Cerebral Hemodynamics With rTMS in Alcohol Dependence: A Randomized, Sham-Controlled Study

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The authors studied cerebral hemodynamics in alcohol dependence and evaluated their changes with application of high-frequency rTMS. A prospective, single-blind, randomized, parallel-group, sham-controlled clinical study was conducted with patients with alcohol dependence (*DSM-IV-TR*). The study population comprised 25 subjects each in active rTMS, sham rTMS, and healthy control groups. At baseline, cerebral hemodynamic indices were measured with transcranial Doppler sonography. Subjects in the active rTMS group received 10 sessions of rTMS daily; the sham group was administered sham rTMS with the same parameters. Cerebral hemodynamic parameters were repeated 5 minutes after the last rTMS session. At baseline, mean velocity (MV) of both middle cerebral artery (MCA; R-MCA: p=0.003; L-MCA: p=0.002) and anterior cerebral artery (ACA; R-ACA: p=0.003; L-ACA: p=.001) was significantly reduced. Pulsatility index (PI) of MCA ($p<0.001$) and resistance index (RI) of ACA (R-ACA: p=0.009; L-ACA: p=0.008) were increased in alcohol-dependent subjects in comparison with healthy controls. In the active rTMS group, except L-MCA PI, significant differences were observed in values of MV, PI, and RI of both MCA and ACA following rTMS intervention; such changes were not evident in the sham rTMS group. The changes in mean difference in MV of L-MCA (p=0.006) and L-ACA (p=0.015) were statistically significant in the active rTMS group, in comparison with the sham group. Significant differences were also observed between the two groups postintervention, in RI of L-MCA (p=0.001) and ACA (R-ACA: p=0.010; L-ACA: p=0.015). Alcohol dependence may result in altered cerebral hemodynamic parameters, which can be improved with high-frequency rTMS application.

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Alcohol abuse is a worldwide problem causing serious physical, psychological, social, and economic consequences. Chronic alcohol intake has been found to increase blood viscosity, impair erythrocyte deformability, and cause dehydration, resulting in alterations of cerebral blood flow measures.[1] Transcranial Doppler (TCD) sonography is a noninvasive radiological tool used for assessing the hemodynamics of the basal cerebral arteries, which can thus indirectly reflect the relative changes in regional cerebral blood flow velocity (CBFV) and vascular wall resistance.[2] TCD has been used to evaluate the relative CBFV changes in various psychiatric disorders, such as depression;[3–5] schizophrenia;[6–8] panic disorder;[9] and substance use disorders, including alcohol and marijuana abuse and dependence.[1,10–14] The various cerebral hemodynamic indices measured by TCD include mean flow velocity (MV), which is the average of the edge frequency over a cardiac cycle, and the pulsatility index (PI) and resistance index (RI), which provide an estimation of the downstream vascular resistance. The low PI and RI of the cerebral vasculature reflect the brain's unique metabolic need, which requires continuous blood flow throughout the cardiac cycle.[15,16]

Previous studies on the natural course of cerebral hemodynamics in alcohol dependence have revealed its vasoconstrictive effect, which leads to increased vascular resistance and significant global reduction of regional cerebral blood flow, especially during the first two days of withdrawal, which gradually normalizes over the next few days.[1,12] Increase in blood viscosity, dehydration, and impairment of autoregulation of cerebral blood flow can result in abnormal erythrocyte morphology and increased erythrocyte fragility. These changes produce reduction in CBFV, ultimately resulting in increased risk for ischemic brain infarctions and other cerebrovascular accidents. Chronic alcohol intake has been identified as a risk factor in development of diabetes mellitus, hypertension, and coronary artery disease, all of which can further add to the risk of cerebrovascular accident.[12] The therapeutic interventions in relation to alcohol dependence should target not only craving reduction but also normalization of altered cerebral hemodynamics as a part of primordial prevention for cerebrovascular diseases.

In alcohol dependence, benzodiazepines are used for detoxification, and, to date, no studies have investigated the effect of benzodiazepines in altering the cerebral hemodynamic changes. So, at present, there is no approved treatment available for correcting the altered cerebral hemodynamics in patients with alcohol dependence. High-frequency prefrontal repetitive transcranial magnetic stimulation (rTMS)

has been found to reduce craving-related measures in alcohol and other substance dependence. In our previous two studies,[17,18] we found an anticraving effect of rTMS in alcohol dependence; hence, we intended to explore the possible additional effect of rTMS application on the altered cerebral hemodynamics in patients with alcohol dependence.

METHODS

Study Design

The present study is a prospective, hospital-based, single-blind, randomized, parallel-groups, sham-controlled clinical study conducted at the Central Institute of Psychiatry, Kanke, Ranchi, India. Subjects were recruited according to inclusion and exclusion criteria. Randomization was done by means of a computer-generated random list, and after randomization the patients were assigned to the active and sham rTMS groups. The study population comprised 75 subjects (with the exclusion of three patients who dropped out of the study): 25 subjects each in the active rTMS, sham rTMS, and healthy control groups. At baseline, demographic and relevant clinical data, including cerebral hemodynamic indices, were collected. Subjects in the active rTMS group received 10 sessions of 10-Hz rTMS daily over the right dorsolateral prefrontal cortex, and the sham group was administered rTMS with the same parameters, but with a figure-of-eight sham coil. Cerebral hemodynamic parameters were repeated 5 minutes after the last rTMS session by TCD sonography.

Subjects

The subjects were right-handed, male patients 18–60 years old, with a diagnosis of alcohol dependence according to *DSM-IV-TR*, after resolution of withdrawal symptoms (i.e., Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal [CIWA-Ar] score of $\leq$10).[19] The Handedness Preference Schedule (Hindi version) was used to determine the handedness of the patients. Patients with comorbid psychiatric, major medical, or neurological disorders or with a pacemaker or metal in any part of the body were excluded from the study. The control group comprised 25 healthy male volunteers aged between 18 and 60 years.

Outcome Measures

Demographic and other relevant clinical data were collected. Baseline measurement of middle cerebral artery (MCA) and anterior cerebral artery (ACA) blood flow velocities of both sides was done by Multi-Dop X4 ultrasound system, along with a computer-assisted pulsed 2-MHz Doppler device (DWL Multidop, Sipplingen, Germany), after a resting and relaxation period of at least 5 minutes. Transtemporal route of insonation was used for measuring the various cerebral hemodynamic indices. This "spectrum" of different frequency shifts (velocities) was visually displayed with Fast Fourier transform, from which the various spectral parameters were analyzed and the hemodynamic indices were measured. To detect and monitor CBFV in the MCA territory, we examined the M_1 segment of the ipsilateral and contralateral MCA using a 2-MHz probe. Similarly, for ACA, the A_1 segment of both sides was used to monitor CBFV. TCD was performed according to the following parameters: sample volume, 10–12 mm; depth, 40–55 mm for MCA (M_1 segment), 60–75 mm for ACA (A_1 segment); power, 100 mW/cm^2; filter, 50 Hz; gain, 30%. The transtemporal approach was used to locate the MCA and ACA. The hemodynamic indices, including MV, PI, and RI of MCA and ACA were documented at baseline before rTMS began and again 5 minutes after the last rTMS.

The motor threshold (MT) for the left abductor pollicis brevis (APB) was determined with the Neuropack Sigma evoked potential measuring system (Nihon Kohden, Japan), with a figure-of-eight-shaped coil at 1-Hz frequency, according to the Rossini-Rothwell algorithm. Ten daily sessions (five per week, for 2 weeks) of rTMS treatments (done with the Magstim Rapid device; Magstim Company Ltd., Whitland, Wales, United Kingdom) were administered over the right dorsolateral prefrontal cortex (DLPFC; at 110% of the MT determined) with an air-cooled figure-of-eight coil, angled tangentially to the head. To find the hand area of the motor cortex, we positioned the center of the figure-of-eight TMS coil 5 cm lateral to the vertex on the interauricular line and angled the handle 45° away from the sagittal plane. We determined the right prefrontal cortex rTMS stimulation site by measuring 5 cm anterior and in a parasagittal line from the point of maximum stimulation of contralateral APB muscle.[20] At the right prefrontal cortex, active high-frequency (10-Hz) stimulation was administered for 4.9 seconds per train, with an intertrain interval of 30 seconds and a total of 20 trains per session. Each patient received 1,000 pulses per day. The sham group was administered rTMS with the same parameters, but with a figure-of-eight sham coil. Measurement of ACA and MCA blood flow velocities of both sides by TCD sonography was repeated 5 minutes after the last active or sham rTMS. After completion of the last TCD recording, patients were given medications as decided by the treating team.

Ethical Issues

The study was approved by the Institute Ethics Committee, and the procedures followed in this study are in accordance with the ethical standards laid down by the Indian Council of Medical Research's ethical guidelines for biomedical research on human subjects (as of 2006). A written informed consent was taken from all the subjects participating in the study, after explanation of the patient's diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed treatment (rTMS), alternative treatment, and the risks and benefits of the alternative treatment.

Statistical Analysis

The data were analyzed with SPSS (version 20; SPSS Inc., Chicago). One-way analysis of variance (ANOVA), followed

TABLE 1. Baseline Cerebral Hemodynamic Data in Study Groups[a]

Parameter	Mean±SD			p Value (One-Way ANOVA)	Tukey-Kramer Multiple-Comparison Posttest (q Value)		
	Healthy Control (H)	Sham rTMS (S)	Active rTMS (A)		H vs. S	H vs. A	S vs. A
R-MCA MV[b]	60.12±10.4	51.24±9.3	52.84±8.8	0.003*	4.653*	3.815*	0.839
L-MCA MV[b]	59.92±9.3	51.76±8.8	52.4±8.4	0.002*	4.611*	4.250*	0.362
R-ACA MV[b]	48.12±6.4	42.08±6.6	43.24±6.3	0.003*	4.719*	3.813*	0.906
L-ACA MV[b]	48.68±6.0	42.64±6.1	43.08±5.6	0.001*	5.104*	4.732*	0.372
R-MCA PI	0.71±0.09	0.92±0.11	0.94±0.11	<0.001*	9.842*	10.599*	0.757
L-MCA PI	0.74±0.09	0.93±0.10	0.92±0.10	<0.001*	9.463*	9.061*	0.403
R-ACA PI	0.90±0.08	0.95±0.14	0.96±0.11	0.12	NA	NA	NA
L-ACA PI	0.91±0.08	0.96±0.12	0.97±0.10	0.10	NA	NA	NA
R-MCA RI	0.56±0.07	0.62±0.07	0.62±0.06	0.028	NA	NA	NA
L-MCA RI	0.57±0.07	0.63±0.07	0.62±0.06	0.020	NA	NA	NA
R-ACA RI	0.63±0.08	0.67±0.07	0.69±0.06	0.009*	2.809	4.446*	1.634
L-ACA RI	0.62±0.08	0.66±0.07	0.68±0.06	0.008*	3.013	4.461*	1.447

[a] Posttest was done only when the p value of one-way analysis of variance (ANOVA) was significant ($p<0.02$). Abbreviations: ACA, anterior cerebral artery; L, left; MCA, middle cerebral artery; MV, mean flow velocity; NA, not applicable; PI, pulsatility index; RI, resistance index; R, right; rTMS, repetitve transcranial magnetic stimulation.
[b] In centimeters per second.
*$p<0.02$.

by Tukey-Kramer multiple-comparison posttest, was used to compare baseline demographic and clinical variables among the healthy control, sham rTMS, and active rTMS groups. Paired t test was used to compare the hemodynamic changes in the sham control and active groups before and after intervention. Comparison of mean hemodynamic changes of the sham and active rTMS groups was done by unpaired t test. In our study, three main hemodynamic parameters (MV, PI, RI) were assessed through multiple comparisons; hence, Bonferroni correction was done, and the level of statistical significance was set at $p<.02$ (two tailed).

RESULTS

In our study, mean age in the healthy control, sham rTMS, and active rTMS groups was 8.7 years, 7.8 years, and 7.1 years, respectively. The mean±SD duration of alcohol dependence was 7.6±2.9 years in the active rTMS group and 6.4±2.8 years in the sham rTMS group, without any statistically significant difference between the groups. The time from last drink until the rTMS intervention period (duration for detoxification and wash-out time for Lorazepam) varied from 14 to 18 days (until CIWA-Ar scores were ≤10). Table 1 shows the comparison of baseline hemodynamic indices (i.e., the MV in centimeters per second, PI, and RI) in the MCA and ACA, among the three groups.

Comparison of Baseline Parameters

One-way ANOVA followed by Tukey-Kramer multiple-comparison posttest revealed that the MV in both right and left MCA and ACA was significantly reduced in both active and sham rTMS groups in comparison with the healthy control group. Posttest also revealed that there was no statistically significant difference between the sham and active rTMS groups at baseline. In both right and left MCA, PI was increased significantly in both active and sham rTMS groups in comparison with the healthy control group, and no significant difference was found between the sham and active rTMS groups at baseline. In the case of PI of ACA, the results of the one-way ANOVA show that there was no significant difference between the groups and, hence, posttest was not applicable. The RI of both right and left ACA was significantly increased in the active rTMS group in comparison with the healthy control group. Posttest revealed that there was no significant difference between the sham rTMS and healthy control groups or between the sham and active rTMS groups.

Hemodynamic Changes in Active and Sham rTMS Groups Following Intervention

Table 2 reflects the changes in MV, PI, and RI of both MCA and ACA in the active and sham rTMS groups following rTMS intervention. In the active rTMS group, except for left MCA PI, statistically significant differences were observed in values of MV, PI, and RI of both MCA and ACA, before and after rTMS intervention. However, in the sham rTMS group, no statistically significant changes were observed in MV, PI, or RI of both MCA and ACA at baseline and following rTMS intervention.

Comparison of Changes in Hemodynamic Parameters Between Active and Sham rTMS Groups Following Intervention

Table 3 compares the mean changes in MV, PI, and RI of both MCA and ACA, between the active and sham rTMS groups following rTMS intervention. The difference in MV of left MCA and left ACA was statistically significant between the active and sham rTMS groups following rTMS intervention. Significant differences were also observed between the two groups, postintervention, with respect to RI of both right and left MCA and ACA. However, no significant differences were observed between the groups with regard to PI of both right and left MCA and ACA.

TABLE 2. Changes in the Cerebral Hemodynamic Parameters in Sham rTMS and Active rTMS Groups After rTMS Intervention[a]

	Sham rTMS Group				Active rTMS Group			
Parameters	First Visit	Second Visit	p Value[b]	95% CI for Difference in Mean	First Visit	Second Visit	P Value[b]	95% CI for Difference in Mean
R-MCA MV[c]	51.24±9.3	52.04±9.1	0.09	−1.7458 to −0.1458	52.84±8.8	55.16±7.1	<0.001*	−3.3006 to 1.3394
L-MCA MV[c]	51.76±8.8	52.20±7.4	0.19	−1.1149 to −0.2349	52.4±8.4	54.56±7.4	<0.001*	−3.1828 to −1.1372
R-ACA MV[c]	42.08±6.6	42.84±5.6	0.07	−1.5965 to −0.0765	43.24±6.3	45.48±5.4	<0.001*	−3.3143 to −1.1657
L-ACA MV[c]	42.64±6.1	43.28±5.7	0.08	−1.3734 to −0.0934	43.08±5.6	45.40±4.6	<0.001*	−3.4858 to −1.1542
R-MCA PI	0.92±0.11	0.89±0.11	0.13	−0.0088 to 0.0648	0.94±0.11	0.89±0.09	0.018*	0.0081 to −0.0799
L-MCA PI	0.93±0.10	0.89±0.09	0.09	−0.0052 to −0.0692	0.92±0.10	0.88±0.08	0.026	0.0047 to −0.0673
R-ACA PI	0.95±0.14	0.92±0.11	0.09	−0.0068 to −0.0788	0.96±0.11	0.91±0.11	0.002*	0.0221 to −0.0899
L-ACA PI	0.96±0.12	0.93±0.11	0.07	−0.0032 to 0.0672	0.97±0.10	0.92±0.09	0.001*	0.0291 to −0.0829
R-MCA RI	0.62±0.07	0.61±0.08	0.22	−0.0029 to 0.0117	0.62±0.06	0.60±0.07	<0.001*	0.0080 to −0.0192
L-MCA RI	0.63±0.07	0.62±0.08	0.07	−0.0004 to 0.0092	0.62±0.06	0.60±0.07	<0.001*	0.0125 to −0.0284
R-ACA RI	0.67±0.07	0.66±0.06	0.07	−0.0005 to 0.0125	0.69±0.06	0.67±0.06	<0.001*	0.0121 to −0.0223
L-ACA RI	0.66±0.07	0.65±0.06	0.06	−0.0001 to 0.0201	0.68±0.06	0.66±0.05	<0.001*	0.0102 to −0.0298

[a] Abbreviations: ACA, anterior cerebral artery; CI, confidence interval; L, left; MCA, middle cerebral artery; MV, mean flow velocity; PI, pulsatility index; R, right; RI, resistance index; rTMS, repetitve transcranial magnetic stimulation.
[b] Paired t test.
[c] In centimeters per second.
*p<0.02.

DISCUSSION

Previous studies on cerebral hemodynamic changes with alcohol intake have reported contradictory findings.[1,12,14] The studies have evaluated the effect of acute alcohol intake, chronic alcoholism, and withdrawal state-related changes on various cerebral hemodynamic indices but have involved small sample sizes. In view of the same, the present study was designed and conducted on a larger sample, to evaluate the exact changes in various cerebral hemodynamic indices in subjects with alcohol dependence and the relative changes in the cerebral hemodynamics with rTMS application.

TABLE 3. Comparison of Changes in Cerebral Hemodynamic Parameters in Sham rTMS and Active rTMS Groups After rTMS Intervention[a]

	Mean Difference			
Parameters	Sham rTMS Group	Active rTMS Group	P Value[b]	95% CI for Difference in Mean
R-MCA MV[c]	0.80	2.32	0.026	0.1928 to 2.8472
L-MCA MV[c]	0.44	2.16	0.006*	0.5262 to 2.9138
R-ACA MV[c]	0.76	2.24	0.029	−2.8064 to −0.1536
L-ACA MV[c]	0.64	2.32	0.015*	−3.0218 to −0.3382
R-MCA PI	0.03	0.05	0.520	−0.0341 to 0.0661
L-MCA PI	0.04	0.04	0.870	−0.0513 to 0.0433
R-ACA PI	0.03	0.05	0.450	−0.0332 to 0.0732
L-ACA PI	0.03	0.05	0.460	−0.0272 to 0.0592
R-MCA RI	0.01	0.02	0.040	−0.0181 to −0.0003
L-MCA RI	0.01	0.02	0.001*	−0.0250 to −0.0069
R-ACA RI	0.01	0.02	0.010*	−0.0193 to −0.0031
L-ACA RI	0.01	0.02	0.015*	−0.0237 to −0.0037

[a] ACA, anterior cerebral artery; CI, confidence interval; L, left; MCA, middle cerebral artery; MV, mean flow velocity; PI, pulsatility index; R, right; RI, resistance index; rTMS, repetitve transcranial magnetic stimulation.
[b] Unpaired t test.
[c] In centimeters per second.
*p<0.02.

The findings of our study indicate reduction in MV in cerebral basal arteries in patients with alcohol dependence in comparison with healthy controls. The RI of ACA and the PI of MCA of both sides were increased significantly in subjects with alcohol dependence when compared with healthy controls. In earlier studies, ethanol in low concentration has been reported to increase the systolic, diastolic, and MV and significantly decrease the PI in the MCA, by reducing the cerebrovascular resistance.[14,16] But in a sham-controlled study by Gdovinova with subjects with chronic alcohol intake in heavy amounts, significantly reduced MV was found in both the right as well as the left MCA, in comparison with healthy volunteers, which implicates the role of increased blood viscosity, erythrocyte deformability, or dehydration in chronic alcoholism.[1] In another study conducted with heavy alcohol drinkers, the changes in CBFV were measured by 2-MHz TCD, and erythrocyte deformability was determined by the method of cation-osmotic hemolysis and compared with healthy controls. The mean CBFV in the left and right MCA was found to be significantly decreased in the acute stage, with a significant increase after 14 days of withdrawal, whereas the erythrocyte deformability showed only a small change.[12] In our study, the decreased mean blood flow velocity in the active and sham rTMS groups can be explained on the basis of chronic alcoholism producing increasing blood viscosity and erythrocyte deformability. Chronic alcohol intake could have produced atherosclerotic changes of cerebral blood vessels and increased intimal layer thickening, which can explain the increased PI and RI of the major cerebral basal arteries.

In our study, subjects with alcohol dependence who received active high-frequency (10-Hz) rTMS at right DLPFC showed a significant increase of MV in cerebral basal arteries following rTMS intervention. Except for left MCA PI, there was significant reduction in the PI and RI of both MCA

and ACA after rTMS intervention. However, the patients with alcohol dependence who were subjected to sham rTMS did not show any significant change in any cerebral hemodynamic parameters. We compared the mean change of the various cerebral hemodynamic parameters between the active and sham rTMS groups. The comparative analysis revealed that there was a significant increase in MV of the left MCA and ACA in the active compared with the sham rTMS group. There was a reduction in RI in the active rTMS as compared with the sham rTMS group, but there was no statistically significant change in PI of basal cerebral arteries between the groups. Our extensive literature review revealed that similar rTMS studies on cerebral hemodynamics in alcohol-dependent populations are lacking. Hence, to discuss the abovementioned findings of our study, we reviewed the results (and their possible explanation) of similar studies involving healthy individuals. In a TCD study following TMS application in healthy individuals, Sander et al found a significant increase in MV of ipsilateral MCA, ranging from 5.3% for single stimuli to 8.5% for triple TMS stimuli (10 Hz, 80%−100% of MT) when applied to the motor cortex.[21] In a similar study, 3- and 6-Hz rTMS of the occipital cortex induced an increase of the ipsilateral posterior cerebral artery flow velocity between 10.2% and 12.8%.[22] In 20 healthy subjects, the MV and PI were measured by TCD, and oxygen consumption was recorded continuously and averaged, directly after rTMS application to the left hemisphere; a maximal increase in CBFV was seen only in the left MCA during 10-Hz and 20-Hz stimulation, whereas the PI and blood oxygen were found to be unchanged during the entire procedure.[2] However, a TCD study involving healthy subjects reported that low-frequency rTMS (0.9 Hz, at 90% of MT) produced a temporary decrease of maximal CBFV in the ipsilateral MCA, followed by an increase in the contralateral MCA, in persons receiving active rTMS, as compared with sham stimulation.[20] The increase in CBFV following high-frequency rTMS application has been hypothesized to be possibly due to dilatation of the small cerebral resistance vessels. The changes observed in our study only in the active rTMS group reflect the vasodilatory effect of high-frequency rTMS on the small cerebral resistance vessels.

Limitations of the study were that it did not include a double-blind study design and a longer patient follow-up to check the sustainability of the changes in hemodynamic parameters and clinical response.

CONCLUSIONS

From the findings of our study, it can be concluded that the altered cerebral hemodynamic parameters seen in alcohol dependence can be improved with high-frequency rTMS application. To produce the sustained beneficial effects of rTMS on cerebral hemodynamic derangements in alcohol dependence, the rTMS protocol should be optimized and prospectively followed up over a longer time frame.

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