographic and clinical data

Table 2 shows sociodemographic data, adverse effects, and clinical results. Assessments with MCSD scores were homogenous (Group A: Mean = 15.75 ± 2.45; Group B: Mean = 15.08 (4.01); p = 0.710) indicating participant unbiased response[11].

Depression and anxiety symptoms assessment with clinical scales

Depression/Anxiety baseline symptoms were in the range of moderate to severe with no differences among groups: HADRS (p = 0.249), MADRS (p = 0.869), BDI (p = 0.666), and HAM-A (p = 0.429) (Table 2).

Pre-post treatment analysis

Group-A

Outcomes showed differences for HADRS, MADRS, BDI (p = 0.003), and HAM-A (p = 0.005). The percentage decrease scores and the effect size were larger for this group on BDI (Table 2).

Group-B

Significant differences were found in the three scales of depression (p = 0.005) and anxiety (p = 0.011). The effect size on clinical scales was larger for this group on HADRS, MADRS, and HAM-A (Table 2). Percentage reduction in depressive symptomatology was larger for Group B with HADRS (86.88%-p = 0.005) and MADRS (85.26%-p = 0.005).

Scales related to suicidal risk behavior

Baseline scores were similar in both groups $PSRS_M$ (p = 0.918), HADRS-3 (p = 0.786), BDI-9 p = 0.90 (Figs. 1B-D). BHS (p = 0.440) and MADRS-10 (p = 0.699) (Fig. 2).

Pre-post treatment analysis

Group-A

Results showed differences $PSRS_M$ and HADRS-3 ($p < 0.05$ and $p < 0.005$, Figs. 1B and C); BDI for the last 2 weeks ($p < 0.05$; Fig. 1D); BHS ($p < 0.05$ and $p < 0.005$).

Group-B

Analyses showed differences in $PSRS_M$ ($p < 0.005$) in the last 3 weeks, HADRS-3 ($p < 0.005$), and BDI-9 ($p < 0.005$) in the last 2 weeks (Table 2 and Figs. 1B-D).

Table 2. Sociodemographic and clinical analysis of both groups under iTBS treatment

Statistical sociodemographic of the participants of the study on both iTBS treatment groups. Demographic data of the participants of the study (n = 23) (Mean ± SD)						
Group	Age	Gender (n)		Years of academic education	Number of lifetime of depressive episodes	Lifetime suicide attempts
		Men (n = 8/36.36%)	Women (n = 15/63.63%)			
A (n = 11)	38.00 ± 12.05	4		7	15.45 ± 2.84	4.63 ± 2.76
B (n = 12)	41.25 ± 10.25	4		8	15.83 ± 2.16	5.41 ± 3.11
Adverse effects during treatment with iTBS (%)						
Headaches after session	Headaches during the day	Dizziness		Nausea	Auditory discomfort	Seizures
A	9.09	0		9.09	0	0
B	9.09	9.09		9.09	0	0

On BHS ($p < 0.05$), HR (CI = 95%) showed a higher percentage of suicidal thoughts absence for Group B (Table 2).

Discussion

To our knowledge, this is the first study comparing an accelerated iTBS protocol (3 sessions) with an approved iTBS procedure to observe clinical effectiveness on non-structured and semi-structured suicide thinking. Regarding the decrease in depressive and anxiety symptoms, both groups achieved ≥ 70% reductions. This is similar to the results found by Desmayter et al.[12] and Baeken et al.[13], in a 4-day Sham versus control study (n = 50 and n = 45, respectively), with reductions of up to 50% for those who received active iTBS (5-daily sessions). Nonetheless, our study seeks a larger follow-up through time, to observe the clinical evolution of our participants and, also evaluating hopelessness and suicidal risk behaviors, where the changes in both groups showed differences ($p \leq 0.05$) in PSRS. Concerning to the clinical outcomes, our study found a decrease in suicidal thinking in a higher percentage of the population, as well as a greater tolerance to pulses compared to rates reported by Richard et al. 2022, on depressed patients with suicidal thinking (n = 22). Their results showed an 18.2% response-to-treatment rate, and an 18.5% rate of tolerance to receive 1,800 pulses daily. This raises the question of whether the differences between this study and ours could be due to the fewer daily sessions with Group B compared to the 5 daily sessions carried out by Richard et al. However, statistically speaking, the percentage decrease in suicidal thinking was greater in our clinical trial, and we were able to measure this effectiveness by also including the effect size. Although we consider the relevance of achieving clinical effectiveness and risk reduction on suicidal thinking in a shorter period, we also seek to maintain this effect over time, as seen in the statistical significance of our study (Table 2). Despite both groups obtaining the outcomes, Group B had a better response to treatment overall. Regarding the absence of suicidal thinking each week, HR analysis showed Group B had a higher chance to see these thoughts reduced, which highlights the relevance of creating preventive approaches by monitoring suicidal thinking at an early onset stage by reducing the risk of impulsive behavior and early suicide attempts, while continuing to assess the evolution of the patients' behavior under treatment. It is important to underline that during the study, none of the patients achieved any structured suicidal ideation or direct lethal behaviors that could threaten at any moment the life of the patient. We secured that by providing the participants, psychiatric and psychological assessments with specialized personnel along with having at all times contact with patient's primary support network and communication and feedback with the patient's adscripted health services. Having this in mind, our purpose, as we stated before, is to look for approaches by monitoring early onset of suicidal thinking instead of acting on the severe stages when there are more threats to the patient's life.

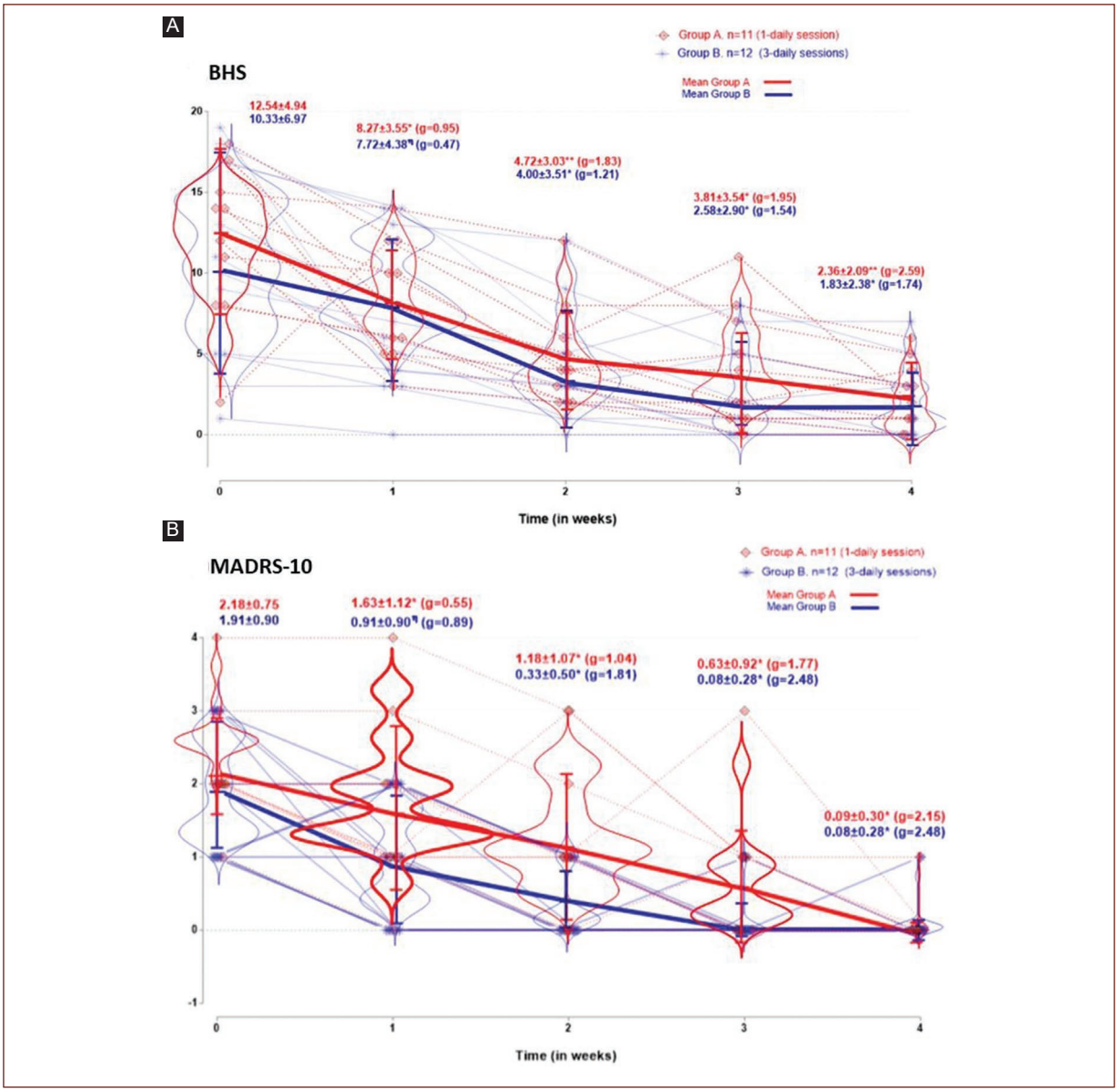

Figure 2. Risk of variables associated with suicidal behavior was assessed with. **A:** beck hopelessness scale. Suicidal ideation structure can be assessed with. **B:** montgomery-asberg rating depression scale item-10. The X axis shows the evaluation time in terms of weeks: 0 (baseline), 4 (post-treatment). The red (Group-A) and blue (Group-B) violin plots represents the distribution of the subjects throughout time. The Y axis shows the clinical scale scores. p-value ($p < 0.05$*; $p < 0.01$**; $p < 0.001$***; h = non-significant). Group A (n = 11); Group B (n = 12). g = Size Effect with Hedges g.

Conclusion

This study is a glimpse into what we can do by comparing several forms of stimulation throughout time to understand more suitable stimulation protocols in response to harmful thinking and behavior. Limitations on the study related to the pandemic did not allow us to compare a 5-sessions per-day protocol. Other limitations are related to the small sample size for each group, which is crucial to understand in the long term the effects of an early onset intervention and the impact of suicidal behavior on clinical depressed patients.

Since we did not face any threats of suicide or more structured suicidal thoughts during the course of the study, we have to look ahead for if this type of intervention represents an innovation in terms of improve the quality of life of the patient without achieve peaks of unnecessary risks that in terms of availability of places for hospitalization, interventions, and resources,

could be represent a more dynamic intervention that does not imply to put a pause in other aspects of the life of the patient such as productivity and a quicker recover from their symptoms.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality of data. The authors declare that they have followed their center's protocols for the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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