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

Emi Inayama,1 Yosuke Yamada,2 Masatsugu Kishida,1 Mineaki Kitamura,4 Tomoya Nishino,4 Keiko Ota,5 Kanae Takahashi,6 Ayumi Shintani,7 and Tatsuyoshi Ikenoue8,9

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.

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 published 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=_CMzWGlteDCY). 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
anxiety score immediately before cannulation was also assessed after the procedure. The degree of change in BP and salivary amylase was calculated by measuring the values immediately before wearing the headphones and immediately after the procedure. The VAS pain score, VAS anxiety score, BP, and adverse events were assessed at each intervention session from HD2–HD13. STAI Y-1 and salivary amylase were measured only during HD4, HD7, HD10, and HD13.

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 later 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 music periods, 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 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 2.7 mm (IQR, −9.2 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.
Discussion

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (n=121)</th>
<th>Early Group (n=61)</th>
<th>Later Group (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>64 (54, 70)</td>
<td>64 (54, 69)</td>
<td>67 (57, 71)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>86 (71)</td>
<td>48 (79)</td>
<td>38 (63)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 (158, 171)</td>
<td>166 (159, 171)</td>
<td>164 (156, 170)</td>
</tr>
<tr>
<td>Prescription dry weight for dialysis, kg(^a)</td>
<td>61.5 (51.4, 70.5)</td>
<td>62.5 (54.3, 70.5)</td>
<td>60.4 (49.3, 70.2)</td>
</tr>
<tr>
<td>Time since initiation of hemodialysis, yr</td>
<td>4.0 (2.0, 10.0)</td>
<td>3.0 (2.0, 8.0)</td>
<td>4.5 (2.0, 11.0)</td>
</tr>
<tr>
<td>Cause of CKD, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>53 (44)</td>
<td>27 (44)</td>
<td>26 (43)</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>6 (5)</td>
<td>3 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>38 (31)</td>
<td>18 (30)</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Benign nephrosclerosis</td>
<td>18 (15)</td>
<td>8 (13)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Urological complications</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type of vascular access, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>115 (95)</td>
<td>57 (94)</td>
<td>58 (97)</td>
</tr>
<tr>
<td>Superficialized artery(^b)</td>
<td>5 (4)</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Arteriovenous graft</td>
<td>1 (0.8)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Use of topical analgesics, n (%)(^c)</td>
<td>63 (52)</td>
<td>33 (54)</td>
<td>30 (50)</td>
</tr>
<tr>
<td>Favorite type of music, n (%)(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic</td>
<td>32 (26)</td>
<td>15 (25)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Others</td>
<td>68 (56)</td>
<td>35 (57)</td>
<td>33 (55)</td>
</tr>
<tr>
<td>None</td>
<td>21 (17)</td>
<td>11 (18)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>VAS pain score at baseline, mm(^e)</td>
<td>24.7 (16.5, 42.3)</td>
<td>24.3 (16.9, 40.9)</td>
<td>28.0 (14.5, 44.3)</td>
</tr>
<tr>
<td>VAS anxiety score at baseline, mm(^f)</td>
<td>18.0 (9.3, 32.7)</td>
<td>20.0 (9.3, 34.2)</td>
<td>16.3 (9.8, 32.5)</td>
</tr>
<tr>
<td>STAI Y-2(^d)</td>
<td>43 (35, 47)</td>
<td>40 (34, 46)</td>
<td>44 (38, 48)</td>
</tr>
</tbody>
</table>

Number of patients (percentage) is used for nominal variables and median (first quartile, third quartile) for continuous variables. “Early group” denotes the early-sequence group, “Later group” the later-sequence group.

\(^a\)The prescription dry body weight for dialysis is the weight at which the patient’s volume status is neither overhydrated nor underhydrated. The weight is set according to the physician’s discretion. The patient’s weight is lowered to this value by removing fluid during dialysis at each dialysis session. The dry body weight at HD1 is shown as the representative value here.

\(^b\)The brachial artery, found between the muscles, is surgically elevated to the subcutaneous level to facilitate direct puncture of the artery from the body surface (33).

\(^c\)Topical analgesics include patch-type and application-type analgesics. Participants who used topical analgesics during two or three sessions among the HD2–HD4 sessions were classified as the user group.

\(^d\)Favorite type of music include patch-type and application-type analgesics. Participants who used topical analgesics during two or three sessions among the HD2–HD4 sessions were classified as the user group.

\(^e\)Visual analog scale (VAS) score at baseline means the average score of the first “no sound” period (HD2–HD4).
Table 2. Outcomes of the music period compared with the control (white noise) period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysisa</th>
<th>Change from “No Sound” Periodb</th>
<th>Adjusted Difference (Music Period – White Noise Period) (95% Confidence Interval)c</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS pain score, mmid</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)</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>−2.3 (−9.7, 3.0)</td>
<td>−0.3 (−6.5, 3.7)</td>
<td>−12% (−22 to −2)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS anxiety score, mmid</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)</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)</td>
</tr>
<tr>
<td>Systolic BP, mm Hge</td>
<td>Primary analysis</td>
<td>1 (−4, 6)</td>
<td>1 (−6, 8)</td>
<td>1 mm Hg (−1 to 2)</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)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hge</td>
<td>Primary analysis</td>
<td>1 (−4, 4)</td>
<td>1 (−2, 5)</td>
<td>−1 mm Hg (−2 to 1)</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)</td>
</tr>
<tr>
<td>STAI Y-1, points**</td>
<td>Primary analysis</td>
<td>−1 (−4, 2)</td>
<td>−1 (−3, 2)</td>
<td>−1 points (−2 to 1)</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)</td>
</tr>
<tr>
<td>Salivary amylase, kIU/Ld</td>
<td>Primary analysis</td>
<td>−1 (−20, 25)</td>
<td>0 (−17, 17)</td>
<td>−15% (−37 to 14)</td>
</tr>
<tr>
<td></td>
<td>Per-protocol</td>
<td>−2 (−27, 25)</td>
<td>0 (−16, 18)</td>
<td>−12% (−36 to 20)</td>
</tr>
</tbody>
</table>

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

aPrimary 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).

bThe 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.

cCarry-over effect was not detected in any of the analyses. The adjusted difference and P value were calculated using a linear mixed model adjusted for the baseline score of the VAS and treatment period.

dBecause 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 between music and white noise periods per week. Negative values for the adjusted difference indicate the percentage of decrease in outcome values during the music period relative to the white noise period.

eThe adjusted difference represents the difference within patient between 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, and positive values indicate an increase.

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
## Table

<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.

- **Adjusted difference (95% CI)**: 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.
- **P-value for interaction**: The significance of the interaction was assessed using a linear mixed model.

### Acknowledgments

The funders were not involved in the study design, data collection, analysis, or interpretation. This trial was performed at five outpatient maintenance hemodialysis facilities: Jisyukai Ueda Kidney Clinic (Nagano, Japan), Nagasaki Renal Centre (Nagasaki, Japan), Fujijera Keijinkai Clinic (Osaka, Japan), Mihama Narita Clinic (Chiba, Japan), and Hakuyu Chiyo Clinic (Osaka, Japan). The staff at the above facilities contributed to data collection for this study. We want to sincerely thank Dr. Satoshi Funakoshi, Ms. Mariko Kawafuchi, Ms. Miyuki Higuchi, and other staff at the Nagasaki Renal Center; Dr. Wataru Tsukada, Mr. Ryoji Kido, Mr. Takashi Kosuge, and other staff at the Ueda Kidney Clinic; Dr. Koichi Murakami, Dr. Motoyuki Masai, Dr. Toyohiko Yoshida, and other staff at the Mihama Narita Clinic; Dr. Tetsuya Kitamura, Dr. Hideki Yamahara, and other staff at the Fujijera Keininkai Clinic, and Dr. Noriyuki Okada at the Hakuyu Chiyo Clinic for contributing to data collection. We also thank Dr. Ayumu Kitawaki and Dr. Yoshitaka Okada at the Rakuwakai Otowa Hospital, who provided information regarding music therapy. The authors are also indebted to members of the Summer Camp for Research Design by iHope International (http://www.i-hope.jp/), who provided the information, education, and opportunity to undertake this project.

### 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 protocol 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
28. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ: Anatomically distinct dopamine release during anticipation...


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E.I., Y.Y., and M.K. contributed equally to this manuscript.

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AFFILIATIONS

1Mihama Narita Clinic, Chiba, Japan
2Department of Nephrology, Shinshu University School of Medicine, Nagano, Japan
3Division of Nephrology, National Cerebral and Cardiovascular Center, Osaka, Japan
4Department of Nephrology, Nagasaki University Hospital, Nagasaki, Japan
5Center for Clinical Research and Innovation, Osaka Metropolitan University Hospital, Osaka, Japan
6Department of Biostatistics, Hyogo College of Medicine, Hyogo, Japan
7Department of Medical Statistics, Osaka City University Graduate School of Medicine, Osaka, Japan
8Human Health Science, Kyoto University Graduate School of Medicine, Kyoto, Japan
9Data Science and AI Innovation Research Promotion Center, Shiga University, Shiga, Japan
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Supplemental Summary 1. Evidence before this study (systematic review)

The sources (databases, journals, or book reference lists, among others) searched
1. PubMed
2. Cochrane Central Register of Controlled Trials (CENTRAL)

Criteria used to include or exclude studies (including the exact start and end dates of the search)
- The targeted studies
  Studies whose objective is investigating whether music reduces cannulation pain in hemodialysis patients.
- Types of studies
  We considered only randomized controlled trials.
- Participants
  Inclusion criteria: All studies involving hemodialysis patients undergoing cannulation procedures on peripheral blood vessels, including hemodialysis access.
  Exclusion criteria: Patients undergoing cannulation on areas other than peripheral blood vessels.
- Intervention and comparator
  This review considered studies that evaluated the effectiveness of music on pain during cannulation in hemodialysis patients.
  Intervention: Music
  Comparator: No music or sham intervention
- Report characteristics
  We applied no restrictions on language, length of follow-up, publication status, or date of publication.
- Types of outcome measures
  Pain for cannulation: only self-reported

The search terms used
For PubMed
#1 “Catheterization”[mh]
#2 “Catheterization, Peripheral”[mh]
#3 “Phlebotomy”[mh]
#4 “Infusions, Intravenous”[mh]
#5 “Injections, Intravenous”[mh]
#7    #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8    “Music”[mh]
#9    "Music therapy”[mh]
#11   #8 OR #9 OR #10
#13   #7 AND #11 AND #12

For Cochrane CENTRAL
#1    MeSH descriptor: [Catheterization] explode all trees
#2    MeSH descriptor: [Catheterization, Peripheral] explode all trees
#3    MeSH descriptor: [Phlebotomy] explode all trees
#4    MeSH descriptor: [Infusions, Intravenous] explode all trees
#5    MeSH descriptor: [Injections, Intravenous] explode all trees
#6    ((cannula*) OR (catheter*) OR (Phlebotom*) OR (Venesection*) OR (Venipuncture*) OR ((pain*) AND ((needl*) OR (intravenous))) OR ((needl*) AND (procedure*)) OR (((injection*) OR (infusion*) OR (punctur*)) AND ((intravenous) OR (vein*) OR (Drip) OR (blood vessel*) OR (vascular) OR (Arteriovenous Fistula*))) OR ((intravenous) AND (Drip))):ti,ab,kw
#7    #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8    MeSH descriptor: [Music] explode all trees
#9    MeSH descriptor: [Music Therapy] explode all trees
#10   ((Music*) OR rhythm* OR (melod*) OR (singing) OR (sing) OR (song) OR (songs) OR (improvis*)):ti,ab,kw
#11   #8 OR #9 OR #10
#12   #7 AND #11

Search results (Mar 17th, 2021): PubMed 957, Cochrane CENTRAL 1,640
The study included in the qualitative synthesis

<Shabandokht-Zarmi H 2017>
### Summary of the RCTs included in this review and our study

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Study design</th>
<th>Interventions</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Shabandokht-Zarmi H, 2017     | A desire to listen to the music; the age of 18 years and older; not diagnosed with neuropathic disorders; no history of depression; treated with hemodialysis for at least 3 months; not administered tranquilizers, analgesics, or sedatives 3 h before the study; not taken recent antipsychotic medications or tranquilizers; not being cognitively impaired; no hearing and visual impairments (for marking the VAS-pain); not habitually listening to music during hemodialysis | Acute pain in other parts of the body; more than one attempt for fistula puncturing; any changes in the physical status during the study (occurrence of acute conditions such as hypertension or vomiting); withdrawal from the study; death | Multicenter, open-label, parallel 3 groups RCT | 1. **Music group**  
A few pieces of familiar Persian folklore/traditional/soothing music were initially selected by the experimenter on the basis of patients' social and cultural backgrounds and were then offered to the music group during a session before the intervention. The music group listened to self-selected and preferred music using an MP4 DOLPH player through an XP-H828 headphone 6 min before needle insertion into a fistula until the end of the venipuncture.  
2. **Headphone group**  
The headphone group wore a headphone without listening to music.  
3. **Control group**  
The control group did not receive any intervention. | VAS pain score of fistula cannulation |
Inayama E, 2021
(The current study)

Patients over the age of 20 years who are undergoing outpatient hemodialysis three times a week; who have received dialysis for more than 6 months; who experienced pain during cannulation based on a prior questionnaire. **The use of analgesics is allowed throughout this trial.**

Not willing to participate; have a hearing, writing, or visual impairment; are paralyzed; face difficulty communicating; have a psychiatric disorder or dementia; undergoing hemodialysis less than three times per week; receiving dialysis through an indwelling catheter.

Multicenter, single-blind, crossover RCT

1. **Music period**
The participants started listening to music through the headphones 8 min before the start of the cannulation and underwent the puncture while listening to music. The music played was Mozart’s Sonata for two pianos in D major, K.448’, which is known to have the ‘Mozart effect’ and has been validated in many studies on music therapy.

2. **White noise period (placebo-control)**
The participants similarly listened to white noise. White noise has the same intensity at all audible frequencies, unlike music, which is defined as an orderly arrangement of sounds consisting of melody, harmony, rhythm, tone, and pitch.

**Primary outcome**
VAS pain score of hemodialysis access cannulation

**Secondary outcomes**
VAS anxiety score, State-trait anxiety inventory (Y-1), measurement of salivary amylase activity, blood pressure

RCT, Randomized control trial, VAS, visual analog scale.
Quality of the evidence (risk of bias) for the targeted outcome: pain reduction during cannulation

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Experimental</th>
<th>Comparator</th>
<th>Outcome</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>Overall</th>
<th>Bias in measurement of the outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shabandokht-Zarmi H 2017</td>
<td>Music</td>
<td>No sound (wearing headphones)</td>
<td>VAS pain score</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Low risk</td>
</tr>
<tr>
<td>Inayama E 2021 (The current study)</td>
<td>Music</td>
<td>White noise</td>
<td>VAS pain score</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Notes: The Risk of Bias 2 (ROB2) tool [https://methods.cochrane.org/risk-bias-2](https://methods.cochrane.org/risk-bias-2) was used.

**The detailed explanation of differences in the judgement of ROB2 between these studies (D4 and D5)**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Shabandokht-Zarmi H 2017</th>
<th>Inayama E 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain</td>
<td>Signalling question</td>
<td>Response</td>
</tr>
<tr>
<td>Bias in measurement of the outcome</td>
<td>4.1 Was the method of measuring the outcome inappropriate?</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>4.3 Were outcome assessors aware of the intervention received by study participants?</td>
<td>Y</td>
</tr>
</tbody>
</table>

VAS, visual analog scale.
### 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>It may have been affected because they did not take measures to prevent information bias resulting from open-label design</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN</td>
<td>The participants were aware of the intervention content. However, the assessment of the outcome was not thought to be influenced because white noise was set as the control, and the method was devised to conceal the hypothesis of the superiority of music from the participants</td>
<td></td>
</tr>
</tbody>
</table>

### 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

<table>
<thead>
<tr>
<th></th>
<th>PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>

#### Risk of bias judgement

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
</table>

### 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?

<table>
<thead>
<tr>
<th></th>
<th>NI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>The statistical analysis plan was published previously (Trials. 2019;20:631.), and the analysis was conducted in accordance with the plan</td>
</tr>
</tbody>
</table>

#### Risk of bias judgement

|   | Low |

### 5.2 ... multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>In accordance with the study protocol</td>
</tr>
</tbody>
</table>

### 5.3 ... multiple eligible analyses of the data?

<table>
<thead>
<tr>
<th></th>
<th>PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>In accordance with the study protocol</td>
</tr>
</tbody>
</table>

#### Risk of bias judgement

<table>
<thead>
<tr>
<th></th>
<th>Some concerns</th>
</tr>
</thead>
</table>

#### Overall bias

<table>
<thead>
<tr>
<th></th>
<th>Risk of bias judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>High</td>
</tr>
<tr>
<td>L</td>
<td>Low</td>
</tr>
</tbody>
</table>

ROB2, Risk of bias 2; VAS, visual analog scale
Summary of the study results

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Effect size* [95%CI]</th>
<th>Effect size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shabandokht-Zarmi H 2017</td>
<td>37</td>
<td>-33.2% [-50.7 to -15.7]</td>
<td></td>
</tr>
<tr>
<td>Inayama E 2021 (The current study)</td>
<td>117</td>
<td>-12.2% [-21.1 to -2.3]</td>
<td></td>
</tr>
</tbody>
</table>

CI, Confidence interval
We calculated the point estimates and 95% CI of the effect size using the inverse variance method. We converted the results to percentages for comparison with the results of our study.
Supplemental Figure 1. Conceptual diagram of the interventions applied in this study.

* The true music effect indicates the effect of an orderly arrangement of sound that consists of melody, harmony, rhythm, tone, and pitch, which is the definition of ‘music’. We investigated the presence of a ‘true music effect’. ‘White noise’ was used as the control to eliminate the effects of headphones and other sounds. ‘No sound’ was used to evaluate the effect of wearing headphones.
Supplemental Figure 2. Explanation of intervention procedures and timing of outcome measurement

Participants' pre-values of BP and S-AMY were measured. Then, the participants wore headphones and began listening to each intervention (music, white noise, or no sound). After listening for 8 min, the cannulation operator started the procedure (disinfection of the puncture site, puncture, catheter placement, and connection with the dialysis circuit). The participants underwent vascular puncture while listening to each intervention. After the cannulation procedure, the participants' BP was measured, and dialysis was started. The participants removed the headphones at the start of dialysis and immediately evaluated their pain using the VAS pain score, VAS anxiety score, and STAI Y-1, and the post-value of S-AMY was measured.

* BP, VAS pain scores, and VAS anxiety scores were measured for HD2–HD13. STAI Y-1 and S-AMY were measured for HD4, HD7, HD10, and HD13.

HD, hemodialysis; BP, blood pressure; S-AMY, salivary amylase concentration; STAI Y-1, State-Trait Anxiety Inventory Y-1; VAS, visual analog scale
Supplemental Figure 3. Extracted QQ plots to confirm the assumptions of the mixed-effects model (normality of residuals)

Because of a potential issue in assuming the normality of the residuals, the outcomes were log-transformed.
Supplemental Figure 4. Changes in median visual analog scale (VAS) pain scores in each session (with reference to the previous “no sound” period)

Results of the full analysis set cohort for the primary analysis. The change was calculated using the mean VAS pain scores of the three sessions in the no-sound period before each period (the music and white noise periods) as the baseline value. The bars show the median difference in the VAS pain scores from the baseline for each session. Error bars indicate the interquartile range. Pink bars indicate that participants were listening to music and gray bars indicate that they were listening to white noise. Missing data occurred in 28 sessions (4.0%) out of a total of 702 sessions (6 sessions per participant). HD denotes hemodialysis.
### Supplemental Table 1. Characteristics of participants in the full analysis set cohort at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants (N=117)</th>
<th>Early group (N=58)</th>
<th>Later group (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64 [54, 70]</td>
<td>64 [53, 69]</td>
<td>67 [57, 71]</td>
</tr>
<tr>
<td><strong>Male sex – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84 (72)</td>
<td>47 (81)</td>
<td>37 (63)</td>
</tr>
<tr>
<td><strong>Height – cm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>166 [158, 171]</td>
<td>166 [159, 171]</td>
<td>165 [156, 170]</td>
</tr>
<tr>
<td><strong>Prescription dry weight for dialysis – kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61.0 [51.4, 70.5]</td>
<td>62.8 [54.4, 70.9]</td>
<td>59.7 [49.3, 69.6]</td>
</tr>
<tr>
<td><strong>Time since initiation of hemodialysis – years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0 [2.0, 10.0]</td>
<td>3.5 [2.0, 8.8]</td>
<td>5.0 [2.5, 11.0]</td>
</tr>
<tr>
<td><strong>Cause of chronic kidney disease – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>52 (44)</td>
<td>26 (45)</td>
<td>26 (44)</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>6 (5)</td>
<td>3 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>36 (31)</td>
<td>17 (29)</td>
<td>19 (32)</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Benign nephrosclerosis</td>
<td>18 (15)</td>
<td>8 (14)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Urological complications</td>
<td>1 (0.9)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Type of vascular access – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>111 (95)</td>
<td>54 (93)</td>
<td>57 (97)</td>
</tr>
<tr>
<td>Superficialized artery</td>
<td>5 (4)</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Arteriovenous graft</td>
<td>1 (0.9)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Use of topical analgesics – n (%)</strong></td>
<td>63 (54)</td>
<td>33 (57)</td>
<td>30 (51)</td>
</tr>
<tr>
<td><strong>Favorite type of music – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical</td>
<td>32 (28)</td>
<td>15 (26)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Others</td>
<td>67 (57)</td>
<td>34 (59)</td>
<td>33 (56)</td>
</tr>
<tr>
<td>None</td>
<td>18 (15)</td>
<td>9 (16)</td>
<td>9 (15)</td>
</tr>
<tr>
<td><strong>VAS pain score at baseline – mm</strong></td>
<td>24.7 [16.5, 42.3]</td>
<td>24.3 [16.9, 40.9]</td>
<td>28.0 [14.5, 44.3]</td>
</tr>
<tr>
<td><strong>VAS anxiety score at baseline – mm</strong></td>
<td>18.0 [9.3, 32.7]</td>
<td>20.0 [9.3, 34.2]</td>
<td>16.3 [9.8, 32.5]</td>
</tr>
</tbody>
</table>

Data pertaining to nominal variables are expressed as the number of cases [n] (percentage, %) and continuous variables as median [first quartile, third quartile]. ‘Early group’ denotes the early sequence group and ‘Later group’ the later sequence group.

VAS, visual analog scale; STAI Y-2, State-Trait Anxiety Inventory Y-1
Supplemental Table 2. Characteristics of participants in the per-protocol set cohort at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants (N=99)</th>
<th>Early group (N=49)</th>
<th>Later group (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age – years – years</td>
<td>65 [55, 71]</td>
<td>64 [54, 69]</td>
<td>68 [57, 71]</td>
</tr>
<tr>
<td>Male sex – n (%)</td>
<td>72 (73)</td>
<td>42 (86)</td>
<td>30 (60)</td>
</tr>
<tr>
<td>Prescription dry weight for dialysis – kg</td>
<td>61.5 [51.6, 70.7]</td>
<td>63.2 [54.8, 71.5]</td>
<td>60.0 [49.3, 68.7]</td>
</tr>
<tr>
<td>Time since initiation of hemodialysis – years</td>
<td>4.0 [2.0, 11.0]</td>
<td>4.0 [2.0, 11.0]</td>
<td>4.0 [2.0, 10.75]</td>
</tr>
<tr>
<td>Cause of chronic kidney disease – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>46 (47)</td>
<td>23 (47)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>31 (31)</td>
<td>14 (29)</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Benign nephrosclerosis</td>
<td>15 (15)</td>
<td>6 (12)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Urological complications</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type of vascular access – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>93 (94)</td>
<td>45 (92)</td>
<td>48 (96)</td>
</tr>
<tr>
<td>Superficialized artery</td>
<td>5 (5)</td>
<td>3 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Arteriovenous graft</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Use of topical analgesics – n (%)</td>
<td>50 (51)</td>
<td>27 (55)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Favorite type of music – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical</td>
<td>27 (27)</td>
<td>13 (27)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Others</td>
<td>59 (60)</td>
<td>28 (57)</td>
<td>31 (62)</td>
</tr>
<tr>
<td>None</td>
<td>13 (13)</td>
<td>8 (16)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>VAS pain score at baseline – mm</td>
<td>28.0 [16.0, 42.5]</td>
<td>24.7 [16.7, 41.3]</td>
<td>28.2 [14.4, 46.6]</td>
</tr>
<tr>
<td>VAS anxiety score at baseline – mm</td>
<td>18.0 [8.3, 32.7]</td>
<td>19.0 [8.0, 32.7]</td>
<td>17.3 [9.6, 32.6]</td>
</tr>
</tbody>
</table>

Data pertaining to nominal variables are expressed as the number of cases [n] (percentage, %) and continuous variables as median [first quartile, third quartile]. ‘Early group’ denotes the early sequence group and ‘Later group’ the later sequence group.

VAS, visual analog scale; STAI Y-2, State-Trait Anxiety Inventory Y-1.
**Supplemental Table 3. Overall mean and standard deviation of outcome values in each period**

<table>
<thead>
<tr>
<th>Outcomes (unit)</th>
<th>Full analysis set cohort</th>
<th>Per-protocol set cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>VAS pain score (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White noise period</td>
<td>25.4</td>
<td>18.0</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before white noise)</td>
<td>26.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Music period</td>
<td>23.6</td>
<td>17.5</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before music)</td>
<td>26.7</td>
<td>17.1</td>
</tr>
<tr>
<td><strong>VAS anxiety score (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White noise period</td>
<td>20.5</td>
<td>17.7</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before white noise)</td>
<td>19.8</td>
<td>15.4</td>
</tr>
<tr>
<td>Music period</td>
<td>18.2</td>
<td>15.3</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before music)</td>
<td>21.6</td>
<td>18.0</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White noise period</td>
<td>-10</td>
<td>11</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before white noise)</td>
<td>-11</td>
<td>10</td>
</tr>
<tr>
<td>Music period</td>
<td>-10</td>
<td>13</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before music)</td>
<td>-11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White noise period</td>
<td>-4</td>
<td>6</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before white noise)</td>
<td>-5</td>
<td>7</td>
</tr>
<tr>
<td>Music period</td>
<td>-5</td>
<td>6</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before music)</td>
<td>-5</td>
<td>6</td>
</tr>
<tr>
<td><strong>State-Trait Anxiety Inventory Y-1 (points)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White noise period</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before white noise)</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>Music period</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before music)</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td><strong>Salivary amylase concentration (kIU/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White noise period</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before white noise)</td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>Music period</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>&quot;No sound&quot; period (before music)</td>
<td>32</td>
<td>39</td>
</tr>
</tbody>
</table>

* The amount of change from the pre-cannulation value to the post-cannulation value is indicated. **Post-value used for the analysis is shown.

For outcomes that are measured three times, the mean of the three times in each participant is calculated and the mean and SD of all participants in the cohort for that value is displayed.

VAS, visual analog scale; SD, standard deviation.
## Supplemental Table 4. Information on cannulation operators and cannulation failure (overall sessions)

<table>
<thead>
<tr>
<th>Items</th>
<th>Music period</th>
<th>White noise period</th>
<th>No sound period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of sessions</td>
<td>343</td>
<td>342</td>
<td>682</td>
</tr>
<tr>
<td>Occupation of cannulation operator – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>187 (55)</td>
<td>189 (55)</td>
<td>374 (55)</td>
</tr>
<tr>
<td>Medical engineer</td>
<td>156 (46)</td>
<td>149 (44)</td>
<td>304 (45)</td>
</tr>
<tr>
<td>Medical doctor</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Experience of the cannulation operator in dialysis room work – years</td>
<td>10.0 [4.0, 15.0]</td>
<td>10.0 [4.0, 16.0]</td>
<td>10.0 [4.0, 15.0]</td>
</tr>
<tr>
<td>Occurrence of cannulation failure – n (%)</td>
<td>7 (2)</td>
<td>8 (2)</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>

Missing data were not entered in this table. Data pertaining to nominal variables are expressed as the number of sessions [n] (percentage) and continuous variables as median [first quartile, third quartile].
Supplemental Table 5. The regression coefficient estimates for each variable of linear mixed-effect regression analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
<th>lower_95CI</th>
<th>upper_95CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>2.266</td>
<td>2.061</td>
<td>2.471</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Music period*</td>
<td>-0.130*</td>
<td>-0.237*</td>
<td>-0.023*</td>
<td>0.02</td>
</tr>
<tr>
<td>4th week (vs. 2nd week)</td>
<td>-0.104</td>
<td>-0.214</td>
<td>0.007</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline pain score</td>
<td>0.025</td>
<td>0.02</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Objective variable: ln (VAS pain score)**

HD5-7 was represented as the 2nd week, HD11-13 as the 4th week. The variable of the 4th week (vs. 2nd week) was included in the model to account for the period effect. Baseline pain score was the average of three VAS pain scores of the previous no sound period.

*Because the VAS pain score was logarithmically incorporated into the model, the effect size on the VAS pain score was the exponentiated value of the regression coefficient estimate. Therefore, the percent change from the white noise period (-12.2% [95% CI, -21.1 to -2.3]) is shown in Table 2.*

lower_95CI, lower value of 95% confidence interval; upper_95CI, upper value of 95% confidence interval; VAS, visual analog scale
Supplemental Table 6. P-values calculated by Wilcoxon rank-sum test for the carry-over effect

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Full analysis set</th>
<th>Per-protocol set</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS pain score</td>
<td>0.90</td>
<td>0.69</td>
</tr>
<tr>
<td>VAS anxiety score</td>
<td>0.90</td>
<td>0.45</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory Y-1</td>
<td>0.81</td>
<td>0.47</td>
</tr>
<tr>
<td>Salivary amylase concentration</td>
<td>0.54</td>
<td>0.93</td>
</tr>
</tbody>
</table>

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 using the Wilcoxon rank-sum test.
All P-values > 0.05; No significant carry-over effect was detected.
VAS, visual analog scale
**Supplemental Information 1. Study protocol including the statistical analysis plan**

**Summary of this research**

<table>
<thead>
<tr>
<th>Title</th>
<th>Music reduces pain during hemodialysis access cannulation: a multicenter randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Researchers</td>
<td>Mineaki Kitamura, Emi Inayama, Yosuke Yamada, Masatsugu Kishida, Mineaki Kitamura, Tomoya Nishino, Keiko Ota, Kanae Takahashi, Ayumi Shintani, and Tatsuyoshi Ikenoue</td>
</tr>
</tbody>
</table>
| Funding | TERUMO Foundation for Life Sciences and Arts  
The Shinsyu Public Utility Foundation for the Promotion of Medical Sciences  
The AIBA Works Medical Research Grant |
| Sample size | 120 |
| Study duration | From the date that permission was provided by the director of the joint research facility until March 31, 2020 (registration deadline: October 31, 2019). |
| Setting | This trial was performed at five outpatient maintenance hemodialysis facilities: Jisyukai Ueda Kidney Clinic, Nagasaki Renal Center, Fujiidera Keijinkai Clinic, Mihama Narita Clinic, and Hakuyu Chiyoda Clinic. |
| Study design | A prospective, multi-facility, single-blind, crossover, randomized controlled trial. Participants were allocated to either of the 2 groups below.  
1. Early sequence group: patients received the puncture while not listening to sound (only wearing headphones) during the first (run-in) week (no-sound period) while listening to music during the second week (music period), listening to no sound during the third (wash-out) week (no-sound period), and while listening to white noise during the fourth week (white noise period).  
2. Later sequence group: the no-sound period commenced in the first (run-in) week, white noise during the second week, no-sound during the third (wash-out) week, and music during the fourth week. |
| Primary study objectives | To clarify whether music therapy can truly alleviate pain, measured using a VAS metric, during puncture into a shunt blood vessel, as compared with white noise. |
| Primary outcome measures | The VAS pain scores during the puncture. |
| Secondary objectives | To clarify whether the reduction of anxiety is related to the mechanism of reduction of vascular puncture pain by music therapy. |
| Secondary outcome measures | 1. VAS anxiety score  
2. Blood pressure  
3. Heart rate  
4. STAI (state scale: Y-1)  
5. Salivary amylase |
| Inclusion criteria | 1. Patients over 20 years old across the five facilities who have undergone outpatient hemodialysis three times a week for more than 6 months.  
2. Patients who have indicated feeling pain during puncture based on the preliminary questionnaire. |
| Exclusion criteria | 1. Patients undergoing outpatient dialysis less than three times a week or four times a week or more.  
2. Patients receiving dialysis through an indwelling catheter.  
3. Patients who did not agree to participate.  
4. Patients with hearing impairments.  
5. Patients who cannot provide a self-assessment on a tablet PC for reasons such as difficulty in communicating, psychiatric disorders, visual or writing impairments, paralysis, or dementia.  
6. Patients who the principal investigator judges to be inappropriate as research subjects. |
| Treatment description | **Trial interventions**  
The intervention for this protocol was ‘listening to sound’. The patient wore headphones connected to a tablet PC. The sound was provided by the Research electronic data capture system on a tablet PC. To reduce noise other than the sound from the headphones, we used a noise-canceling function. The specific intervention is outlined below.  
**Music**
The patients listened to music during cannulation in the music condition. Mozart’s Sonata for 2 pianos in D major (K.448) was used. Eight minutes after listening to the piece, the operator began the puncture procedure (including disinfection, puncture, and blood withdrawal). The patient then finished listening to the piece after the puncture.

**White noise**
The patients listened to white noise during cannulation in the white noise condition. White noise comprises the same intensity of all frequencies within the range of human audition. White noise has no orderly arrangement regarding melody, harmony, rhythm, tone, or pitch, which is required for a sound to be considered musical. White noise was chosen as a control condition to isolate the effect of wearing headphones (headphones effect) and the effect of stimulating hearing with sound (sound effect).

**No-sound**
The no-sound period included wearing headphones with no sound present. Outer noise was canceled out by the headphones. This intervention was used during the run-in and washout periods. During this period, we attempted to diminish the placebo effect using headphones.

**Sample size**
The sample size was 120. We conducted a pilot two-arm randomized controlled trial at four facilities, whereby eight hemodialysis patients were assigned randomly into either of the two groups: group 1 listened to Mozart, and group 2 listened to the news on the radio. The primary outcome was a puncture pain evaluated via a VAS. In the pilot study, the mean VAS results were 20.5 mm in group 1 and 25.4 mm in group 2. All VAS scores were normally distributed, with a standard deviation of 12.0 mm. Based on these results, we computed that 95 patients are needed to observe a treatment effect based on this effect size at a power of 80% with a two-sided significance level of 5%. Assuming participant attrition, we will recruit a total of 120 participants.

**Primary analyses**
The VAS score of pain at the time of puncture.
The VAS score of pain in the silence before each period (music period and white noise period) was used as the baseline.
A linear mixed model was applied to compare the means of the three repeated outcome measures between the music and the white noise periods. For the outcome that accompanies the baseline measures, the mixed model compared the mean of three repeated change scores between the two periods. Compound symmetry was used for variance-covariance to estimate dependency among the repeated measures. The two-sided significance level was set at 0.05. The normality of the residuals was confirmed via Q-Q plots, and the mathematical transformation of the outcome variable was performed if necessary.

**Secondary analyses**
*VAS score of anxiety at the time of puncture*
The VAS score of anxiety in the silence before each period (music period and white noise period) was used as the baseline.
The difference between the change from baseline to the music period and the change from baseline to the white noise period were compared. This endpoint was analyzed using the same methodologies as the primary endpoint.

*Blood pressure and heart rate*
The degree of change from the pre-listening value to the post-listening value was evaluated as the outcome. The value in the silence before each period (music period and white noise period) was used as the baseline.
The difference between the change from baseline to the music period and the change from baseline to the white noise period was compared. This endpoint was analyzed using the same methodologies as the primary endpoint.

*State-Trait Anxiety Inventory (STAI)*
The value in the silence before each period (music period and white noise period) was used as the baseline.
The difference between the change from baseline to the music period and the change
from baseline to the white noise period was compared. This endpoint was analyzed using the same methodologies as the primary endpoint.

*Salivary amylase activity*

The amount of change from the pre-listening value to the post-listening value was evaluated as the outcome. The value in the silence before each period (music period and white noise period) was used as the baseline.

The difference between the change from baseline to the music period and the change from baseline to the white noise period was compared. This endpoint was analyzed using the same methodologies as the primary endpoint.

<table>
<thead>
<tr>
<th>Safety and monitoring</th>
<th>Safety assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As punctures are a regular procedure in a hemodialysis session and listening to sounds is not a majorly invasive procedure, there is no expected harm for patients from participating in this intervention, as no negative effects of music therapy have been reported in prior studies. The saliva collection method is also harmless. Nevertheless, participant safety was ensured during the protocol.</td>
</tr>
<tr>
<td></td>
<td>Monitoring</td>
</tr>
<tr>
<td></td>
<td>The person at the independent data-coordinating center monitored the input data and the procedure, which could be confirmed using the data log on REDCap, where input times and listening times were recorded.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interim analysis</th>
<th>Interim analysis was not carried out.</th>
</tr>
</thead>
</table>

Research plan for elucidating the alleviation of puncture pain at the beginning of hemodialysis by auditory stimulation

Research General Manager
Division of blood purification, Nagasaki University Hospital
Nagasaki University Graduate School of Biomedical Sciences
Assistant professor
Mineaki Kitamura
Introduction

Study background

Aim and significance of the study

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Music therapy summary

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Restricted drugs and therapies

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Other treatments

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Intervention discontinuation

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Secondary outcomes

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Expected advantages

Expected disadvantages

Expected adverse events/complications

The whole trial discontinuation

Responses to adverse events

Responses and compensations for health damage of research subjects

Handling of personal information/samples/information

Protection of personal information

Duration and locations of information storage

How to discard samples and information

How to send samples and information

The records of sending and receiving of samples and information

How to deal with information when participants withdraw consent

Handling of deviations from the research plan

Changes to research plans, among others

Expense research subjects bear

Research plan registration and publication of research results

Research plan registration

Publication of research results

Disclosure to research subjects

Attribution of research results

Funding and conflicts of interest

Funding

Conflicts of interest

Study monitoring

Monitoring
22.2 Auditing
23 Study implementation system
24 Supplements
25 References
1 Introduction
All researchers involved in this research implemented the study in compliance with the Declaration of Helsinki (revised in October 2013) and Ethical Guidelines for Medical Research for Humans (2014 Ministry of Education, Culture, Sports, Science and Technology / Ministry of Health, Labor and Welfare Notification No. 3; partially revised on February 28, 2017). This research was conducted with the approval of the chief ethics committee at Nagasaki University Hospital and the permission of the director of the research institutions.

2 Study background
When kidney disease reaches its end stage, most patients undergo hemodialysis at least three times per week, approximately 150 times a year. At the beginning of each session, patients often experience severe pain; various external analgesics have been developed to alleviate this pain. However, approximately 20% of hemodialysis patients experience excruciating pain, such as a visual analogue scale (VAS) score of more than 30 mm. In fact, feelings of anxiety and depression play a partial role in puncture pain, which cannot be easily reduced via external analgesics. However, certain sedatives or antidepressants that improve anxiety and/or depression can induce hypotension and physical dependence. Moreover, prescribing analgesics, sedatives, or antidepressants can be expensive, and such expenses can be a serious issue for patients and insurers.

From these points of view, the present study attempted to elucidate the effects of music therapy on pain management. Music therapy is safe, inexpensive, and has been shown to attenuate the pain and anxiety associated with several diseases. However, few studies have examined the effect of music therapy on pain during blood vessel puncture in hemodialysis patients. The aim of this study was to elucidate whether music therapy mitigates the pain caused by vessel puncture procedures.

Several previous studies assessing the effectiveness of music used only a no-sound control group, which could produce a potential ‘placebo effect’ in the intervention. Therefore, this study adopted white noise as the control to better extract the true effect of music therapy. As an intervention, Mozart’s Sonata for two pianos in D major (K.448), which has been verified as the ‘Mozart effect’, has been used in several studies.

3 Aim and significance of the study
The main aim of this study was to elucidate whether music therapy can alleviate puncture pain in comparison to white noise. A ‘no sound’ period was included to eliminate the placebo effect derived from the headphones. Salivary amylase, an objective stress marker, was also evaluated. We speculate that if the effect of music therapy is proven, music therapy was used at many hemodialysis facilities to alleviate puncture pain.
4 Study Methods

4.1 Study design

Presence or absence of invasion: No invasion.
Reason for no invasion: There is no substantial health hazard as a result of listening to music or white noise. In addition, the measurement of salivary amylase requires collecting saliva, but subjects only have to place the tip of test strip in their oral cavity for 30 s. Following this, no substantial health damage was expected if the subjects had their salivary amylase levels measured.

With or without intervention: With intervention.

Characteristics of research: Verification research.

Trial type: Randomized Trial.

Study blindness: Single-blind.

4.2 Summary of study

This was a prospective, multi-facility, single-blind, crossover, randomized controlled trial. Subjects were allocated randomly and equally to either the early-sequence or later-sequence group. For the early sequence, patients were punctured while not listening to sound (only wearing headphones) during the first (run-in) week (no-sound period), while listening to music during the second week (music period), to no-sound during the third (wash-out) week (no-sound period), and to white noise during the fourth week (white noise period). For the later sequence, the no-sound period commenced in the first (run-in) week, white noise during the second week, no sound during the third (washout) week, and music during the fourth week.
4.3 Summary of music therapy

In this study, tablet personal computer (tablet PC) and headphones were used to listen to music. Subjects were expected to listen to Mozart's music "Sonata for Two Pianos in D major" K.448 or white noise through headphones connected to the tablet PC. As described above, the no-sound period was included in the schedule.

According to the Japanese Society for Rights of Authors of Music (JASRAC), there are no copyright concerns involved with listening to Mozart's music. Music therapy is not covered by health insurance in Japan, but it is one of the worldwide-recognized therapies, as its review is reported in leading overseas journals. Although there have been numerous reports on music therapy so far, there have been no reports of health hazards caused by this therapy. Therefore, the safety of the research subjects was ensured.

**Insurance coverage**

Since music therapy is not covered by health insurance, the equipment were prepared by the research committee using research funding. In addition, since ordinary dialysis therapy is included in clinical practice,
subjects were treated under normal insurance medical care.

4.4 Study subjects and inclusion and exclusion criteria

[Subjects]
This trial was performed at five outpatient maintenance hemodialysis facilities: Jisyukai Ueda Kidney Clinic, Nagasaki Renal Center, Fujidera Keijinkai Clinic, Mihama Narita Clinic, and Hakuyu Chiyoda Clinic. Eligible subjects were patients over the age of 20 years, who were undergoing outpatient hemodialysis three times a week, had received dialysis for more than six months, and indicated experiencing pain during puncture based on a prior questionnaire across the five facilities.

[Selection criteria]
Subjects were eligible if they satisfied the following criteria:
(1) Age: Patients aged 20 years or older at the time of obtaining consent.
(2) Sex: Both sexes.
(3) Inpatients/outpatients: Outpatients only.
(4) Outpatients undergoing maintenance hemodialysis three times a week who had been on dialysis for more than 6 months.
(5) Patients experiencing puncturing pain in clinical practice were evaluated using a prior questionnaire. The questionnaire enquired the following:
   Q-1) Do you feel pain when your hemodialysis access is cannulated?
      Answer) A. Always; B. Sometimes; C. Never.
   Q-2) Please answer Q-2 if you answered B on Q-1. How often do you feel pain?
      Answer) A. Once a week or more; B. Less than once a week.
Patients who answered A on Q-1, B on Q-1, and A on Q-2 were considered to have experienced pain and were eligible to participate.

[Rationale]
(1) Ethical considerations.
(2) There should not be any sex differences in puncture pain.
(3) Outpatients are expected to be able to collect data more stably.
(4) This study should be conducted on patients who are punctured steadily, and six months after the initiation of hemodialysis is considered a sufficient period for stable punctures.
(5) It is difficult to evaluate the effect of interventions unless subjects experience pain.

[Exclusion criteria]
Patients who correspond to any items of the following were to be excluded:
(1) Patients undergoing outpatient dialysis less than three times a week or four times a week or more.
(2) Patients receiving dialysis through an indwelling catheter.
(3) Patients who did not agree to participate.
(4) Patients with hearing impairments.
(5) Patients who cannot provide a self-assessment on an tablet PC for reasons such as difficulty in communicating, psychiatric disorders, visual or writing impairments, paralysis, or dementia.
(6) Patients who the principal investigator judges to be inappropriate as research subjects.

[Rationale for exclusions]
(1) This study was conducted by evaluating parameters three times a week.
(2) Cannulation procedure is not required to start hemodialysis.
(3) This was a prospective interventional study.
(4) A musical intervention could not be conducted in these participants.
(5) The outcomes of this study were based on self-assessment.
(6) To ensure the safety of the subjects and to conduct this research properly, in this situation, the research committee determines the suitability of each subject.

4.5 Study duration
From the date that permission was provided by the director of the joint research facility until March 31, 2020 (registration deadline: October 31, 2019).
4.6 Study procedures and evaluation schedule

The time for each intervention was about 10 min before and after AV fistula cannulation and each intervention was performed as follows. First, the blood pressure and pulse of subjects before the start of the intervention were measured. The tablet PC was prepared and the subject put on headphones so that the subject could listen to the interventional sounds, such as no sound, music, or white noise. At that time, subjects were asked by an examiner whether the volume was appropriate. The patient then finished listening to the sounds after the punctures. After 8 min, the cannulation procedure was initiated. Then, the AV fistula was punctured, and hemodialysis was initiated (so the AV fistula was punctured after about 10 minutes, the cannulation procedure (skin disinfection, applying a tourniquet, needle puncture, and placement of the outer cylinder) was started 8 minutes after the participants began listening to the music. From the results of the pilot study, it was found that if the puncture procedure was started at that time, two needles would be punctured around 10 min, and then the intervention was terminated. Blood pressure and heart rate were measured before and after the puncture. The subjects evaluated the VAS of pain, which was the primary outcome, and the VAS of anxiety, which was the secondary outcome, using an online questionnaire on the tablet PC screen. The research subjects filled in the forms and sent them to the outcome collection terminal. Subsequently, the puncture clinician filled in the puncture condition data. Regarding the data input, REDCap installed on the tablet PC was used. REDCap is a data collection management system developed by Vanderbilt University in the United States with the support of the clinical and translational science award (CTSA). Data management was carried out at Nagasaki University Hospital with the cooperation of Osaka City University, which operates REDCap.
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○ Indicates matters that should be done before the intervention.
● Indicates matters that should be performed after the intervention.

STAI, State-Trait Anxiety Inventory; VAS, Visual Analog Scale

4.7 Data collection

(1) **Background factors collected**: Sex, date of birth, height, weight, body mass index, duration of hemodialysis, history of smoking, cause of kidney dysfunction, music preferences, and State-Trait Anxiety Inventory (STAI-Y-2). The STAI is a commonly used measure to assess trait and state anxiety.

(2) HD, HDF, higher sodium dialysate, dialysis time, blood flow, dialysate, dialysate flow rate, dry weight, dialysate temperature were also collected.

(3) **History of diseases**: skin diseases, chronic heart failure, collagen disease, diabetic complications, liver disease, cancer, and AIDS.

(4) **Medication**: Oral medication, use of topical anesthetic for pain relief during punctures, single use of analgesic 6 h before dialysis.

(5) **Pain evaluation (VAS score)**: measured immediately after dialysis initiation The cannulation operator punctures both the blood removal side and the blood return side and asked participants to describe the most painful puncture pain during the series of puncture procedures. To avoid causing bias such as underreporting by the person applying the puncture, the person who punctured the AV fistula was not able to know the results.

(6) **Anxiety evaluation (VAS score)**: measured immediately after the start of dialysis in the same way as the
pain VAS scores.

(7) **Anxiety evaluation (STAI):** During the screening period, after the start of dialysis, the research subjects were asked to fill out the form using an tablet PC. The STAI before the start was (Y-2), and only (Y-1) was measured at the third time each week after starting the interventions.

(8) **Salivary amylase:** Salivary amylase, which is a marker of stress, was measured during the last week. A dry clinical chemistry analyzer, salivary amylase monitor (medical device notification number 27B1X00045000073, distributor Nipro Co., Ltd.) was used for the measurements. Subjects were asked to place the measuring tip in their oral cavity for 30 s, and the activity was measured with a measuring device.

(9) **Blood pressure/heart rate measurement:** Blood pressure/heart rate was measured 10 min before the puncture and immediately after the puncture.

(10) **Amount of water removed during dialysis**

(11) **Other dialysis conditions:** The patient’s position at the time of puncture (sitting or lying), weather at the time of the test collected information from the nearest AMeDAS point to the facility, occupation of cannulation operator, years of dialysis room work of the cannulation operator, number of puncture needle gauges, and puncture sites.

4.8 **Prohibited drugs and therapies**
No restrictions.

4.9 **Restricted drugs and therapies**
Listening to other music or watching TV while listening to the music intervention or white noise and while wearing the headphones.

4.10 **Regulations of reducing and halting drugs**
No regulations.

4.11 **Other treatments**
If a patient does not participate in this study, he or she can receive regular hemodialysis therapy.

4.12 **Response after the end of the research**
The musical intervention was discontinued upon completion of the study. After that, the research subjects were provided with the most appropriate medical care available.

5 **Intervention discontinuation in subjects**

5.1 **Intervention discontinuation criteria**
The interventions were discontinued if the following occurred:

- The shunt was occluded and vascular anastomosis was re-created surgically.
- The participant died or was transferred to another hospital.
- The participant wished to terminate his or her participation.

**Missing data**
If data collection was interrupted, it was resumed when possible. This may occur because

- A participant is hospitalized.
- The hemodialysis access was narrowed, and percutaneous transluminal angioplasty (PTA) was performed.
- Haemodialysis access is occluded, and blood flow restarts via non-surgical treatment such as massage or PTA.
- Study continuation is difficult because of unavoidable circumstances to participants or medical staff.

In the event of any other situation, researchers decided on a response.

5.2 **Responses after discontinuation**
The research was discontinued if the research subject met the above criteria. Regarding the regular treatment of the subjects after discontinuation, the subject did not have any potential disadvantages.

6 **Case registration and allocations**

Allocation method: Permutated block randomization.
**Allocation factor:** Stratified by the facility.

**Case registration method:** EDC (electronic data capture).

**Registration/allocation executing agency:** Osaka City University.

A statistician who was not involved in the enrolment or assignment of patients created a randomized table (random allocation sequence) for each facility using the permuted block method, in which the block size (2 or 4) was randomly generated. Patients who met the inclusion criteria and did not meet the exclusion criteria were randomly assigned to the early or later group at enrolment (HD1).

Case registration was performed using electronic data capture (EDC). The representatives of each facility carried out the study implementation plan after it was reviewed by the facility's ethics review committee prior to the registration of subjects. EDC was used for research subject registration, and eCRF input was provided to the researchers and collaborators at participating facilities that have been approved by the Ethics Review Board. We used REDCap (Vanderbilt University, Tennessee, USA), which is operated by Osaka City University. With REDCap, we confirmed that eligible subjects met all the selection criteria and did not meet any of the exclusion criteria. Each facility representative or examination collaborator entered the necessary information on the eCRF registration pages and registers. Personal accounts and passwords were required for registration.

Research subject registration REDCap system (EDC)
(Test URL: http://ocu.jp/redcap-saas)

**Blinding procedure**

We explained to the patients that the first and third periods were no-sound periods and that the second and fourth periods were music or white noise periods when informed consent was obtained. Operators also received these explanations in advance; moreover, during the no-sound period, they were informed when it was a no-sound period on the tablet’s screen.

If participants were told that the aim of this study was to assess the efficacy of music therapy, a demand characteristic, which refers to participants playing the role of a ‘good participant’ by altering their behavior in order to obtain the researchers’ expected outcome, could emerge, resulting in information bias. Therefore, we did not tell participants that we were assessing the efficacy of music intervention. Essentially, participants were not aware of whether music or white noise would be more soothing. Specifically, we stated, ‘both sounds are considered effective, and we will examine which one is more effective’ in order to alleviate any potential demand characteristics.

As the patients could not be blinded to the treatment allocation, it was important that the person evaluating the outcome measure of the VAS was blinded to the study. Although the outcome evaluator needed to also perform the randomization, we created an automated process in REDCap to randomly choose and play either the music or the white noise without letting the study personnel know which sound was being played. Along with randomization, they were blinded to the music operation and evaluation procedures, including measuring VAS, in the following manner: the operator dispensed the sounds from REDCap; however, the REDCap screen does not indicate whether music or white noise is being played. Participants wore headphones while the music or white noise was being played, and they were instructed not to tell the cannulation operator what sound is being played. The patients provided VAS and STAI scores via an online questionnaire via REDCap. Therefore, the operator did not see these results.

**Outcomes**

**7.1 Primary outcome**

The primary outcome was the VAS pain score during puncture. The difference from the baseline (no sound period) was used for evaluation. The VAS comprises a 100-mm line. The leftmost value was 0, indicating no pain. The rightmost value was 100, indicating maximum pain. Patients marked a point with their fingers on the screen. Although patients received at least two punctures during each dialysis session, pain was only evaluated once per session. The highest pain score during the sessions was used.

**7.2 Secondary outcomes**

The VAS score for anxiety was registered by the subject using a tablet PC immediately after the puncture.
This scale was 100 mm in length and was linear. The leftmost side of the scale, 0, indicating no anxiety at all, and the rightmost is 100, indicating maximum anxiety. The subject placed a finger on the measuring rod in REDCap on the tablet PC screen in order to make their selection.

**Blood pressure/heart rate measurement**
Blood pressure and heart rate were evaluated 10 min before and immediately after the puncture.

**HD4, HD7, HD10, HD13 (STAI questionnaire entry, salivary amylase measurement)**

**State-Trait Anxiety Inventory (STAI)**
Each patient's state anxiety via the STAI (Y-1) was assessed immediately after the puncture during the no-sound, music, and white noise periods. The subject evaluated and submitted their responses using an online questionnaire created using REDCap. The STAI consists of 40 questions, with 20 questions in the first half being Y-1 and 20 questions in the second half being Y-2. During the screening period, Y2 (HD1) was measured. In the non-sound period, the music period, and the white noise period (HD4, HD7, HD 10, HD13), Y-1 was measured.

**Salivary amylase activity**
Salivary amylase activity fluctuates based on autonomic nervous system activity, thus making it a reliable marker of mental and physical stress. A salivary amylase monitor (NIPRO, Co., Osaka, Japan) and a corresponding test strip (NIPRO, Co.) were used. Saliva was collected using a test strip placed under the tongue for approximately 30 s, and the amylase concentration in the saliva was immediately measured. Salivary amylase levels were evaluated before and after the puncture at the end of the no-sound, music, and white noise periods, respectively.

### 7.3 Safety assessment
After each intervention period, adverse events were assessed.

### 8 Sample size estimation

**Number of target cases**
120 cases.

**[Rationale]**
We conducted a pilot two-arm randomized controlled trial at four facilities (UMINID 000024754) (approved by the Ethics Committee of Nagasaki University Hospital 16103101); eight hemodialysis patients were randomly assigned to either of two groups: group 1 listened to Mozart, and group 2 listened to the news on the radio. The primary outcome was puncture pain evaluated using a VAS. In our pilot study, the mean VAS results were 20.5 mm in group 1 and 25.4 mm in group 2. (Effect size: 4.9 mm) All VAS scores were normally distributed, with a standard deviation of 12.0 mm. Based on these results, we determined that 95 patients were needed to observe a treatment effect based on this effect size at a power of 80% with a two-sided significance level of 5%. Assuming about 20% participant attrition, we intended to recruit a total of 120 participants.

As the proposed study is a crossover trial wherein the statistical power is assumed to be greater than that of a two-arm design, we believe that our study is adequately powered.

In this study, to ensure the invariance of the listening content, we decided to use white noise as a control instead of news.

### 9 Statistical analysis

#### 9.1 Analysis of primary endpoints

**9.1.1 VAS score of pain at the time of puncture**

The VAS score of pain in the silence before each period (music period and white noise period) was used as the baseline.

A linear mixed model was applied to compare the means of the three repeated outcome measures between the music and white noise periods. For the outcome that accompanies the baseline measures, a mixed model compared the means of the three repeated change scores between the two periods. Compound symmetry was used for variance-covariance to estimate the dependency among the repeated measures. The two-sided significance level was set at 0.05. The normality of the residuals was confirmed via Q-Q plots, and the mathematical transformation of the outcome variable was performed if necessary. As for the missing data, only the data at the time when the missing data occurred were excluded in the linear mixed model. For
example, if during the intervention week, one HD treatment had missing data, the mixed model only included two measures of pain that week.

The mixed-model approach was chosen based on a Monte Carlo simulation study to compare the statistical power of three different analytical strategies, which include the following.

1) Paired $t$-test to compare the two means of the three pain scores between the two periods (the unit of observation in the analysis was the within-patient mean score of the three scores; the analysis included two mean scores per patient).
2) Linear mixed model to compare the two means of the three pain scores between the groups (the unit of observation was the same as in 1).
3) Linear mixed model to compare the six pain scores between the two periods (the unit of observation was the pain score; the analysis included six observations per patient).

The third approach was chosen because it appeared to be superior to other approaches, as it provides the largest statistical power to detect statistical significance while controlling for type I errors. In addition, the direct inclusion of all six observations allowed us to control for time-dependent confounders, such as personnel effects from the operators performing the cannulation.

9.2 Analysis of secondary endpoints

9.2.1 VAS score of anxiety at the time of puncture

The value in the silence before each period (music period and white noise period) was used as the baseline. The difference between the change from baseline to the music period and the change from baseline to the white noise period was compared. This endpoint was analyzed using the same methodology as the primary endpoint.

9.2.2 Blood pressure, heart rate

The amount of change from the pre-listening value to the post-listening value was evaluated as the outcome. The value in the silence before each period (music period and white noise period) was used as the baseline.

The difference between the change from baseline to the music period and the change from baseline to the white noise period was compared. This endpoint was analyzed using the same methodology as the primary endpoint.

9.2.3 State-Trait Anxiety Inventory (STAI)

The value in the silence before each period (music period and white noise period) was used as the baseline.

The difference between the change from baseline to the music period and the change from baseline to the white noise period was compared. This endpoint was analyzed using the same methodology as the primary endpoint.

9.2.4 Salivary amylase activity

The amount of change from the pre-listening value to the post-listening value was evaluated as the outcome. The value in the silence before each period (music period and white noise period) was used as the baseline.

The difference between the change from baseline to the music period and the change from baseline to the white noise period was compared. This endpoint was analyzed using the same methodology as the primary endpoint.

9.3 Interim analyses

As mentioned above, participation in this study had no known harm to patients. Interim analyses were not performed in this study.

9.4 Analysis set

A complete or full analysis set (FAS) was used. FAS was obtained when participants were allocated to the early-sequence or later-sequence after eligibility, and VAS pain scores were available for one or more cannulations during the music or white noise conditions. Furthermore, a target group conforming to the implementation plan was defined as per the protocol set (PPS). For PPS, when an observation is discontinued by stopping the protocol, the subsequent data are not used in the analysis. Analysis of primary and secondary outcomes is the main focus of FAS. We also performed analyses targeting PPS to confirm the stability of the analytic outcomes.
10 Informed consent
10.1 Method of acquisition of informed consent
The researchers gave each subject a consent explanation document approved by the director of the research institution, a written explanation, an opportunity to ask questions, and sufficient time for the subjects to decide whether or not to agree to participate. After confirming that the subject understood the contents of this study, written consent was obtained.

<Explanation content>
1) Research implementation plan
2) Materials used for research
3) Protection of privacy and personal information
4) Expected benefits and disadvantages
5) Conflict of interest
6) Privacy protection
7) Notice of research results
8) Cost
9) Research benefits

10.2 Responses after withdrawal
If a subject withdrew consent to participate in the research, the subject was asked to sign the consent withdrawal form and the researchers confirmed the withdrawal of consent. In addition, researchers who confirmed the withdrawal of consent recorded this in the medical records. All data of the subjects who withdrew their consent were excluded from the analysis.

11 Expected advantages and disadvantages (side effects / complications)
11.1 Expected advantages
There was no direct benefit to the subjects by participating in this study. These research results may contribute to future medical progress.

11.2 Expected disadvantages
There was no increase in the financial burden of participants in the study. The start of dialysis was delayed by approximately ten minutes because it took time to receive the intervention before the puncture. In addition, it took approximately one min to collect the saliva samples. Since the patients imputed their VAS scores after the punctures, the free time of the patient during dialysis was reduced by approximately five min.

11.3 Expected adverse events/complications.
Unless subjects listened to sounds at a very high volume, no health hazards were present.

12 Whole trial discontinuation
The principal investigator considered whether to continue the research if it was extremely difficult to reach the planned number of cases due to difficulties in enrolling the research subjects. In addition, the principal investigator would report to the head of the research institution without delay if the research was to be completed or discontinued if any of the following events occurred, along with a summary of the research results:
   - There is no medical significance in continuing the research.
   - The study reached the end of the scheduled period.

13 Responses to adverse events
Since this study was a non-invasive study, no response to adverse events was assumed.

14 Responses and compensation for health damage of research subjects
Since this study is a non-invasive study, the researchers did not cover or compensate for health hazards. If a subject complained of poor physical conditions during the research period, appropriate treatments were provided within the insured medical treatment parameters.
15 Handling of personal information/samples/information

15.1 Protection of personal information

Persons involved in this research (including external parties) complied with applicable laws and ordinances regarding the protection of research subjects’ personal information. In addition, the parties concerned made maximum efforts to protect the personal information and privacy of the subjects. The personal details obtained in this study are not to be disclosed without justifiable reasons. This rule was also applied to researchers in charge of this study, even after they left their positions. Researchers were cautious as to not disclose private information when reporting results.

15.2 Duration and locations of information storage

[Information management methods]

When information related to this research was handled, numbers (identification codes) that were not related to the personal information of subjects were given, and a correspondence table was created so that the research subjects and the identification codes could be linked. This correspondence table was not allowed to be taken out of the hospital, and the correspondence table was stored on paper and preserved in a locker that could be locked. Data were managed on REDCap, and only registered researchers at each facility could access it. Researchers needed to log in to REDCap with their passwords. Data analysis was performed on the data output from the EDC on an Excel file that was locked with a password.

Participating facilities were also asked to obey the regulations of each facility regarding the storage method and storage location of samples and information associated with research.

The samples and information obtained in this study were stored as specified above. Regarding the storage period, they were stored for at least the period shown below, but they will also continue to be stored as long as possible after that.

<table>
<thead>
<tr>
<th>The materials applied to the ethics committee</th>
<th>Storage period</th>
<th>Storage media</th>
<th>Storage place</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation table</td>
<td>10 years after the research is completed</td>
<td>Electronic media</td>
<td>Division of blood purification, Nagasaki University Hospital</td>
</tr>
<tr>
<td>Case report documents</td>
<td>10 years after the research is completed</td>
<td>Electronic media</td>
<td>Division of blood purification, Nagasaki University Hospital</td>
</tr>
<tr>
<td>Correspondence table</td>
<td>10 years after the research is completed</td>
<td>Paper</td>
<td>Division of blood purification, Nagasaki University Hospital</td>
</tr>
<tr>
<td>Analysis data</td>
<td>10 years after the research is completed</td>
<td>Electronic media</td>
<td>Division of blood purification, Nagasaki University Hospital</td>
</tr>
</tbody>
</table>

Other research facilities are also required to maintain the materials of the Ethics Committee, the materials related to the information used for the research (including the copy of the provided data), and the correspondence table for at least 10 years after the research is completed. The storage medium and storage locations will obey the regulations of each research facility.

15.3 How to discard samples and information

Information related to this research were disposed of appropriately in accordance with the regulations of each research facility.

15.4 How to send samples and information

The data obtained in this study were input to the REDCap operated by Osaka City as soon as each facility collects information on the research subjects. At the end of the study, the records of cases downloaded from the EDC and audit trails were stored and managed by the Division of Blood Purification, Nagasaki University Hospital.
15.5 The records of sending and receiving of samples and information
This research was conducted with the consent of the participants. Considering that the research subjects provided their consent and their names, the participating facilities will properly store the consent forms and correspondence table for 10 years (unified with 15.2 above).

15.6 How to deal with information when participants withdraw consent
All data of research subjects who withdrew their consent were excluded from the analysis, and all samples were discarded.

16 Handling of violations from the research plan
Due to unavoidable reasons, such as emergency avoidance, the principal investigator or other researchers may deviate or change the study protocol before obtaining prior agreement with the principal investigator and prior approval from the chief ethics committee at Nagasaki University Hospital. In that case, the principal investigator or other researchers were to promptly submit the proposal to the principal investigator and ethics committee. If the research plan had to be revised, the reasons and details of deviations or changes from the original plan were to be submitted and approved by the principal investigator and the chief ethics review committee.
If there was a deviation from the original implementation plan, the principal investigator or other researchers recorded all deviations along with appropriate reasons. If the principal investigator or other researchers became aware of the study not complying with the ethical guidelines for clinical research, they were to report to the head of their research institutions (the ethics committee and so on) and take necessary measures. Thereafter, the situation and results of the measures were to be reported to the Minister of Health, Labour and Welfare and other public organizations by the head of the research institution to which the principal investigator belongs, with the cooperation of the researchers.

17 Changes to the research plan
Any researcher was to obtain permission from the director of the chief research institution in advance when changing or revising the research plan or consent explanation document for this research. After obtaining permission from the director of the chief research institution, the principal investigator should notify the other facilities of the revised points.
Other researchers who belong to other facilities were to revise the research plan in accordance with the regulations of each research facility. Until the director of each research institution allows it, researchers were not allowed to implement the study and explain the revised research plan.

18 Expense research subjects bear
Since all the medical examinations performed in this study were conducted within health insurance coverage, the study subjects were not asked to pay any additional fee. In addition, 1000 yen worth of Quo cards were given to the subjects who participated in this research.

19 Research plan registration and publication of research results
19.1 Research plan registration
Prior to conducting the research, the principal investigator registered the outline of the research at the National University Hospital Directors' Meeting (UMIN). In addition, the registered research plan would be updated according to changes and progress.

19.2 Publication of research results
When the research was completed, the principal investigator was to publish the results without delay, taking necessary measures to protect the human rights and interests of the subjects and associated people. The results of this research were to be presented at the Japanese Society for Dialysis Therapy and the American Society of Nephrology and were published in English journals.

19.3 Disclosure to research subjects
The head of the research institutions will promptly respond to requests for disclosure of personal information related to the subjects or their deputies. The legal representatives are subjects’ spouses, parents, children, siblings or grandchildren, grandparents, relatives living together, or those who are considered to be similar to relatives; however, they should be adults (excluding minors).
20 Attribution of research results
This research may cause patent rights and economic benefits based on these, but those rights belong to the research institutions or researchers conducting the research, and the subjects do not have any rights. The results of the research based on this research plan belong to the researchers.

21 Funding and conflicts of interest:
21.1 Funding
This research was supported by the TERUMO Foundation for Life Sciences and Arts 2017 Research and Development Grant (representative: Tatsuyoshi Ikenoue; grant No. 203170600060, 2017), the Shinshu Public Utility Foundation for the Promotion of Medical Sciences (representative: Yosuke Yamada; no grant number), and the AIBA Works Medical Research Grant (representative: Yosuke Yamada; grant number 151061).

21.2 Conflicts of interest
There are no “possible conflicts of interest” that affect the outcome of the study and the interpretation of the results in the planning, implementation, and reporting of this study. The researchers involved in this research should declare necessary matters in accordance with the provisions of the Conflict-of-Interest Management Guidelines for Clinical Research at each research facility and should be reviewed and approved by the Conflict of Interest Review Committee of each research facility.

22 Study monitoring and auditing
22.1 Monitoring
An independent data-coordinating center (National Cerebral and Cardiovascular Center) monitored the input data using the data log on REDCap, which recorded the input times and listening times.

22.2 Auditing
Since this study is a non-invasive intervention study, there are no plans for auditing.

23 Study implementation system
This research was conducted under the following system.

<<Research General Manager>>
Division of Blood Purification, Nagasaki University Hospital, Assistant Professor Mineaki Kitamura

<<Contact / Inquiries>>
Division of Blood Purification, Nagasaki University Hospital,
Address: 1-7-1 Sakamoto, Nagasaki, Japan 852-8501
Telephone: 095-819-7358

<<Research Executive Office>>
Division of Blood Purification, Nagasaki University Hospital,
Address: 1-7-1 Sakamoto, Nagasaki, Japan 852-8501
Telephone: 095-819-7358

<<Joint research facilities>>
Nagasaki Renal Center: Mineaki Kitamura
Mihama Narita Clinic: Emi Inayama
Jisyukai Ueda Kidney Clinic: Yosuke Yamada
Fujiidera Keijinkai Clinic: Tatsuyoshi Ikenoue
Hakuyu Chiyoda Clinic: Noriyuki Okada

<<Research cooperation organization>>
Research design: Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan.
EDC operation, case allocation, registration, and statistical analysis: Department of Medical Statistics, Osaka City University Graduate School of Medicine, Osaka, Japan
Supervision of music therapy: Rakuwakai Kyoto Music Therapy Research Center

The research system is also published on the Internet.
http://www.kicks-studygroup.com/

24 Supplements
None.

25 References


11. Japan Meteorological Agency website