Mexiletine in spinal and bulbar muscular atrophy: a randomized controlled trial

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Abstract

Objective: Patients with spinal and bulbar muscular atrophy (SBMA) often experience muscular weakness under cold exposure. Methods: In our previously conducted observational study, we assessed nerve conduction and grip strength to examine the effect of cold exposure on motor function, based on which we conducted a randomized controlled trial to evaluate the efficacy and safety of mexiletine hydrochloride in SBMA (MEXPRESS). Results: In the observational study, 51 consecutive patients with SBMA and 18 healthy controls (HCs) were enrolled. Of the patients with SBMA, 88.0% experienced cold paresis. Patients with SBMA exhibited greater prolongation of ulnar nerve distal latency under cold (SBMA, 5.6 ± 1.1 msec; HC, 4.3 ± 0.6 msec; p < 0.001); the change in the distal latencies between room temperature and cold exposure conditions correlated with the change in grip power. In the MEXPRESS trial, 20 participants took mexiletine or lactose, three times a day for 4 weeks with a crossover design. There was no difference in distal latencies at room temperature and under cold exposure between mexiletine and placebo groups as the primary endpoint. However, tongue pressure and 10-sec grip and release test under cold exposure were improved in the mexiletine group. There were no serious adverse events throughout the study period. Interpretation: Cold paresis is common and associated with prolongation of distal latency in SBMA. The results of the phase II clinical trial revealed that mexiletine showed short-term safety, but it did not restore cold exposure-induced prolongation of distal latency.

Introduction

Spinal and bulbar muscular atrophy (SBMA), or Kennedy’s disease, is a slowly progressing lower motor neuron and muscular disease characterized by bulbar and limb muscle weakness.1–3 SBMA is caused by the expansion of a CAG repeat within the first exon of the androgen receptor (AR) gene.4 The mutant AR protein harboring an extended polyglutamine tract induces degeneration of motor neurons and skeletal muscles in a testosterone-dependent manner.2,5 Muscular weakness generally manifests between 30 and 60 years of age and is preceded by prodromal symptoms such as hand tremors and muscle cramps by 10–20 years.2,6 Although leuprorelin acetate has been demonstrated to restore the bulbar function of patients at an early stage, other symptomatic therapies have yet to be established.7,8

Patients with SBMA often experience muscular weakness under cold exposure that affects activities of daily living (ADLs).9 Cold paralysis is hypothesized to be
caused by motor neuron and skeletal muscle membrane hyperexcitability in various neuromuscular disorders, due to a reduction in resting chloride conductance and/or gain-of-function in voltage-dependent sodium channels, both of which lead to excessive sodium currents. A recent study has supported a role for hyperexcitability of motor neurons and skeletal muscle fibers leading to abnormal sodium currents in SBMA pathophysiology. Mexiletine, a sodium channel blocker, is used to suppress muscle hyperexcitability in cardiac diseases as well as restore nerve activity in several neuromuscular diseases such as diabetic neuropathy, non-dystrophic myotonia, and Machado–Joseph disease. However, its effectiveness as a symptomatic therapy for SBMA has not been confirmed to date.

To elucidate the pathophysiology of SBMA based on clinical findings and develop a symptomatic therapy in an integrated manner, we conducted a cross-sectional observational study focusing on the motor symptoms of patients with SBMA under cold exposure. Based on the results of the observational study, we conducted a phase II clinical trial of mexiletine (MEXPRESS trial).

Methods

Overall study design

This study consisted of two parts. A preceding observational study prospectively collected neurological and neurophysiological data regarding cold paresis in patients with SBMA (observational study on cold exposure in SBMA). In the subsequent randomized clinical trial, which was based on the findings of the observational study, we evaluated the efficacy and safety of mexiletine in patients with SBMA (MEXPRESS trial).

Observational study on cold exposure in spinal and bulbar muscular atrophy

Standard protocol approvals, registration, and patient consents

This observational study was conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Human Genome/Gene Analysis Research, and Ethical Guidelines for Medical and Health Research Involving Human Subjects and was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine (approval number: 2015-0241). Before study enrolment, participants provided written informed consent after receiving sufficient information regarding the Ethics Review Committee approval, favorable/unfavorable aspects of the study, and other relevant details. The observational study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000020426) in January 2016, prior to the commencement of the recruitment period.

Participants

We investigated consecutive male patients diagnosed with SBMA based on genetic testing who were already registered in our registry system of neuromuscular diseases. We excluded patients with SBMA aged >80 years at the time of study enrolment or those with severe complications, such as cardiovascular diseases, serious infectious diseases, post-operation, terminal cancer, or debilitation. Disease onset was defined as when the patient initially noticed weakness or bulbar symptoms. Furthermore, we recruited age-matched male volunteers without any neurological disorders or illnesses as healthy controls (HCs). All participants were Japanese and were observed at Nagoya University Hospital between January 2016 and March 2019.

Assessment of motor function and muscle mass, blood tests, nerve conduction study, and genetic analysis

We defined cold paresis as sudden and relevant loss of force that affected ADLs when exposed to cold temperatures. Participants completed a questionnaire on whether their ADLs were affected by cold exposure, affected body lesions, duration of cold paresis from disease onset, and type of impaired activity such as eating, writing, dressing, grip and release, pinch, gait, and bulbar symptoms. We assessed disease severity using the following functional parameters: the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS), and quantitative muscle strength as grip power. We also performed blood tests, dual-energy X-ray absorptiometry to evaluate muscle mass, nerve conduction study (NCS), and genetic testing. We conducted NCS of the peripheral nerves using Nicolet Viking EDX (Natus Medical Incorporated, Pleasanton, CA, USA). We performed NCS of the ulnar nerve at room temperature and under cold exposure. We recorded distal latencies, compound muscle action potentials (CMAPs), and conduction velocities from the dominant abductor digitii minimi muscles after electrical stimulation of the ulnar nerves at the wrist. For each index, we calculated the difference at room temperature and under cold exposure. Furthermore, we conducted a repeated short exercise test (SE test) at room temperature on the dominant hand. Participants performed a maximal voluntary isometric movement for 5–10 sec with the fingers spread to their
maximum extent. We stimulated the ulnar nerve immediately after the movement and, thereafter, every 10 sec for up to 1 min. The SE test was deemed positive if CMAPs decreased immediately after the exercise. The dominant upper limbs were cooled down for 7 min in cold water at 15°C, followed by a repeat SE test (cooling test).20–23 Similar to the SE test, the cooling test was deemed positive if CMAPs decreased immediately after exercise under cold exposure. For the cold exposure condition, we monitored skin temperature and maintained it at 20–25°C using a thermoscope. Other detailed procedures are described in the Supplemental Methods.24

**Statistical analysis**

We used the unpaired t-test or Mann–Whitney U-test to compare continuous variables between two groups and Pearson’s correlation coefficient to analyze correlations among parameters. We considered p-values <0.05 as significant, and correlation coefficient (r) > 0.3 as correlation.25 All data are presented as mean ± standard deviation (SD) unless otherwise stated. We performed statistical analyses using the Statistical Package for the Social Sciences (SPSS) version 28.0 J software (IBM Japan, Tokyo, Japan).

**MEXPRESS trial**

**Standard protocol approvals, registration, and patient consents**

A placebo-controlled, randomized, double-blind, multicenter, crossover study on the efficacy and safety of mexiletine hydrochloride in SBMA (MEXPRESS) was conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Human Genome/Gene Analysis Research, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and Clinical Trials Act by the Japanese government. Based on the preceding observational study on cold exposure in SBMA, we planned to conduct a clinical trial to evaluate the efficacy and safety of mexiletine hydrochloride in patients with SBMA following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations.26,27 With regard to patient and public involvement, we shared clinical trial information with the Japanese advocacy groups of SBMA. We conducted a randomized, double-blind, placebo-controlled, 2 × 2 crossover, phase II trial at three centers to assess the safety and efficacy of mexiletine hydrochloride in patients with SBMA in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Supplementary Materials).28 The treatment period was 4 weeks, separated by a 1-week washout period.29 The trial was approved by the Certified Review Board of Nagoya University Graduate School of Medicine (approval number: 2016–0501, CRB4180004). The inclusion and exclusion criteria are listed in Table S1. The study (protocol version 01.02.00) was registered in the UMIN Clinical Trials Registry (UMIN000026150) on February 15, 2017, prior to the commencement of the recruitment period. This study was also registered in the Japan Registry of Clinical Trials (jRCTs041180106) after the enforcement of the Clinical Trials Act.

The study participants were recruited via the Japanese advocacy groups of SBMA and outpatient settings of study sites. Investigators and/or coinvestigators provided sufficient information via informed consent forms, and all participants provided their written informed consent for participation in the trial prior to screening.29 After obtaining informed consent, we screened potential participants for eligibility within 4 weeks prior to study enrolment by assessing vital signs, grip power, blood tests, and electrocardiograms. Dual-energy X-ray absorptiometry (DXA) was performed to evaluate muscle mass expressed as appendicular lean soft tissue (ALST).

**Intervention**

Detailed procedures of the intervention are described in our previous paper.29 Briefly, the participants started oral administration within 4 weeks after screening. Each participant took an over-encapsulated 100 mg of mexiletine hydrochloride (Boehringer Ingelheim GmbH, Ingelheim, Germany) or over-encapsulated lactose 100 mg orally, three times a day for 4 weeks during intervention periods 1 and 2. As mexiletine hydrochloride has a half-life of 10 hours in the blood, we set a 7-day washout period between the two intervention periods (Fig. S1). We assessed study participants four times during the trial: on the first day of intervention period 1 (V1), first day of intervention period 2 (V2), first day of intervention period 2 (V3), and last day of intervention period 2 (V4). All participants underwent neurological assessments, NCS, and tests of motor and pulmonary function. Additional details of the intervention are provided in the Supplemental Methods.

**Outcome measures**

Based on the results of the observational study, the change from baseline of the difference in distal latencies of the ulnar nerve at the wrist of the dominant hand between room temperature and under cold exposure conditions at V2 and V4 was adopted as the primary endpoint. Distal latency consists of conduction times of the motor nerve terminal, neuromuscular junction, and muscle fibers. It is also known that distal latency is prolonged in patients with ALS with upper limb weakness.30 The
validity of examining the ulnar nerve between room temperature and under cold exposure conditions was based on a previous report. Secondary outcome measures included quantitative muscle strength of the upper limbs both at room temperature and under cold exposure, tongue pressure, a 15-foot timed walk test, ALSFRS-R, SBMAFRS, 36-Item Short Form Health Survey (SF-36), Individualized Neuromuscular Quality of Life questionnaire (INQoL), respiratory function values, blood tests, and patient-reported severity scores of stiffness, weakness, and pain. Detailed secondary outcome measures are described in the Supplemental Methods.

Sample size calculation
Sample size was estimated based on the observational study on cold exposure in SBMA. In brief, we calculated the sample size based on the assumption that the mean value of the difference in distal latencies under cold exposure in patients with SBMA would be approximately 60% of the difference in distal latencies HCs. Under the assumptions of no carryover effect; period effect; or interactions among patients, treatments, and periods, we estimated that a sample size of 10 patients per group would provide 80% power to detect a 0.768 difference for the primary endpoint between the treatment groups, with a two-sided α level of 0.05 and an SD of 0.9 in both groups.

Randomization and blinding
Randomization, stratified by disease duration (<10 or ≥10 years from onset) and CAG repeat size in the AR gene (38–49 or ≥50 copy number), was performed using computer-generated random codes assigned by a central interactive web response system at Nagoya University Hospital. A medical doctor who specializes in clinical trials at the external facility was delegated as the “allocator” who was responsible for treatment allocation; the allocator ensured that mexiletine hydrochloride and placebo were indistinguishable in appearance and packaging, the allocation code/list was kept in a sealed envelope, and the allocation was concealed before key opening.

Efficacy data analyses
In the primary analysis, we examined the efficacy of mexiletine hydrochloride using a mixed-effect model for the primary endpoint. Secondary endpoints were analyzed using a mixed-effect model, chi-square test, unpaired t-test, or Wilcoxon signed-rank test depending on the characteristics of the data. All analyses were conducted based on the intention-to-treat (ITT) principle, which included all randomly assigned patients who received the study medication and provided at least one post-baseline efficacy datum, as well as the per-protocol set, which included all ITT patients with no important protocol violations relevant to assessing the efficacy of the study agent. The t-test for carryover effects was considered significant if p < 0.10. The mixed-effect model for period effects was considered significant if p < 0.05. A two-sided p-value < 0.05 was considered statistically significant. We performed all statistical analyses using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). The study protocol and statistical analysis plan have been published.

Safety and tolerability data
We evaluated safety in all patients who received the study agent at least once. We conducted safety and tolerability assessments such as subjective and objective neurological symptoms, including cold paresis, vital signs, medical examination findings, clinical laboratory data, electrocardiogram results, and the intensity of adverse events (AEs) for each patient. We confirmed subjective neurological symptoms at every visit and via weekly phone calls by the principal investigator, sub-investigator, or clinical research coordinators. Each AE was coded to a preferred term and associated with an organ system according to an established and validated adverse reaction dictionary (MedDRA/J, version 18.0). An independent data and safety monitoring board monitored AEs.

Results
Observational study on cold exposure in spinal and bulbar muscular atrophy
Clinical characteristics and blood chemistry values
A total of 51 consecutive patients with SBMA and 18 HCs were assessed in the observational study. The clinical characteristics of all study participants are presented in Table 1. The mean age at examination was equivalent between the groups. The total scores of ALSFRS-R and SBMAFRS were lower in patients with SBMA than in HCs. Serum creatine kinase and testosterone concentrations were higher in patients with SBMA than in HCs. The characteristics of patients with SBMA, such as age at examination, age at onset, motor functional scores, and AR CAG repeat size, were similar to previously reported values.

Symptoms, quantitative muscle strength, and nerve conduction study at room temperature and under cold exposure
Of 51 patients with SBMA, 45 (88.0%) experienced cold paresis (Table 2). Cold paresis was observed more
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Table 1. Clinical background of subjects in the observational study.

|                      | SBMA (n = 51) | HC (n = 18) | p-value¹ |
|----------------------|---------------|-------------|----------|
| Age at examination, years | 55.7 ± 10.3   | 57.2 ± 10.0 | NS       |
| Male sex             | 51 (100%)     | 18 (100%)   | NS       |
| Duration from onset, years | 10.5 ± 5.9    | NA          | NS       |
| ALSFRS-R             | 40.0 ± 2.8    | 48.0 ± 0.0  | <0.001   |
| SBMAFRS              | 40.1 ± 6.0    | 55.9 ± 0.2  | <0.001   |
| Laboratory data      |               |             |          |
| Creatine kinase, IU  | 1019.6 ± 715.2 | 125.0 ± 73.2 | <0.001 |
| Creatinine, mg/dL    | 0.47 ± 0.13   | 0.86 ± 0.10 | <0.001   |
| Testosterone, ng/mL  | 9.4 ± 5.6     | 6.3 ± 2.3   | <0.05    |
| HbA1c (NGSP), %      | 5.8 ± 0.8     | 5.9 ± 0.9   | NS       |
| CAG repeat size in AR gene | 48.8 ± 4.2    | NA          |          |
| ALST mass, g         | 16598.7 ± 3329.0 | 23468.5 ± 2826.4 | <0.001 |

ALFRS-R, revised Amyotrophic Lateral Sclerosis Functional Rating Scale; ALST, appendicular lean soft tissue; AR, androgen receptor; HC, healthy controls; NA, not applicable; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; SBMA, spinal and bulbar muscular atrophy; SBMAFRS, Spinal and Bulbar Muscular Atrophy Functional Rating Scale. Data are presented as the mean ± standard deviation.

¹Differences among the SBMA and HC groups were analyzed using the chi-square test, unpaired t-test, or Mann–Whitney U-test.

frequently in the upper limbs than in the lower limbs or bulbar musculature. Approximately half of the patients with SBMA first noticed cold paresis within 5 years from disease onset, and the number of patients who experienced cold paresis gradually increased thereafter (Fig. S2). Notably, 10 (22.2%) patients experienced cold paresis even before the onset of muscle weakness, indicating that cold paresis could be a prodromal symptom. Grip power was significantly decreased after cooling in patients with SBMA compared with that in HCs (Table 2). Similarly, the change in grip power with cooling was larger in patients with SBMA than in HCs.

In NCS, distal latency was larger, and CMAP was lower in patients with SBMA at room temperature than in HCs (Table 2), similar to previously reported values.⁵⁵,⁶⁶ Although the differences in CMAP and conduction velocity at room temperature and under cold exposure were equivalent between patients with SBMA and HCs, the difference in distal latency was larger in patients with SBMA than in HCs (Fig. 1A, Table 2). Concordant with patient complaints, grip power decreased under cold exposure, and NCS revealed prolonged distal latency as a characteristic finding in patients with SBMA. Furthermore, 25.5% of patients with SBMA were positive for the cooling test, which is used to evaluate the severity of depolarizing block in cold conditions such as paramyotonia congenita (Table 2).

Distal latency as an objective biomarker for cold paresis in patients with spinal and bulbar muscular atrophy

The change in distal latencies between room temperature and under cold exposure conditions correlated with the change in grip power (r = −0.320, p = 0.022) in patients with SBMA (Fig. 1B). Furthermore, the difference in distal latencies between room temperature and under cold exposure conditions was significantly larger in patients with SBMA with cold paresis than in those without cold paresis (Fig. 1B, Table S2). Age, ADL scales such as ALSFRS-R and SBMAFRS, CAG repeat size in the AR
gene, and ALST mass were equivalent between patients with SBMA and those without cold paresis. However, grip power under cold exposure was reduced and distal latency after cold exposure was prolonged in patients with SBMA with cold paresis compared with those in patients without cold paresis (Table S2).

**MEXPRESS trial**

**Participant flowchart**

Figure 2 presents a flowchart of participant enrolment in the clinical trial. From April 2017 through June 2018, 22 patients with SBMA were assessed for eligibility. We excluded two patients due to Brugada-type patterns on electrocardiogram. A final total of 20 patients were enrolled and randomly assigned to receive either mexiletine or placebo. The first patient was enrolled on August 17, 2017. None of the patients dropped out during the clinical trial period, and all patients were included in the full analysis set.

**Baseline characteristics of patients**

We assessed 20 patients with SBMA (mean age, 56.1 years; range, 35–79 years). The mean CAG repeat length was 48.4 (range, 43–58). The baseline characteristics of the two groups were similar. However, more patients were treated with leuprorelin acetate in the mexiletine group than in the placebo group (Table 3).

**Outcomes and estimations**

There was no significant difference in distal latencies at room temperature and under cold exposure conditions as the primary endpoint between the mexiletine and placebo groups (Table 4). ALSFRS-R was improved in the mexiletine group, but this was not statistically different from the placebo group. Values obtained in quantitative motor function tests such as tongue pressure and 10-sec grip and release, which are key clinical indices in patients with SBMA, were improved in the mexiletine group. Although grip strength, timed walk, and respiratory function tests were improved in the mexiletine group, these values were not statistically different from those in the placebo group. Mexiletine also improved body pain based on patient reports of pain severity scores (treatment effect estimate, −0.53; 95% confidence interval [CI], −1.02 to −0.04; \( p = 0.035 \)) and subscales of SF-36 (treatment effect estimate, 6.39; 95% CI, 0.65 to 12.13; \( p = 0.031 \)) (Table S3). To evaluate the carryover and period effects, results with participant differences are presented separately for each period (Table S4). We did not observe a period effect in this trial (Table S5).

**Ancillary analysis**

We compared the difference in NCS and motor function between patients with and without prior treatment with leuprorelin acetate (Table S6). Distal latency was
decreased and motor function tests such as grip power and 10-sec grip and release test were increased both at room temperature and under cold exposure in both groups after the oral administration of mexiletine. ALSFRS-R was also improved in both groups. There was a between-group difference in tongue pressure but no difference in the effects of mexiletine on motor function between patients with and without a history of treatment with leuprorelin acetate.

Safety
There were no serious AEs throughout the clinical trial period. The most common AE was gastrointestinal disorder, which was observed in eight participants in the mexiletine group and six participants in the placebo group (Table 5). One cardiac AE (sinus tachycardia) was reported in the mexiletine group, but it was determined to be unrelated to the investigational drug. These AEs were resolved on follow-up visits, phone calls, or electrocardiograms.

Discussion
The principal symptom of SBMA is muscle weakness that is exacerbated under cold exposure. However, the pathophysiology of this symptom has yet to be elucidated, and, currently, there are no available treatments to improve motor function. In the present study, 88.0% of patients...
with SBMA reported paralysis under cold exposure. Some patients were aware of muscle weakness only under cold exposure even before they noticed daily muscle weakness, suggesting that cold paresis is a prodromal symptom of SBMA, in addition to hand tremors and cramps. Our study also demonstrated that in patients with SBMA, cold exposure induced a prolongation in distal latency of the ulnar nerve, the magnitude of which correlated with the decrease in grip power. This finding instigated us to conduct a clinical trial of mexiletine, which is a sodium channel blocker that suppresses excessive sodium current under cold conditions. The results of the phase II clinical trial revealed that mexiletine improved tongue pressure and grip and release test findings but did not restore the cold exposure-induced prolongation of distal latency.

Low temperatures slow the kinetics of the Na/K-pump due to a reduction in its ATPase activity, leading to slow conduction velocity and muscle weakness.\textsuperscript{11,37,38} Electrophysiological studies have suggested that upregulation of persistent nodal sodium conductance causes changes in axonal excitability, leading to motor neuron death.\textsuperscript{39} Similarly, the depolarization of muscle fibers depends on the influx of Na\textsuperscript{+} ions; therefore, lower temperatures prolong the depolarization of each muscle fiber. In a biological study, immunofluorescence revealed downregulation of CLCN1 protein in the muscles in a knock-in mouse model of SBMA, leading to abnormal sodium currents.\textsuperscript{5} The discrepancy between the high incidence of subjective cold paresis and the low positivity in cooling test suggests that the major cause of cold paresis in SBMA is not paramyotonia. Cold paresis has been reported in various neuromuscular diseases, suggesting that the biological basis for this phenomenon is multifactorial. Cold exposure exacerbates weakness in neuromopathies and juvenile muscular atrophy of distal upper extremity (Hirayama’s disease) by inducing motor axonal excitability.\textsuperscript{40} A similar mechanism may underlie in the cold paresis in SBMA. Another explanation for the low positivity in cooling test is the sensitivity of the examination. The cooling test is negative in some subjects with chloride channelopathy, indicating the limitation of this method to detect paramyotonia.\textsuperscript{21} Although the mechanism of cold paresis is not fully understood, these findings suggest that abnormal sodium currents play a role in SBMA pathogenesis, and ultimately, in cold paresis in patients with SBMA.

Our NCS revealed prolonged distal latencies with cold exposure in patients with SBMA. Although distal latency consists of conduction times of the motor nerve terminal, neuromuscular junction, and muscle fibers, there was no significant difference in conduction velocity at room temperature and under cold exposure between patients with SBMA and HCs. Previous studies have reported neuromuscular disorders associated with abnormal sodium currents due to denervation and hyperexcitability of muscle membranes,\textsuperscript{30,41,42} suggesting the prolonged distal latency under cold exposure in patients with SBMA observed in the present study may reflect hyperexcitability due to abnormal sodium currents.

Table 3. Baseline characteristics of the two treatment sequence groups.

| Treatment sequence | Mexiletine then placebo (n = 10) | Placebo then mexiletine (n = 10) |
|---------------------|----------------------------------|----------------------------------|
| Age, mean (range), y| 55.2 ± 9.0                       | 56.9 ± 13.0                      |
| Male sex | 10 (100%) | 10 (100%) |
| CAG repeat length | 48.6 ± 4.3 | 48.2 ± 3.9 |
| Body weight, kg  | 60.7 ± 8.1 | 67.4 ± 12.4 |
| Previously treated with leuprorelin acetate | 5 (50%) | 0 (0%) |
| Nerve conduction study | 3.09 ± 0.84 | 2.44 ± 0.66 |
| Difference in distal latencies between room temperature and cold exposure conditions, msec | 3.47 ± 0.63 | 3.21 ± 0.58 |
| Distal latencies (room temperature), msec | 6.56 ± 1.14 | 5.65 ± 0.89 |
| Distal latencies (under cold exposure), msec | 38.90 ± 4.23 | 37.60 ± 1.65 |
| ALSFRS-R | 38.40 ± 7.65 | 36.40 ± 2.99 |
| Tongue pressure, kPa | 18.03 ± 7.67 | 13.89 ± 4.41 |
| Grip power (room temperature), kg | 17.97 ± 8.10 | 16.98 ± 4.54 |
| Grip power (under cold exposure), kg | 16.13 ± 6.87 | 15.44 ± 4.46 |
| 10-sec grip and release test (room temperature), times | 28.30 ± 6.52 | 27.50 ± 5.17 |
| 10-sec grip and release test (under cold exposure), times | 18.00 ± 3.89 | 17.70 ± 4.50 |
| Pinch power (room temperature), kg | 2.75 ± 0.66 | 3.19 ± 1.79 |
| Pinch power (under cold exposure), kg | 2.55 ± 0.85 | 3.03 ± 1.73 |
| Timed walk test, second | 4.46 ± 1.79 | 5.19 ± 1.35 |
| %FVC | 84.26 ± 17.58 | 91.26 ± 9.52 |
| %PEF | 70.77 ± 25.93 | 73.21 ± 9.52 |
| Total lean mass, g | 41683.2 ± 7899.1 | 46634.2 ± 8592.6 |
| Serum CK, IU/L | 808.1 ± 533.3 | 1132.2 ± 983.4 |
| Serum Cr, mg/dL | 0.45 ± 0.18 | 0.42 ± 0.12 |
| Serum testosterone, mg/L | 11.06 ± 6.49 | 8.67 ± 5.27 |

Data are presented as the mean ± standard deviation. ALSFRS-R, revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CK, creatinine kinase; Cr, creatinine; %FVC, predicted values of forced vital capacity; %PEF, predicted values of peak expiratory flow; SBMAFRS, Spinal and Bulbar Muscular Atrophy Functional Rating Scale.
| End points                                                                 | Baseline (n = 20) | 4 weeks (n = 20) | Treatment effect estimate (95% CI) | p-value |
|---------------------------------------------------------------------------|-------------------|-----------------|----------------------------------|---------|
| Nerve conduction study                                                   |                   |                 |                                  |         |
| Difference in distal latencies between room temperature and cold exposure conditions, msec |                   |                 |                                  |         |
| Placebo                                                                  | 2.59 ± 0.75       | 2.51 ± 0.64     | −0.02 (−0.26 to 0.21)            | 0.843   |
| Mexiletine                                                                | 2.78 ± 0.71       | 2.49 ± 0.61     |                                  |         |
| Distal latencies (room temperature), msec                                 |                   |                 |                                  |         |
| Placebo                                                                  | 3.26 ± 0.46       | 3.38 ± 0.37     | −0.10 (−0.37 to 0.18)            | 0.475   |
| Mexiletine                                                                | 3.38 ± 0.58       | 3.30 ± 0.53     |                                  |         |
| Distal latencies (under cold exposure), msec                              |                   |                 |                                  |         |
| Placebo                                                                  | 5.84 ± 0.97       | 5.88 ± 0.85     | −0.13 (−0.56 to 0.30)            | 0.533   |
| Mexiletine                                                                | 6.15 ± 1.04       | 5.78 ± 0.99     |                                  |         |
| Difference in CMAP between room temperature and cold exposure conditions, mV |                   |                 |                                  |         |
| Placebo                                                                  | 0.82 ± 1.07       | 1.11 ± 0.93     | −0.21 (−0.72 to 0.29)            | 0.386   |
| Mexiletine                                                                | 1.34 ± 2.03       | 0.92 ± 0.99     |                                  |         |
| CMAP (room temperature), mV                                              |                   |                 |                                  |         |
| Placebo                                                                  | 6.04 ± 1.36       | 5.97 ± 1.63     | 0.16 (−0.25 to 0.57)             | 0.415   |
| Mexiletine                                                                | 5.62 ± 1.90       | 6.09 ± 1.70     |                                  |         |
| CMAP (under cold exposure), mV                                            |                   |                 |                                  |         |
| Placebo                                                                  | 6.86 ± 1.83       | 7.08 ± 2.13     | −0.06 (−0.70 to 0.57)            | 0.832   |
| Mexiletine                                                                | 6.96 ± 1.96       | 7.01 ± 2.18     |                                  |         |
| ALSFRS-R                                                                 |                   |                 |                                  |         |
| Placebo                                                                  | 38.15 ± 3.41      | 37.90 ± 3.65    | 0.51 (−0.10 to 1.12)             | 0.094   |
| Mexiletine                                                                | 38.05 ± 3.25      | 38.40 ± 3.17    |                                  |         |
| SBMAFRS                                                                  |                   |                 |                                  |         |
| Placebo                                                                  | 36.45 ± 6.10      | 36.20 ± 5.89    | 0.30 (−0.49 to 1.09)             | 0.431   |
| Mexiletine                                                                | 36.60 ± 6.04      | 36.55 ± 5.73    |                                  |         |
| Tongue pressure, kPa                                                      |                   |                 |                                  |         |
| Placebo                                                                  | 16.44 ± 6.06      | 16.45 ± 6.30    | 1.33 (0.20 to 2.45)              | 0.023   |
| Mexiletine                                                                | 17.25 ± 6.49      | 17.46 ± 6.61    |                                  |         |
| Grip power (room temperature), kg                                         |                   |                 |                                  |         |
| Placebo                                                                  | 17.62 ± 6.58      | 17.37 ± 6.54    | 0.17 (−0.27 to 0.61)             | 0.429   |
| Mexiletine                                                                | 17.53 ± 6.17      | 17.53 ± 6.52    |                                  |         |
| Grip power (under cold exposure), kg                                       |                   |                 |                                  |         |
| Placebo                                                                  | 16.34 ± 6.43      | 16.08 ± 5.49    | 0.08 (−0.58 to 0.73)             | 0.804   |
| Mexiletine                                                                | 15.92 ± 5.66      | 16.38 ± 6.13    |                                  |         |
| 10-sec grip and release test (room temperature), times                    |                   |                 |                                  |         |
| Placebo                                                                  | 29.70 ± 5.86      | 30.00 ± 6.14    | 0.14 (−1.69 to 1.97)             | 0.872   |
| Mexiletine                                                                | 28.50 ± 5.71      | 30.20 ± 6.05    |                                  |         |
| 10-sec grip and release test (under cold exposure), times                 |                   |                 |                                  |         |
| Placebo                                                                  | 19.35 ± 4.86      | 20.30 ± 5.06    | 1.43 (0.59 to 2.27)              | 0.002   |
| Mexiletine                                                                | 18.85 ± 4.22      | 21.65 ± 4.59    |                                  |         |
| Timed walk test, second                                                   |                   |                 |                                  |         |
| Placebo                                                                  | 4.79 ± 1.48       | 4.95 ± 1.58     |                                  |         |
| Mexiletine                                                                | 4.88 ± 1.60       | 4.77 ± 1.80     | −0.17 (−0.63 to 0.30)            | 0.464   |
| %FVC                                                                      |                   |                 |                                  |         |
| Placebo                                                                  | 87.89 ± 14.38     | 87.65 ± 15.03   |                                  |         |
| Mexiletine                                                                | 88.40 ± 14.38     | 87.81 ± 13.71   | 0.06 (−1.48 to 1.59)             | 0.937   |
| %PEF                                                                      |                   |                 |                                  |         |
| Placebo                                                                  | 72.89 ± 18.28     | 71.34 ± 20.22   |                                  |         |
| Mexiletine                                                                | 71.27 ± 20.58     | 72.25 ± 18.89   | 0.86 (−1.17 to 2.89)             | 0.385   |

Data are presented as the mean ± standard deviation. All treatment effect estimates and CIs were extracted from the mexiletine treatment variable of the fitted mixed model.

ALSFRS-R, revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CMAP, compound muscle action potentials; %FVC, predicted values of forced vital capacity; %PEF, predicted values of peak expiratory flow; SBMAFRS, Spinal and Bulbar Muscular Atrophy Functional Rating Scale.
Mexiletine in SBMA

We, therefore, hypothesized that use-dependent blockers of voltage-gated sodium channels, such as mexiletine hydrochloride, could be effective for improving motor function in patients with SBMA. Our recent study has demonstrated that levels of urinary titin, which is a novel marker of skeletal muscle damage, are elevated in patients with SBMA. In SBMA, the network between skeletal muscles and motor neurons undergoes degeneration. As such, the alleviation of hyperexcitability of motor neurons and muscle fibers by mexiletine hydrochloride may suppress motor neuron degeneration and muscle damage. Mexiletine is known to contribute to improvements in motor function in diseases presenting with cold paresis and does not cause serious AEs when used for a long time in patients with neuromuscular diseases.

Table 5. Adverse events in the MEXPRESS trial.

| Event                                | Mexiletine (n = 20) | Placebo (n = 20) |
|--------------------------------------|---------------------|------------------|
| Total                                | 14, 8 (40.0%)       | 7, 6 (30.0%)     |
| Gastrointestinal disorders           | 6, 6 (30.0%)        | 1, 1 (5.0%)      |
| Nausea                               | 2, 2 (10.0%)        | 0, 0 (0.0%)      |
| Diarrhea                             | 1, 1 (5.0%)         | 1, 1 (5.0%)      |
| Dyspepsia                            | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Epigastric discomfort                | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Loose stools                          | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| General disorders and administration site conditions | 2, 1 (5.0%)       | 1, 1 (5.0%)      |
| Malaise                              | 0, 0 (0.0%)         | 1, 1 (5.0%)      |
| Thirst                               | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Asthenia                             | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Infections and infestations          | 2, 2 (10.0%)        | 0, 0 (0.0%)      |
| Pharyngitis                          | 2, 2 (10.0%)        | 0, 0 (0.0%)      |
| Respiratory, thoracic, and mediastinal disorders | 1, 1 (5.0%)       | 0, 0 (0.0%)      |
| Oropharyngeal discomfort             | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Injury, poisoning, and procedural complications | 1, 1 (5.0%)       | 3, 3 (15.0%)     |
| Mandibular fracture                  | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Contusion                            | 0, 0 (0.0%)         | 3, 3 (15.0%)     |
| Cardiac disorders                    | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Sinus tachycardia                    | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Nervous system disorders             | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Headache                             | 1, 1 (5.0%)         | 0, 0 (0.0%)      |
| Skin and subcutaneous tissue disorders | 0, 0 (0.0%)     | 2, 1 (5.0%)      |
| Itchiness                            | 0, 0 (0.0%)         | 1, 1 (5.0%)      |
| Rash                                 | 0, 0 (0.0%)         | 1, 1 (5.0%)      |

Data are presented as number of adverse events, number of patients with adverse events (prevalence of adverse events).

Based on our observational study, we conducted a placebo-controlled, randomized, double-blind, multicenter, crossover exploratory clinical study of the efficacy and safety of mexiletine hydrochloride in patients with SBMA. As no serious AEs were observed throughout the clinical trial, this study showed the short-time safety of mexiletine in patients with SBMA. The present study did not detect a significant effect of mexiletine on the electrophysiological assessments used as the primary measure in patients with SBMA. However, quantitative motor function tests, such as tongue pressure and 10-sec grip and release test under cold exposure, reported improved scores in the mexiletine group. The discrepancy between electrophysiological parameters and clinical outcomes suggest that the distal latency of the ulnar nerve is insensitive to the pharmacological effect of mexiletine. Alternatively, it is also possible that mexiletine acts by a mechanism which is not strongly associated with distal latency, such as attenuation of membrane hyperexcitability of skeletal muscles. ALSFRS-R, which reflects comprehensive motor function in patients with SBMA, and the grip strength, timed walk, and respiratory function tests, which are components of ALSFRS-R, all tended to improve in the mexiletine group. Given that these symptoms are typical symptoms of SBMA and constitute components of ALSFRS-R, mexiletine has the potential to improve the overall motor function of patients with SBMA. Other findings of the clinical trial included an attenuation of pain in patients with SBMA that received mexiletine. In injured nerves, activities of increased sodium channels cause hyperexcitability, which contributes to increased pain. Mexiletine, which is a sodium channel blocker similar in structure to lidocaine, inhibits abnormal sodium channel-derived excitability in the process of regeneration of injured small myelinated and unmyelinated fibers. Improvements in pain with mexiletine suggest the occurrence of nerve injury associated with sodium currents in SBMA.

This study has several limitations. First, the sample size was relatively small due to the exploratory nature of this study. Moreover, SBMA is a rare neurological disease, and we conducted a crossover study; crossover studies often exhibit carryover and period effects. The results revealed a difference in the comparison of averages for the sum of participant differences among sequences in tongue pressure and grip power at room temperature. Although a 1-week washout period is considered sufficient for crossover studies with mexiletine, further trials may require a longer washout period or parallel design. Although there was no significant period effect, cold paresis is sensitive to the environment, which may have affected the results. To obtain sufficient study power, future studies should increase the number of enrolled patients and conduct a further parallel-group validation trial with functional scales as the primary endpoint. Second, due to the exploratory nature of this study, electrophysiological examinations were used as the primary endpoint, but we did not observe any significant differences. In future trials, a more straightforward patient-
reported outcome or motor function scale should be used as the primary endpoint. Third, mexiletine is approved as a Class 1B antiarrhythmic therapy; however, its long-term risks and benefits for cardiac arrhythmias in SBMA are not fully understood. Patients with SBMA can exhibit Brugada-type ECG patterns. As such, close monitoring of patients for cardiac symptoms and potentially asymptomatic worsening of cardiac health is warranted. The ECG data in our study did not reveal any detrimental cardiac conduction or ventricular repolarization effects due to mexiletine. Additional research is warranted to better understand the cardiac health of patients with SBMA. Fourth, ancillary analyses evaluating the effects of mexiletine with and without leuprorelin acetate were a between-group difference in tongue pressure. Since leuprorelin acetate has been reported to slow disease progression in bulbar function in clinical trials, it is possible that mexiletine improved tongue pressure in patients with a previous history of leuprorelin acetate use. Further studies are required to determine the effects of mexiletine on patients with a previous history of leuprorelin acetate use. Finally, as we only enrolled Japanese participants, there is a need to validate the safety of mexiletine in patients of other ethnicities.

In conclusion, most patients with SBMA experienced cold paresis, which was characterized by prolongation of distal latency in NCS. Prolongation of distal latency was correlated with a decrease in grip power. Mexiletine improved tongue pressure and the grip and release test, although it did not restore the cold exposure-induced prolongation of distal latency in patients with SBMA. This study showed the short-term safety of mexiletine in patients with SBMA. Further parallel-group validation trials are warranted to verify the effects of mexiletine on motor function in patients with SBMA.

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Conflicts of Interest

The authors declare that they have no financial or non-financial conflicts of interest regarding the publication of this article.

Author Contributions

S.Y.: Designed and conceptualized the study, acquired clinical data, performed statistical analysis, analyzed the data, interpreted the data, and drafted the manuscript. At.H.: Designed and conceptualized the study, acquired clinical data, analyzed the data; interpreted the data, and revised the manuscript for intellectual content. Y.H., T.I, D.I., Y.K., and T.N.: Acquired clinical data. F.K., Ak.H., and S.S.: Performed statistical analysis. M.K.: Designed and conceptualized the study, analyzed the data, interpreted the data, and revised the manuscript for intellectual content.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Inclusion and exclusion criteria.
Table S2. Comparison of patients with spinal and bulbar muscular atrophy with and without cold paresis.
Table S3. Mixed-model results of patient-reported outcomes and QOL scales.
Table S4. Electrophysiological tests and motor function according to treatment sequence.
Table S5. Carryover and period effects in the MEXPRESS trial.
Table S6. Electrophysiological tests and motor function in patients previously treated or untreated with leuprolrelin acetate.
Figure S1. Flow diagram for MEXPRESS.
Figure S2. Relationship between cold paresis and disease onset. Kaplan–Meier curve estimates of the onset of cold paresis from disease onset in patients with SBMA. SBMA, spinal and bulbar muscular atrophy.