Effect of Music in Reducing Pain during Hemodialysis Access Cannulation
A Crossover Randomized Controlled Trial

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Abstract

Background and objectives Pain during cannulation for vascular access is a considerable problem for patients with kidney disease who are undergoing hemodialysis. We examined whether listening to music can reduce cannulation pain in these patients.

Design, setting, participants, & measurements We conducted a multicenter, single-blind, crossover, randomized trial of 121 patients who reported pain during cannulation for hemodialysis. We compared participants listening to “Sonata for Two Pianos in D Major, K.448” or white noise as control while undergoing the cannulation procedure. The cannulation operator was blinded to the intervention, and the hypothesized superiority of music over white noise was concealed during explanations to the participants. The primary end point was the visual analog scale score for cannulation pain independently evaluated by participants.

Results The primary analysis was on the basis of the modified intention-to-treat principle. The median baseline visual analog scale pain score was 24.7 mm (interquartile range, 16.5–42.3). Median change of the visual analog scale pain score from the “no sound” to the music period was −2.7 mm (interquartile range, −9.2 to 3.6), whereas it was −0.3 mm (interquartile range, −5.8 to 4.5) from “no sound” to white noise. The visual analog scale pain score decreased when listening to music compared with white noise. (Adjusted difference of visual analog scale pain score: −12%; 95% confidence interval, −21 to −2; P=0.02.) There were no significant differences in the secondary outcomes of anxiety, BP, or stress assessed by salivary amylase (adjusted difference of visual analog scale anxiety score −8%, 95% confidence interval, −18 to 4; P=0.17). No intervention-related adverse events were reported.

Conclusions Listening to music reduced cannulation pain in patients on hemodialysis, although there was no significant effect on anxiety, BP, or stress markers.

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Introduction

Cannulation pain is a major concern in patients with kidney failure undergoing hemodialysis, who require as many as 150 hemodialysis sessions annually, and experience pain each time cannulation is performed for vascular access (1). Pain is one of the main reasons for patients withdrawing from hemodialysis treatment (2). Approximately 20% of patients undergoing hemodialysis feel considerable cannulation pain, despite the administration of topical analgesics (1). Moreover, topical analgesics can cause skin problems, leading to infection and vascular failure (3). Anxiolytics and antidepressants may be prescribed for reducing pain; however, they can cause hypotension and physical discomfort (4) and are costly.

Numerous studies have shown that listening to music reduces a variety of pain (5), such as pain associated with cancer, surgical treatment (6), lumbar puncture in children (7), and prostate biopsy (8). Music can also reduce anxiety, which has been shown to reinforce pain (9). Music has the advantage of being safer and less expensive than traditional analgesics. Therefore, music may be a useful analgesic for patients on hemodialysis experiencing frequent analgesics. However, studies investigating the effects of music on patients on hemodialysis are limited (Supplemental Summary 1), and it remains unclear whether music reduces vascular access cannulation pain.

This study aimed to verify the hypothesis that music decreases the pain of vascular access cannulation in outpatients undergoing maintenance hemodialysis. Many previous studies assessing efficacy of music used only a “no sound” control group (5),
which could create a potential placebo effect for the intervention (10). This study instead used white noise as control to better assess the true music effect, as many other studies of music and sound have done (Supplemental Figure 1) (6,11,12).

**Materials and Methods**

**Study Design**
This was a prospective, multicenter, single-blind, crossover, randomized controlled trial conducted at five dialysis facilities in Japan. The trial protocol is available in Supplemental Information 1. Details of the objectives, design, and methods of the trial have been previously (13). This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000032850) on July 1, 2018.

**Ethics Approval**
The proposed protocol was approved by the chief ethics committee at Nagasaki University Hospital (registration number 18061813) and each research facility. This study was performed in accordance with the tenets outlined in the Declaration of Helsinki. All enrolled patients provided informed written consent before participation.

**Participants**
A complete list of eligibility criteria is provided in the protocol (13). Inclusion criteria were age ≥20 years, undergoing hemodialysis for ≥6 months, undergoing outpatient dialysis three times weekly, and reporting pain during cannulation in a preliminary questionnaire identifying patients who experienced cannulation pain on a weekly basis. Key exclusion criteria were the refusal to participate, hearing impairments, and inability to provide a self-assessment on a tablet personal computer (PC).

**Randomization and Masking**
After participant eligibility was assessed, background information was collected on the enrollment day (HD1; each hemodialysis visit is denoted as HDn, where n denotes the visit number), and participants were assigned 1:1 to the early-sequence group (early group) or later-sequence group (later group) by centralized randomization using the permuted block method stratified at the facility (Figure 1). A statistician involved in neither patient enrollment nor allocation created the random allocation sequence, with a block size of two or four chosen at random. Participants were observed for 4 weeks, and each weekly period comprised three hemodialysis treatments. The first week and third week (washout period) were set as “no sound” periods and involved wearing headphones that made no sound. In the early group, the second week was set as the music listening period (music period) and the fourth week as the white noise listening period (white noise period), and vice versa for the later group. Random allocation, data management, and sound supply via headphones were all carried out online using the Research Electronic Data Capture (REDCap) system version 8.1.13 (Vanderbilt University, Nashville, TN).

This study was a single-blinded trial, with the allocation concealed from operators using REDCap. To conceal the sound the participant was listening to from the cannulation operator, participants listened with headphones connected to a tablet PC whose screen did not indicate which sound was being played. Participants also performed evaluations and data transmission on the tablet PC, blinding all staff to results of the evaluation. Because it was not possible to completely conceal the intervention from participants in this study, an explanation was devised to conceal the hypothesis of the superiority of music from the participants. We explained that “both music and white noise may effectively alleviate cannulation pain, and we would like to verify which is superior” as the study aim.

**Procedures**
Interventions and data collection were performed during hemodialysis cannulation (Supplemental Figure 2) three times per week for a total of 12 dialysis sessions (HD2–HD13; Figure 1). During the “no sound” period, the participants wore headphones that did not play any sound during the 8 minutes before the start of the cannulation procedure and underwent the vascular access puncture while wearing headphones (Study protocol (13); Supplemental Information 1). During the music period, the participants started listening to music through the headphones 8 minutes before the start of the cannulation procedure and underwent a puncture while listening to music. The music used was Mozart’s “Sonata for Two Pianos in D Major, K.448,” which is known to have the “Mozart effect,” as validated by multiple music therapy studies (14–16). During the white noise period, participants similarly listened to white noise (available at https://www.youtube.com/watch?v=_CMzWGteDCY). White noise has the same intensity at all audible frequencies (10,17), unlike music, which is defined as an orderly arrangement of sounds consisting of melody, harmony, rhythm, tone, and pitch (18) (Supplemental Figure 1). We used headphones manufactured by JVC Kenwood Co. (Kanagawa, Japan) and tablet PCs by Bluedot Co. (Chiba, Japan). The use of analgesics was allowed throughout this trial.

**Outcomes**
The primary end point was the visual analog scale (VAS) pain score during vascular access cannulation. The leftmost value was 0 mm, indicating no pain. The rightmost value was 100 mm, indicating maximum pain. As secondary end points, the VAS anxiety score indicating anxiety experienced immediately before cannulation (0 mm, no anxiety; 100 mm, maximum anxiety), State-Trait Anxiety Inventory (STAI) Y-1 score evaluating state anxiety (score 20, no anxiety; score 80, maximum anxiety), and changes in BP and salivary amylase concentration (as a marker of mental and physical stress), before and after the procedure were measured. A detailed method of measuring salivary amylase can be found in Supplemental Information 1.

The VAS pain score, VAS anxiety score, and STAI Y-1 were evaluated by each participant immediately after the cannulation procedure was completed and headphones were removed (Supplemental Figure 2). To avoid disturbing the participant’s concentration on the sound, the VAS
The collection of patient characteristic information. On HD2, enrollment and randomization were performed, along with the allocation of patients. Enrollment and randomization were performed, along with the collection of patient characteristic information. On HD2–HD13, the intervention was carried out, and outcome data were collected.

Statistical Analysis

Sample size estimation was on the basis of results of a two-arm pilot study, and treatment effect was assumed to be 4.9 mm with 12.0 mm SD. We calculated that 95 participants were needed to observe the treatment effect at a power of 80% with a two-tailed significance level of 5%. Accounting for participant attrition, the target number of patients was set at 120.

This study had a crossover design, and the carry-over effect was examined by comparing the mean value of the sum at six points of the VAS pain score in the “no sound” period between the early group and the latter group using the Wilcoxon rank-sum test. VAS pain and anxiety scores were analyzed by applying linear mixed models. The mixed model used six VAS scores: three scores measured during the music period, and three during the white noise period. In the mixed effect model, the mean value of the three VAS scores (not log-transformed) taken during the baseline period preceding each of the music and the white noise periods was entered as an explanatory variable, along with an indicator variable for the comparison groups (music or white noise) and an indicator variable for periods (fourth week or second week).

Compound symmetry was used for variance-covariance to estimate dependency among the repeated measures. As for the missing data, only the data at the time when the missing data occurred were excluded in the linear mixed model. Linear mixed models on the available data control type I error rates and can derive estimators with comparatively small bias under the missing at random model (19,20). During the analysis of each outcome, a QQ plot was drawn to confirm the assumptions (residual normality) of the mixed effect model (Supplemental Figure 3). As a result, normality was not found in the residuals for VAS pain score, VAS anxiety score, or salivary amylase. Therefore, the absolute value of each measurement was logarithmically transformed for use in the analysis. Because some of the degrees of changes in salivary amylase resulted in a negative value, they could not be log-transformed and a post value was therefore used. The treatment effects of these log-transformed outcomes were shown as the logarithmic difference between the music and the white noise periods. The exponentiated main effect of treatment gives us the ratio of the geometric mean VAS pain score with music against the geometric mean VAS pain score with white noise. Therefore, the results of these log-transformed outcomes were reported as percentages. The percentage also has high clinical validity because the threshold at which a patient perceives a change in pain to be noteworthy is influenced by the intensity of their baseline pain (21).

Data analysis was on the basis of the modified intention-to-treat principle. A full analysis set was obtained when eligible participants were allocated to the early or later group, and VAS pain scores were available for one or more cannulations during the music or white noise interventions. Furthermore, a target group conforming to the implementation plan was defined as the per-protocol set, for which when an observation was discontinued by stopping the protocol, the patient’s data were not used in the analysis. The primary analysis of the primary and secondary outcomes was the main focus of the full analysis set. We also performed analyses targeting the per-protocol set to confirm the stability of the analytic outcomes. R software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. Interim analyses were not performed.

After conducting prespecified analyses (13), we considered the possibility of heterogeneity due to differences in patient characteristics, because the analgesic effect of music was smaller than expected. Therefore, a subgroup analysis...
was performed \textit{post hoc} on the basis of participants' use of topical analgesics, severity of pain at baseline, and favoring of classic music. A data and safety monitoring center reviewed the unblinded trial data.

**Results**

A total of 121 participants undergoing maintenance hemodialysis were enrolled from five institutions between August 27, 2018 and June 26, 2019 (Figure 2). The median age was 64 years (interquartile range [IQR], 54–70); 86 participants (71\%) were men, and the median baseline pain score (median of the mean pain score of HD2–4, “no sound” period) was 24.7 mm (IQR, 16.5–42.3) (Table 1). The full analysis set cohort used for primary analysis included 58 and 59 participants in the early and later groups, respectively, due to 4 participants dropping out before the intervention (Supplemental Table 1). The per-protocol set cohort comprised 99 participants after excluding patients who failed to complete all 12 intervention sessions (Supplemental Table 2).

The changes in VAS pain scores from the previous “no sound” period in each session are shown in Supplemental Figure 4. The VAS scores tended to decrease during both the music and white noise periods when compared with the previous “no sound” period. Median change of the VAS pain score from the “no sound” to the music period was 22.7 mm (IQR, 29.2 to 3.6), whereas it was 0.3 mm (IQR, −5.8 to 4.5) from “no sound” to white noise (Table 2).

A summary of outcome values during each period is also shown in Supplemental Table 3. The occupation and experience level of the cannulation operator and the cannulation failure rate were similar between music and white noise periods (Supplemental Table 4).

The effect of music, which is represented as difference between the music period and the white noise control (white noise) period, on the VAS pain score as the primary outcome and the VAS anxiety score as the secondary outcome is shown in Table 2. The adjusted difference for the VAS pain score (music period to white noise period) was −12\% (95\% confidence interval [95\% CI], −21 to −2; \(P=0.02\)), with the scores of the music period being significantly lower compared with the white noise period (Supplemental Table 5). The difference in the VAS anxiety score was −8\% (95\% CI, −18 to 4; \(P=0.17\)), which was not significant. The per-protocol set results were similar. In full analysis set and per-protocol set, no carry-over effect was detected during the music and white noise periods (Supplemental Table 6).

Among the subgroup analyses for the primary outcome, the effect size was larger in participants using topical anesthetics, those with a relatively low baseline pain scores, and those who favored classic music (Figure 3); however, no significant interaction was detected.

According to the other secondary outcome results, there were no significant differences between listening to music versus white noise (Table 2). No adverse events related to the intervention were reported in either group.

![Figure 2. | Trial profile.](image)

The full analysis set cohort for primary analysis included 117 participants, and the per-protocol set cohort for per-protocol analysis included 99 participants.
This trial determined that listening to music significantly decreased VAS pain scores in patients on hemodialysis when compared with a white noise control. However, this study found no significant differences in the secondary outcomes evaluating anxiety, vital signs, and stress markers.

This study has several novel features. First, various factors were considered to reduce the risk of bias (10). In studies investigating music-induced analgesia, the participants cannot usually be blinded to the intervention content; moreover, participants assess their own pain scores. In such patients, the placebo effect, including the Hawthorne effect, could become stronger if participants are aware of the hypothesis of the superiority of music (22). In this study, we used white noise as the control and explained the study to conceal the hypothesis from the participants, to reduce bias (13,23). There has been one previous study evaluating the effects of music on cannulation pain in patients undergoing hemodialysis (24) (Supplemental Summary 1). However, the study had a high risk of bias due to insufficient blinding and using “no sound” as the control, where participants inevitably recognize the superiority of music (10,24). Consequently, there were concerns that their effect size was overestimated due to the placebo effect. There was a 33% decrease in VAS pain scores in the previous study versus a 12% decrease in our study. Also, white noise is expected to remove the effect of the noise of the dialysis unit. Furthermore, in previous studies regarding pain, participants evaluated the pain score in front of the researcher or cannulation operator, creating the possibility of information bias during the outcome measurement (25). In this study, we eliminated this risk by developing a system that let the participants evaluate the outcomes independently using a tablet PC connected to REDCap.

Second, this study also evaluated the analgesic effect of music when used in conjunction with other analgesics. Topical analgesics are widely used during hemodialysis to relieve cannulation pain (26). The previously mentioned study had issues with external validity because patients using analgesics were excluded from analysis (Supplemental...
Summary 1) (24). Conversely, more than half of the participants in our study used topical analgesics, and there was no effect modification by use of topical analgesics. Third, this study evaluated only one music piece, Mozart’s “Sonata for Two Pianos in D Major, K.448.” Because this composition does not have lyrics, its effects would not be influenced by the patient’s linguistic background. Furthermore, this composition is within the public domain and is freely available on many websites. Therefore, this music could potentially alleviate the cannulation pain experienced by patients undergoing hemodialysis easily, safely, and affordably worldwide. Because patients on hemodialysis generally tend to undergo hemodialysis with numerous other patients simultaneously, playing this music in the background might also be effective.

The results of this study indicate “an orderly arrangement of sound consisting of melody, harmony, rhythm, tone, and pitch,” which is the definition of music, may attenuate pain (18). Physical pain is relieved by distraction (27) when emotions such as pleasure are triggered in the central nervous system (28), whereas psychologic pain is relieved by attenuating anxiety (10,29). In this study, because secondary outcomes including the VAS anxiety score, STAI Y-1, and salivary amylase did not improve significantly, music may not relieve psychologic pain when compared with white noise. Music may alleviate physical pain through distraction and by altering the emotional state. This is supported by the result from the subgroup of participants who favored classic music; they were thought to be more easily refocused and emotionally moved by music, and thus tended to experience a stronger pain-relieving effect.

The effect of music on pain relief resulted in 12\% decrease in the VAS score. According to a meta-analysis, a minimum clinically important difference in pain scale should be between 13\% and 85\% decrease (30). Our results suggest that music alone might not be clinically sufficient for pain relief. Nevertheless, because our study design also evaluated the add-on effect of topical analgesics, music might better be considered as an adjuvant pain relief treatment, potentially leading to a reduction in total dose and number of other analgesics required (31).

This study had several limitations. First, the effects of other musical compositions are still unknown. A previous study indicated that music therapy might be more effective when patients choose their music (32); further trials using the participants’ preferred music are required. Second, the participants listened to music through headphones connected to tablet PCs because of the study’s feasibility. Further studies are required to elucidate the effects of other broadcasting devices, such as a speaker system providing background music. Third, this study set each intervention

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### Table 2. Outcomes of the music period compared with the control (white noise) period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis(^a)</th>
<th>Change from “No Sound” Period(^b)</th>
<th>Adjusted Difference</th>
<th>P Value(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Music Period</td>
<td>White Noise Period</td>
<td>(95% Confidence Interval)(^c)</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS pain score, mm(^d)</td>
<td>Primary analysis</td>
<td>-2.7 (-9.2, 3.6)</td>
<td>-0.3 (-5.8, 4.5)</td>
<td>-12% (-21 to -2) 0.02</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>-2.5 (-9.7, 3.0)</td>
<td>-0.3 (-6.5, 3.7)</td>
<td>-12% (-22 to -2) 0.03</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS anxiety score, mm(^d)</td>
<td>Primary analysis</td>
<td>-0.7 (-7.8, 1.7)</td>
<td>0.3 (-2.7, 3.7)</td>
<td>-8% (-18 to 4) 0.17</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>-0.3 (-7.7, 1.8)</td>
<td>0.3 (-2.5, 3.3)</td>
<td>-9% (-20 to 3) 0.14</td>
</tr>
<tr>
<td>Systolic BP, mm Hg(^e)</td>
<td>Primary analysis</td>
<td>1 (-4, 6)</td>
<td>1 (-6, 8)</td>
<td>1 mm Hg (-1 to 2) 0.56</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>1 (-4, 4)</td>
<td>1 (-2, 5)</td>
<td>1 mm Hg (-1 to 3) 0.45</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg(^e)</td>
<td>Primary analysis</td>
<td>1 (-4, 4)</td>
<td>1 (-2, 5)</td>
<td>-1 mm Hg (-2 to 1) 0.27</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>1 (-4, 4)</td>
<td>0 (-2, 5)</td>
<td>-1 mm Hg (-2 to 1) 0.34</td>
</tr>
<tr>
<td>STAI Y-1, points(^e)</td>
<td>Primary analysis</td>
<td>-1 (-4, 2)</td>
<td>-1 (-3, 2)</td>
<td>-1 points (-2 to 1) 0.39</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>-1 (-4, 2)</td>
<td>-1 (-3, 3)</td>
<td>-1 points (-2 to 1) 0.29</td>
</tr>
<tr>
<td>Salivary amylase, kIU/L(^d)</td>
<td>Primary analysis</td>
<td>-1 (-20, 25)</td>
<td>0 (-17, 17)</td>
<td>-15% (-37 to 14) 0.28</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>-2 (-27, 25)</td>
<td>0 (-16, 18)</td>
<td>-12% (-36 to 20) 0.41</td>
</tr>
</tbody>
</table>

VAS, visual analog scale; STAI, State-Trait Anxiety Inventory.

\(^a\)Primary analysis used the data of the full analysis set cohort (n=117). Per-protocol analysis used the data of the per-protocol set cohort (n=99).

\(^b\)The change from “no sound” period is shown as median (first quartile, third quartile). The change was calculated using the mean scores of the three sessions in the no-sound period before each period (the music or white noise periods) as the baseline value. Each median value represents the between patient median calculated using the mean within patient.

\(^c\)Because of the non-normality of the residuals, the VAS pain score, VAS anxiety score, and postvalue of salivary amylase were log-transformed and used as objective variables. Hence, the adjusted difference represents a percent difference within patient relative to the white noise period.

\(^d\)The adjusted difference represents the difference between patient music and white noise periods per week. Negative values for the adjusted difference indicate decrease in outcome values during the music period relative to the white noise period.

\(^e\)Positive values for the adjusted difference indicate decrease in outcome values during the music period relative to the white noise period, and positive values indicate an increase.
P-value that they liked classic music in the questionnaire at the time of enrollment (HD1). 95% CI, 95% confidence interval in this analysis, baseline pain intensity was excluded from the covariates. §The favor group refers to the participants who responded the group with a VAS pain score below the median was classified as the lower group. In the regression model used to calculate the effect size in this analysis, baseline pain intensity was excluded from the covariates. †The favor group refers to the participants who responded that they liked classic music in the questionnaire at the time of enrollment (HD1). 95% CI, 95% confidence interval.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total No.</th>
<th>Adjusted difference (95% CI)*</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>117</td>
<td>–12% (–21 to –2)</td>
<td></td>
</tr>
<tr>
<td>Use of topical analgesics†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>63</td>
<td>–15% (–28 to –1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Not use</td>
<td>54</td>
<td>–9% (–22 to 5)</td>
<td></td>
</tr>
<tr>
<td>Severity of pain at baseline‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>57</td>
<td>–10% (–22 to 5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Lower</td>
<td>59</td>
<td>–14% (–26 to 0)</td>
<td></td>
</tr>
<tr>
<td>Favor of classic music§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favor</td>
<td>32</td>
<td>–15% (–25 to –4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Non-favor</td>
<td>85</td>
<td>–4% (–22 to 18)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. | Forest plot of the effect of music (adjusted difference between music period and white noise period) by the visual analog scale (VAS) pain score in subgroup analyses. *This is the result of the analysis using the full analysis set cohort. The effect size was calculated using a linear mixed model adjusted for the baseline VAS pain score and treatment period. Because of the non-normality of the residuals, the log-transformed VAS pain score was used as the objective variable. Hence, the effect size of music is indicated as a percentage. †Topical analgesics include patch-type and application-type analgesics. Participants who used topical analgesics during two or three sessions among the hemodialysis (HD)2–HD4 sessions were classified as the user group. ‡Mean VAS pain score of HD2–HD4 was defined as the baseline pain. The group with HD2–HD4 VAS pain scores greater than the median (24.7 mm) was classified as the higher group, and the group with a VAS pain score below the median was classified as the lower group. In the regression model used to calculate the effect size in this analysis, baseline pain intensity was excluded from the covariates. §The favor group refers to the participants who responded that they liked classic music in the questionnaire at the time of enrollment (HD1). 95% CI, 95% confidence interval.

Disclosures
A. Shintani reports having consultancy agreements with Kyowa Kirin; receiving research funding from DaiichiSankyo, Kyowa Kirin, and Takeda Pharma; and receiving honoraria from Abbvie, Asahikasei Pharma, Bayer, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Jansen Pharma, Kyowa Kirin, Mallinckrodt Pharma, Maruho, Nihonshinyaku, Nipro, Ono Pharma, Pfizer, Shionogi, Taisho Pharma, Takeda Pharma, Tanabe Pharma, and Torii Pharma. T. Ikenoue reports serving on speakers’ bureau for Kyowa Kirin. All remaining authors have nothing to disclose.

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Author Contributions
T. Ikenoue, E. Inayama, M. Kishida, A. Shintani, and Y. Yamada conceptualized the study; T. Ikenoue, E. Inayama, M. Kitamura, and Y. Yamada were responsible for the data curation; K. Ota, A. Shintani, and K. Takahashi were responsible for the formal analysis; T. Ikenoue and Y. Yamada were responsible for the funding acquisition; T. Ikenoue, E. Inayama, M. Kishida, M. Kitamura,
and Y. Yamada were responsible for the investigation; T. Ikenoue, M. Kitamura, and A. Shintani were responsible for the methodology; T. Ikenoue, E. Inayama, M. Kishida, M. Kitamura, A. Shintani, and Y. Yamada were responsible for the project administration; E. Inayama was responsible for the resources; M. Kishida, K. Ota, and A. Shintani were responsible for the software; T. Nishino and A. Shintani provided supervision; T. Ikenoue was responsible for the validation; T. Ikenoue, M. Kitamura, A. Shintani, K. Takahashi, and Y. Yamada were responsible for the visualization; T. Ikenoue, E. Inayama, M. Kishida, M. Kitamura, and Y. Yamada wrote the original draft; and T. Ikenoue, T. Nishino, and A. Shintani reviewed and edited the manuscript.

Data Sharing Statement
The anonymized datasets can be made available to qualified researcher teams after review and approval of the research proposal and statistical analysis plan. Please contact the corresponding author who can assist the team to gain access to the data.

Supplemental Material
This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00360122/-/DCSupplemental
Supplemental Summary 1. Evidence before this study (systematic review).
Supplemental Information 1. Study protocol including the statistical analysis plan.
Supplemental Table 1. Characteristics of participants in the full analysis set cohort at baseline.
Supplemental Table 2. Characteristics of participants in the per-protocol set cohort at baseline.
Supplemental Table 3. Overall mean and standard deviation of outcome values in each period.
Supplemental Table 4. Information on cannulation operators and cannulation failure (overall sessions).
Supplemental Table 5. The regression coefficient estimates for each variable of linear mixed-effect regression analysis.
Supplemental Table 6. P values calculated by Wilcoxon rank-sum test for the carry-over effect.
Supplemental Figure 1. Conceptual diagram of the interventions applied in this study.
Supplemental Figure 2. Explanation of intervention procedures and timing of outcome measurement.
Supplemental Figure 3. Extracted QQ plots to confirm the assumptions of the mixed-effects model (normality of residuals).
Supplemental Figure 4. Changes in median visual analog scale (VAS) pain scores in each session (with reference to the previous "no sound" period).

References

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