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Pilot randomized active-placebo-controlled trial of low-dose ketamine for the treatment of multiple sclerosis–related fatigue

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Abstract

Background: Fatigue is the most common symptom of MS and has no effective pharmacotherapy.

Objective: To determine the tolerability, safety, and efficacy of low-dose ketamine infusion for MS-related fatigue.

Methods: In this double-blind, randomized, active-placebo-controlled trial, 18 subjects with multiple sclerosis (MS) and reported fatigue received a single intravenous infusion of ketamine (0.5 mg/kg) or midazolam (0.05 mg/kg). The primary outcome was change in Daily Fatigue Severity (DFS) for 7 days following the infusion. Secondary outcomes included Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) measured up to day 28 post-infusion. We analyzed changes in all outcomes using mixed-effect models.

Results: In total, 18 participants were enrolled; 67% participants received ketamine. Side effects of ketamine were transient. No change in the DFS was observed after 7 days (−0.10 point; 95% confidence interval (CI): −0.32, 0.12; $p=0.40$). We observed a trend in reduced FSS scores at 1 week (−5.2 points; 95% CI: −10.4, 0.14; $p=0.06$) and a clinically and statistically significant reduction in MFIS score at day 28 (−13.5 point; 95% CI: −25.0, −1.98; $p=0.04$).

Conclusions: Ketamine infusions were safe and well-tolerated. While no change in DFS after 7 days was observed, secondary analyses suggest a benefit of ketamine infusion for reduction of longer term fatigue severity in people with MS.

Keywords: Multiple sclerosis, fatigue, ketamine, midazolam, randomized controlled trial

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Introduction

Of all the symptoms that can occur with multiple sclerosis (MS), chronic fatigue is the most common and disabling, reported by at least 75% of patients at some point.[1–3] Fatigue, defined as an overwhelming feeling of tiredness and exhaustion, results in negative socioeconomic consequences by limiting patients' daily activities[4] and challenging employment.[5] Despite this substantial impact, fatigue treatments have been inconsistently studied, in part due to poorly understood underlying pathophysiological mechanisms.[6,7] These yet to be defined contributing biological processes and a lack of clear treatment targets have also hampered the development of pharmacologic treatments for MS-related fatigue. There are no medications currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of MS-related fatigue. While several agents have been tested for this indication, methodological limitations in the design, execution, and reporting of those trials have not allowed meta-analyses or systematic reviews make conclusions related to efficacy.[8] Psychostimulants and wake-promoting agents are currently used for the treatment of MS-related fatigue in the clinical practice, with minimal or no evidence supporting their effectiveness. Finding new treatment targets for this disabling symptom of MS is likely to have a substantial positive impact on the quality of life of people living with MS.

MS fatigue has a complex and multifactorial pathophysiology. Neuroendocrine abnormalities and inflammatory cytokines have been proposed to contribute to the development of fatigue in patients with

MS;[9–12] however, studies have failed to show consistent associations.[13–15] Structural and functional brain changes have been found to be associated with MS fatigue. Atrophy in several structures of the brain[16,17] and lesions located in the frontal and parietotemporal white matter[18] may contribute to the pathogenesis of fatigue. Connectivity changes in cortical and subcortical structures have been found in patients with MS fatigue.[19,20] However, this pathophysiological knowledge has not been translated into therapeutic approaches for fatigue.

We recently reported that riluzole, a medication with anti-glutamatergic effects, increased the fatigue severity in patients with relapsing MS who had participated in a clinical trial evaluating potential neuroprotective effects of riluzole versus placebo.[21] Worsening fatigue severity was also observed in three trials of memantine (an N-methyl D-aspartate (NMDA) glutamate receptor blocker) for cognition in people with MS.[22–24] Taken together, these observations motivated us to hypothesize that glutamatergic transmission could play an important role in fatigue pathogenesis and the modulation of this pathways could have potential therapeutic effects on MS-related fatigue. This hypothesis is supported by secondary analyses of other glutamate-modulating therapeutics in other disorders. Ketamine, an open-channel nonselective NMDA receptor antagonist, has profound and rapid antidepressive effects.[25] These effects are mediated, in part, by increasing glutamate release in the prefrontal cortex.[26,27] In one trial of ketamine, versus placebo in patients with bipolar disorder, investigators found a fast and prolonged improvement of fatigue in participants who received ketamine.[12] While the authors subsequently reported that the anti-fatigue effects of ketamine might have been mediated by its effect on improving depression,[28] depression and fatigue are often highly correlated, and both symptoms commonly co-occur in people with MS.[29] Based on these observations, we conducted a pilot study to determine whether modulating glutamatergic pathways with ketamine is safe and efficacious for improving MS-related fatigue and if the anti-fatigue effects are related to the antidepressive effects of this medication.

Materials and methods

Study design and participants

This study was a pilot, randomized, double-blind, active-placebo controlled trial. Eligible subjects were randomized 2:1 to a single intravenous infusion of ketamine versus midazolam (a very short-acting benzodiazepine). We chose the 2:1 allocation ratio in favor of ketamine to encourage participation, as it was more likely for each participant to receive the active medication. Midazolam was used as an active placebo, so the sedative and psychomimetic effects of ketamine would not unblind the staff and the participants. Midazolam has a short half-life and does not have known fatigue-inducing effects. We limited our intervention to only one infusion, as there was no prior safety data of using ketamine in patients with MS, and we wanted to limit the exposure of patients to ketamine. We also did not know how long the possible therapeutic effects of ketamine would last, and timing a subsequent infusion was not possible. Patients were recruited through advertisements and physician referrals from the Johns Hopkins Multiple Sclerosis Center. Recruitment was initiated in February 2019 and completed in August 2019. Eligibility criteria included age 18–65 years, diagnosis of MS according to the 2010 McDonald criteria, able to ambulate (at least 20 ft with or without assistance), self-reported current fatigue and screening-Modified Fatigue Impact Scale (MFIS) score >33, the ability to use a computer or tablet, and access to the Internet and email. Patients were excluded if they had a Beck Depression Inventory (BDI) score of more than 30 at screening, history of other neurodegenerative diseases other than relapsing or progressive MS, were breastfeeding or pregnant, had uncontrolled hypertension at screening (history of high blood pressure and screening systolic blood pressure >160 or diastolic blood pressure >100), history of coronary artery disease, congestive heart failure, severe liver disease, recurrent seizure or epilepsy, history of prior ischemic or hemorrhagic stroke or cerebral vascular aneurysms, was being treated for malignancy, or had a history of alcohol or substance abuse in the past year. To minimize the risk of drug–drug interaction and improve the safety of participants, we excluded patients who were taking certain medications that could potentially interact with ketamine or midazolam (amantadine, anorexiants, anticonvulsants, monoamine oxidase inhibitors, chloral hydrate, oral or intravenous steroids, dextromethorphan, diphenhydramine, ketanserin, methyldopa, metyrosine, non-vitamin K antagonist oral anticoagulation agents, reserpine, scopolamine, St. John's Wort, and warfarin). Patients who were on a steady dose of a medication for fatigue treatment could continue with their medication during the study if it were not one of the prohibited medications. Participants were asked to avoid starting, stopping, or changing the dose of fatigue medications during their 28-day follow-up period.

Standard protocol approvals, registrations, and patient consents

The study was conducted following local laws and regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study protocol and its amendments were approved by The Johns Hopkins University Institutional Review Board. All participants provided written, informed consent before any study-related procedures were conducted. This study was registered with clinicaltrial.gov (NCT03500289).

Randomization and masking

Permuted block randomization, with block sizes of three or six in random order, was prepared by a Johns Hopkins University Investigational Drug Services pharmacist, using Windows Version 6.0 of randomization program "Rand.exe." Study participants and personnel (except the pharmacist) were blinded to treatment allocation until all the participants finished the study procedures.

Procedures

The study intervention was a single intravenous infusion of ketamine (0.5 mg/kg) or midazolam (0.05 mg/kg) administered over 40 minutes. Ketamine and midazolam were diluted in 50 cc of 0.9% saline (for participants weighing less than 100 kg) or 100 cc of 0.9% saline (for participants weighing 100 kg or more). Eligible subjects received the study infusion during the screening visit. After the screening/infusion visit, all the study outcomes were collected remotely and through a web interface. Participants were asked open-ended and directed questions about the adverse events during and after the infusion, as well as on day 7 post-infusion (via email). The schedule for the study procedures and assessments is depicted in Table 1. Vital signs, including respiratory rate, heart rate, blood pressure, oxygen saturation, and heart rhythm, were recorded before the start of the infusion and every 15 minutes until 1 hour after the end of infusion.

Study outcomes

We used several patient-reported fatigue, sleepiness, and depression questionnaires to assess the effects of ketamine up to 28 days post-infusion. As we assumed the anti-fatigue effects of ketamine would be highest early after the infusion (as suggested by post hoc analyses from another ketamine trial[12]), we selected recalled Daily Fatigue Severity (DFS) during the first 7 days post-infusion as the primary outcome of the study. It is a single-item question: "How much fatigue (tiredness, weariness, problems thinking clearly) have you felt today?" with responses ranging from 0 "None at all" to 10 "Extreme Fatigue."[30] The email with the link to the question was sent to the participants at or around 9 p.m. We selected this scale because more traditional, validated, and recommended fatigue scales that are commonly used in MS-related fatigue studies have a look-back period of 7–28 days and, therefore, may not detect possible immediate anti-fatigue effects of ketamine. As secondary outcomes, we included the longer term validated assessments of fatigue severity in people with MS after appropriate look-back periods (e.g. 7 or 28 days). These assessments included (1) quality of life for neurological disorders (NeuroQoL) fatigue item short form, (2) Fatigue Severity Scale (FSS) both at 7 and 14 days post-infusion, and (3) the Modified Fatigue Impact Scale (MFIS) and its component subscales (physical, cognitive, psychosocial) at 28 days post-infusion. Other secondary outcomes compared the effect of ketamine on depression (via Beck Depression Inventory (BDI) and daytime sleepiness (via the Epworth Sleepiness Scale (ESS)) also at 7 and 14 days post-infusion.

Statistical analyses

With a two-sided alpha of 0.05, 12 participants in the ketamine group, and six participants in the midazolam group, the study would have 80% power to detect an average three points difference on the DFS score. However, the magnitude of ketamine effect on MS fatigue was not known, the best measure for MS fatigue was not clear, and this was a pilot trial. For the analysis of the primary and secondary outcomes, we used a random-intercept linear mixed model with restricted maximum likelihood estimate and an unstructured covariance structure. Both the allocation group and time were within-subject covariates, and the interaction between them was included in the models. In sensitivity analyses, we further adjusted the fatigue models for change in BDI scores in order to separate potential antidepressive versus anti-fatigue effects of ketamine. Because of the relatively limited sample size in the pilot study, additional sensitivity analyses applied generalized estimating equations to assess the effect of ketamine infusion on fatigue severity. All analyses were done according to the intention-to-treat principle; significance was evaluated at $p < 0.05$, two-tailed. Analyses were conducted using R Ver 3.6.1 (Vienna, Austria) and Stata Ver 14 (StataCorp, College Station, TX).

Table 1. Study schedule and overview of assessments.

Tests and assessments	Study visit					
	Screening	Infusion visit	Post-infusion days 1–7	Week 1 Post-infusion	Week 2 Post-infusion	Week 4 Post-infusion
Informed consent	X					
Inclusion/exclusion criteria	X					
Medical history	X					
Vital signs	X	X				
Physical examination	X					
Urine pregnancy test	X	X				
Ketamine/midazolam infusion						
EDSS	X					
Daily fatigue severity	X	X	X			
MFIS	X					X
NeuroQoL Fatigue	X			X	X	X
FSS	X			X	X	X
Beck Depression Inventory	X			X	X	X
Epworth Sleepiness Scale	X			X	X	X
Side effects assessment	X			X	X	X

EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale.

Data availability

An anonymized dataset, along with the study protocol, will be shared by request from any qualified investigator 1 year after the publication of the results.

Results

Study population

Eighteen subjects were screened for the study. All were eligible to participate and were randomized to the study drugs (12 ketamine, 6 midazolam; Figure 1). All 18 participants completed all the study procedures. No MS relapses occurred during the study. The demographic and baseline variables of the participants are depicted in Table 2. Broadly, there were no differences in the baseline value between the groups; however, individuals randomized to ketamine infusion had significantly lower BDI scores ($p = 0.02$) and tended to have lower ESS scores (0.09). Ten patients (83.3%) in the ketamine group and five patients (83.3%) in the midazolam group were on an MS disease-modifying therapy (DMT) at the time of the infusion. In the ketamine group, four patients were on ocrelizumab, one patient on natalaizumab, two patients on dimethyl fumarate, one patient on teriflunomide, one patient on glatiramer acetate, and one patient on interferon beta-1b. In the midazolam group, four patients were on ocrelizumab and one patient on alemtuzumab. There was no change in the DMT during the study.

Primary outcome

The results of the models analyzing the primary and secondary outcomes of the study are depicted in Table 3. There was no difference in the trajectory of the DFS score during the first 7 days, post-infusion between the ketamine and midazolam groups (time × intervention interaction p value = 0.40). Adjustment for baseline BDI or adjusting the models for the baseline or change from the baseline in the depression (BDI) scores did not change the results.

Secondary outcomes

The average MFIS score in the ketamine group decreased from 47.1 (standard deviation (SD): 5.9) on

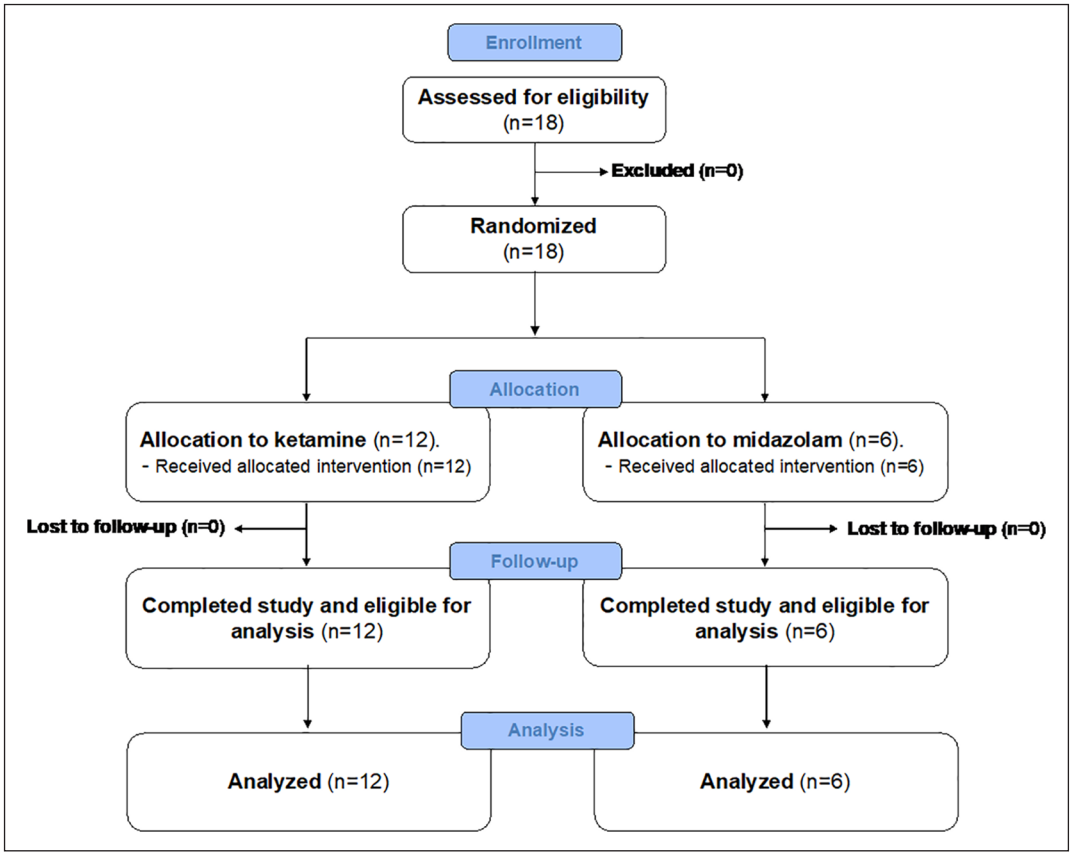

Figure 1. Consort diagram.

day 0 (pre-infusion) to 34.1 (SD: 13.7) on day 28 post-infusion, while the average MFIS score in the midazolam group remained unchanged (48.3 (SD: 4.5) on day 0 (pre-infusion) and 48.8 (SD: 10.3) on day 28 post-infusion). The observed difference in the rate of change between groups was statistically significant (Table 3; Figure 2; $p=0.04$). We observed consistent results for the effect of ketamine infusions on the physical and cognitive subscales of the MFIS (Table 3). Results were also largely consistent with observed changes in 7-day post-infusion FSS scores where participants randomized to ketamine infusions experienced a −5.18 (95% confidence interval (CI): −10.40, 0.14) change in FSS, while those randomized to midazolam did not show a similar trend (mean change: 1.33; 95% CI: −6.16, 8.82). However, this difference in change did not attain statistical significance ($p=0.06$). We did not observe a change in NeuroQoL fatigue *T*-scores. Concerning other MS symptoms, ketamine infusion was not associated with a differential change in ESS or in BDI scores (both $p>0.05$).

For the FSS, NeuroQoL fatigue, ESS, and BDI, none of the models that included day 14 variables showed a statistically significant interaction of time × intervention. Adjusting the fatigue models for the baseline or change from the baseline in the depression (BDI) scores also did not change the results.

Adverse events

The adverse events (AEs) were collected during and up to 1 week after the infusion. AEs were all mild to moderate in intensity. There were no serious AEs. The list of all AEs is depicted in Table 4. The most commonly reported AEs in the ketamine group during and immediately after the infusion were euphoria/elevated mood (9/12), dizziness/lightheadedness (10/12), numbness/tingling in different body parts (10/12), impaired concentration/mental impairment/slowed thinking (7/12) and sleepiness/drowsiness (3/12). All the AEs were transient and resolved in the 1-hour post-infusion observation period. In the first-week post-infusion, the AEs reported included stiffness (1/12), impaired concentration/mental impairment (2/12), depression (1/12), and fever/feeling feverish (2/12). Five of six midazolam recipients reported sleepiness/drowsiness during the infusion, and one

Table 2. Baseline characteristics of the study participants.

	Randomization group		*p* value*
	Midalozam	Ketamine	
	(*n* = 6)	(*n* = 12)	
Demographic and MS characteristics			
Age, years, mean (SD)	49 (8.4)	44 (12.4)	0.50
Age range, min-max	35–58	24–59	
Male sex, *n* (%)	2 (41.7)	5 (33.3)	1.00
Non-white race, *n* (%)	1 (16.7)	3 (25.0)	0.39
MS subtype			1.00
Relapsing–remitting, *n* (%)	10 (83.3)	5 (83.3)	
Secondary progressive, *n* (%)	2 (16.7)	1 (16.7)	
Current use of MS disease-modifying therapy, *n* (%)	10 (83.3)	5 (83.3)	1.00
EDSS, median (IQR)	2.75 (2.12, 4.12)	2.0 (1.25, 3.50)	0.30
Baseline Fatigue and MS Symptom Characteristics			
Ever use of fatigue medications,[a] *n* (%)	5 (83.3)	9 (75.0)	1.00
Current use of fatigue medication,[a] *n* (%)	1 (16.7)	2 (16.7)	1.00
Daily fatigue score, median (IQR)	4.8 (2.8)	6.0 (2.2)	0.44
Total MFIS score, mean (SD)	48.4 (4.6)	44.0 (12.4)	0.67
Physical MFIS score, mean (SD)	22.7 (2.1)	21.2 (5.1)	0.60
Cognitive MFIS score, mean (SD)	20.5 (4.0)	21.8 (4.20	0.61
Psychosocial MFIS score, mean (SD)	5.2 (1.3)	4.2 (1.3)	0.18
Fatigue severity score, mean (SD)	53.0 (5.9)	49.5 (7.8)	0.54
NeuroQoL fatigue severity *T*-score, mean (SD)	56.3 (8.1)	56.1 (3.9)	0.81
Beck Depression Inventory, mean (SD)	16.3 (2.9)	9.9 (5.4)	0.02
Epworth Sleepiness Scale, mean (SD)	9.7 (4.0)	6.5 (3.2)	0.09

EDSS: Expanded Disability Status Scale; MFIS: Modified Fatigue Impact Scale.
*p values are derived using non-parametric tests (Wilcoxon, Fisher's exact), as appropriate.
[a]MS fatigue medications, including amantadine, modafinil, armodafinil, and amphetamine-like psychostimulants.

Table 3. Change in fatigue and key MS symptoms severity.

	Randomization group		*p* value for the difference in the rate of change
	Midazolam	Ketamine	
Change in daily fatigue severity, points/day (95% CI)*	–0.05 (–0.14, 0.24)	–0.05 (–0.19, 0.08)	0.40
Change in secondary outcomes, points/day (95% CI)			
FSS	0.19 (–0.88, 1.26)	–0.74 (–1.49, 0.02)	0.06
NeuroQoL fatigue *T*-score	–0.46 (–1.20, 0.27)	–1.02 (–1.54, –0.50)	0.24
MFIS total	0.02 (–0.35, 0.32)	–0.46 (–0.23, 0.70)	0.04
MFIS physical	0.04 (–0.12, 0.19)	–0.20 (–0.31, –0.09)	0.03
MFIS cognitive	0.00 (–0.16, 0.16)	–0.22 (–0.24, 0.11)	0.05
MFIS psychosocial	0.02 (–0.07, 0.03)	–0.04 (–0.07, 0.00)	0.52
Change in other MS symptoms, points/day (95% CI)			
BDI	0.07 (–0.33, 0.18)	0.07 (–0.25, 0.11)	1.00
ESS	0.11 (–0.11, 0.32)	0.03 (–0.18, 0.12)	0.32

FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale; BDI: Beck Depression Inventory, ESS: Epworth Sleepiness Scale.
*Rates of change are derived from mixed effects models.

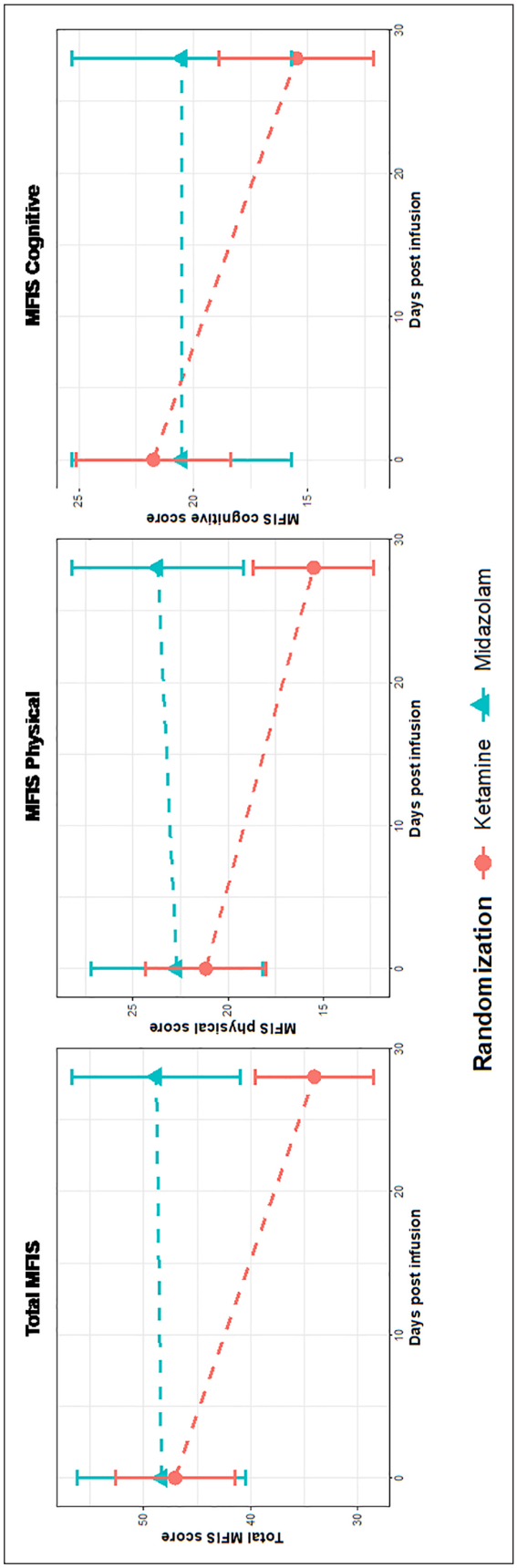

Figure 2. Change in MFIS and relevant subscales associated with ketamine infusion.

Table 4. The list of adverse events, during and up to 1 week after the infusion.

Participants number	Medication	Adverse events during and in 1 hour after the infusion	Severity	Pre-infusion blood pressure	Maximum blood pressure during and up to 1-hour post infusion	Adverse events up to 1 week after the infusion (assessed on day 7 post infusion)	Severity
1	Ketamine	Nausea Vomiting Euphoria Dizziness Altered smell sensation	Moderate Mild Moderate Mild Mild	154/73	173/82	Stiffness	Mild
2	Midazolam	Sleepiness Slurred speech Chills	Mild Mild Mild	109/61	125/72	None	
3	Midazolam	Sleepiness Wooziness Slurred speech Sedation	Mild Mild Mild Mild	127/74	155/81	None	
4	Ketamine	Relaxation Euphoria Tingling in hands/feet Impaired concentration Increased appetite	Mild Mild Mild Mild Mild	123/62	141/81	Impaired concentration Feverish	Mild Mild
5	Ketamine	Lightheadedness Sleepiness Lip numbness Generalized numbness	Mild Mild Mild Mild	123/86	168/104	None	
6	Ketamine	Lightheadedness Dizziness Impaired concentration Slowed thinking Euphoria Hand numbness Dry lips Speech disturbance	Mild Mild Mild Mild Mild Mild Mild Mild	126/84	149/92	Dizziness Tinnitus	Mild Mild
7	Ketamine	Drowsiness Visual disturbance Dizziness Increased salivation Numbness Headache	Mild Mild Mild Mild Mild Mild	127/82	135/76	Insomnia	Moderate
8	Ketamine	Feeling relaxed Euphoria Sensory abnormality Visual disturbance Leg numbness Loss of inhibition	Mild Mild Mild Mild Mild Mild	131/80	168/79	None	
9	Midazolam	Sleepiness Yawning	Mild Mild	111/73	105/66	None	
10	Ketamine	Lightheadedness Euphoria Facial numbness Hot flushes	Moderate Mild Mild Mild	141/79	155/77	None	
11	Midazolam	None		144/86	130/88	None	

(continued)

Table 4. (continued)

Participants number	Medication	Adverse events during and in 1 hour after the infusion	Severity	Pre-infusion blood pressure	Maximum blood pressure during and up to 1-hour post infusion	Adverse events up to 1 week after the infusion (assessed on day 7 post infusion)	Severity
12	Ketamine	Lightheadedness Leg numbness Facial numbness Flushing Foggy feeling in head Impaired concentration	Mild Mild Mild Mild Mild Mild	118/70	125/73	None	
13	Ketamine	Dizziness Euphoria Drowsiness Impaired concentration Word finding difficulty Finger numbness	Mild Mild Mild Mild Mild Mild	126/84	171/95	Fever	Mild
14	Midazolam	Drowsiness	Mild	118/67	142/71	Drowsiness	Mild
15	Ketamine	Dizziness Lightheadedness Dry mouth Flushing Restlessness Mental impairment Numbness Tremulousness Sensation of warmth Euphoria Impaired concentration Altered taste	Mild Mild Mild Mild Mild Mild Mild Mild Mild Mild Mild Mild	141/87	157/85	Mental impairment Depression Fatigue	Mild Moderate Mild
16	Ketamine	Elevated mood Lightheadedness Dizziness Impaired concentration Euphoria Tinnitus	Mild Mild Mild Mild Mild Mild	145/82	178/86	None	
17	Ketamine	Giddiness Euphoria Transient alteration of awareness Face numbness Pain relief Tinnitus Impaired concentration Lightheadedness	Mild Mild Mild Mild Mild Mild Mild	109/67	143/83	None	
18	Midazolam	Sleepiness	Mild	127/76	122/69	None	

participant reported drowsiness at 1 week. The systolic blood pressure increased by at least 20 mmHg during the infusion in 6 of 12 ketamine recipients. Four out of 12 participants in the ketamine group experienced a 25% increase in their systolic blood pressure during the infusion. In these four patients, the infusion was slowed down or temporarily stopped and resumed after the blood pressure reduced (generally in a few minutes).

Discussion

In this pilot, randomized, double-blind, active-placebo-controlled trial, ketamine did not show statistically significant improvement in fatigue severity, as measured by a single question (DFS) up to 7 days post-infusion. However, using traditional, comprehensive, validated, and recommended tools for assessing fatigue in MS, ketamine showed a trend in improving fatigue in 1 week post-infusion (using FSS

questionnaire) and a statistically significant improvement of fatigue as assessed by MFIS on day 28 post-infusion.

During the design phase of the study, although we hypothesized that ketamine would improve fatigue in MS, we did not know how long the therapeutic effect would last. We assumed that the daily measurement of fatigue would provide a better chance of showing the therapeutic effects of ketamine on MS fatigue (as opposed to measuring the outcome on day 7 or 28). However, all the traditional and well-validated fatigue measures in MS have a look-back period. For the FSS and NeuroQoL, the look-back period is 7 days, and for the MFIS, the look-back period is 28 days. So, we could not use these instruments for daily fatigue measures and had to resort to a tool that has been less commonly used in MS research, and its psychometric properties, treatment-responsiveness, and minimal clinically important change levels were not known. Ketamine did not show statistically significant improvement in the scores of this single question asking about the daily fatigue severity. But interestingly, there was a trend in change in the FSS score at 1 week, and the change from the baseline in the MFIS score at day 28 post-infusion was statistically significant. FSS and MFIS are commonly used fatigue measures in MS studies, have been extensively validated,[31] and in the case of MFIS, has been recommended as the instrument of choice for the evaluation of fatigue in MS.[7] MFIS measures the impact of fatigue in multiple domains, including physical, cognitive, and psychosocial. Observing a major therapeutic effect of ketamine on the MFIS and its subdomains at day 28 and to a lesser extent on FSS at day 7, and no effect on the NeuroQoL and DFS during the first week, can have several explanations. It is possible that the anti-fatigue effects of ketamine in MS are delayed and more pronounced if measured several weeks after the infusion. It is also possible that MFIS has a broader coverage of different dimensions of fatigue.

Several groups have studied the minimally important difference of the FSS and MFIS in people with MS and other neurological diseases, such as Parkinson's disease. A recent paper reported the minimal clinically important difference (MCID) in the FSS and MFIS scores in patients with MS to be 0.45 and 4 points, respectively.[32] Another study reported the MCID in the MFIS score in patients with Parkinson's disease was 13.8.[33] The change from the baseline in both FSS (at 1 week) and MFIS (at day 28) in our study was greater than these minimally important differences reported in the literature. So, the effects of ketamine on the fatigue severity were not only statistically significant (in the case of FSS, a trend toward statistical significance); the effects might have been clinically meaningful too. Also, the difference in MFIS at day 28 (which was the most robust and significant finding) may point to the prolonged anti-fatigue effects of ketamine. Both physical and cognitive subscales of MFIS showed a statistically significant improvement in patients who received ketamine. However, the changes in physical subscale were more pronounced. Seeing improvement in both major subdomains of MFIS makes it less likely that the observed results are false positive.

It was reported that the anti-fatigue effect of ketamine in patients with a mood disorder might be mediated by its effects on improving depression.[28] In the current study, adjusting the fatigue models for the BDI scores did not change the results. In fact, we did not see robust antidepressive effects from ketamine in this study. However, significant differences in the baseline BDI scores (with the ketamine group having significantly lower depressive symptoms) might have contributed to these findings.

The adverse effects of ketamine were transient and mostly mild (with a few exceptions of moderate-degree AEs). Most participants who received ketamine reported temporary euphoria, dizziness/lightheadedness, numbness and tingling, and impaired concentration/mental impairment during the infusion. All these AEs resolved during or in 1-hour post-infusion. Interestingly, there was no report of dissociative symptoms in ketamine recipients. A short-lasting increase in the systolic blood pressure was seen in half of the ketamine recipients and necessitated slowing or temporarily stopping the infusion in four recipients. Transient increase in blood pressure is a known side effect of ketamine. We did not find any baseline characteristics that was associated with the development of transient hypertension. In a study reporting the association of ketamine infusions with blood pressure increase in 66 patients with mood disorders, history of hypertension was associated with higher blood pressure peaks during the infusions. Blood pressure returned to baseline during the post-infusion monitoring in all patients. The authors characterized the blood pressure changes as small, well tolerated, and insignificant.[34] In our trial, all participants completed the infusions. The ketamine infusion seemed to be safe and well-tolerated. Having said that, non-pharmacologic treatments, such as cognitive–behavioral therapy, are safe and efficacious for improving fatigue in MS.[35]

This study has several strengths and weaknesses. It was a randomized, double-blind trial. We also used an active placebo to reduce the possibility of unblinding.[36] A similar direction of change in the fatigue severity in multiple well-validated fatigue measures increases the possibility that ketamine might have a truly positive effect on MS fatigue. However, the pilot nature of the study, the small sample size, and negative results on the primary outcome prevent us from drawing any firm conclusion regarding the therapeutic effects of ketamine. The primary outcome of the study (Daily Fatigue Score) was not a validated tool for MS fatigue research. We also did not correct our results for multiple hypothesis testing, as we considered this study to be a pilot. The above-mentioned imbalance in the baseline severity of depressive symptoms between the two groups might have affected the results and is one of the study weaknesses.

Although ketamine is a glutamate NMDA receptor blocker, it leads to glutamate release and increased glutamatergic transmission in the prefrontal cortex.[26] We had reported that long-term use of anti-glutamatergic agents such as riluzole and memantine might be associated with an increase in MS-related fatigue. An increase in the glutamatergic transmission with ketamine in this study showed that modulating glutamatergic transmission in the brain might be a target for the pharmacological treatment of MS-related fatigue. The potential anti-fatigue effects of ketamine, in this study, did not seem to be mediated by its antidepressive effects. Although the primary outcome of this study was negative, because ketamine infusion was associated with large, clinically significant and long-lasting changes in well-validated and multidimensional fatigue measures, we think these results can be the basis for performing a larger study of ketamine or other glutamate modulating agents for MS-related fatigue.

Declaration of Conflicting Interests

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