A musical intervention for respiratory comfort during non-invasive ventilation in the ICU

Electronic supplemental material.

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Methods

Ethics and Funding

The protocol was approved by the Comité de Protection des Personnes Paris-Ile-de-France IV (N°2014-A00643-44), and the Ethics Committee of French Society for Intensive Care Medicine (Société de Réanimation de Langue Française approval CE SRLF 14-21). The French Ministry of Health funded the study with a grant dedicated to nursing care (Programme Hospitalier de Recherche Infirmière et Paramédicale 2013; PHRIP 13-453). No steering committee nor safety monitoring committee was deemed necessary by the ethical committees. The Paris-Nord Clinical Research Unit managed the study.

Randomization and masking

At NIV onset, eligible participants were randomly allocated by one of the investigators, to one of the three study arms, in a 1:1:1 ratio, via a computer-generated, interactive web-response system (Cleanweb®, Telemedecine technologies S.A.S, Boulogne-Billancourt, France). The randomization, programmed in advance by an independent statistician, was balanced by blocks of variable and undisclosed size and stratified on the center, and the presence of a chronic respiratory disease.

Health-care professionals involved in the included patients' care were aware of the randomization arm, as they were involved in the implementation of the intervention. However, the primary outcome was blindly assessed by a nurse or a nurse-assistant from another unit, after having removed and stored all the material. The patients were told not to give any clue as to their randomization arm during evaluation, in order to preserve the blinded nature of the evaluation.

Investigators were unaware of all the data until the end of the trial.

NIV protocol

Size and type of masks were chosen according to the patient's morphology. Initial ventilator settings were chosen to maximize patient's tolerance and minimize air-leaks, in order to obtain a respiratory rate between 15 and 25 cycles per minute, an exhaled tidal volume between 6-10 ml/kg of predicted body weight, and the disappearance of signs of respiratory distress. FiO_2 was set to obtain a minimal pulse oximetry saturation of 92%. Duration of NIV sessions was left at the physician in charge discretion, based on patients' needs. All patients

underwent continuous electrocardiographic and percutaneous oxygen saturation monitoring, and were carefully overseen to detect and treat any complications related to ARF or NIV. Criteria for intubation were those in use in the participating ICUs [1]. Duration of NIV sessions was left at the physician in charge discretion, based on patients' needs.

Conduct of Musical Intervention session

Musical Intervention" (MI) group had dedicated headphones (BOSE AE2®) positioned over their ears, and were shown how to handle the tablet interface (Samsung Galaxy®) by the trained nurse or nurse-assistant. Patient's musical tastes were determined by a caregivers-administered questionnaire, The patients chose their musical program according to their preferences, set the volume level and began a 30-minutes "L-type" MI session[2] (MUSIC CARE© Paris, France). The "L-Type" musical session contains two phases [3]: the downswing phase is achieved by reducing the musical rhythms starting high tempos and a high number of instruments (see online audio excerpt 1) gradually leading to slower tempos and reducing the number of instruments, the frequencies and the volume (see online audio excerpt 2). Then the patient is moved through a maximum relaxation phase with a rhythm of slow pace, and reduced orchestras, resulting in maximum relaxation (bottom of the "L") (see online audio excerpt 3). There were 30 pieces of music, of various types, either classic, or world music originating form Africa, Latin America, Jamaica, Asia of music, pop, or jazz music, all of those composed for the MI purpose.

Assessment of study outcomes

The assessment of respiratory discomfort used an analogic visual scale. The patients were asked to rate the intensity of their dyspnea on a 10-cm long ruler, shaped like an arrow. It is bounded by the "0: no respiratory discomfort (the smallest base of the arrow) and to the right "10: maximal respiratory discomfort" (the head of the arrow). Patients marked directly on the ruler the level of their perception of discomfort. This measure was assessed prior to each NIV session, immediately after NIV was correctly set (5 minutes), at 30 minutes, and at 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hours according to NIV session length. The patients were told not to give any clue as to their randomization arm during evaluation, in order to preserve the blinded nature respiratory discomfort evaluation

The different time-points for the assessment of the evolution of respiratory discomfort, the changes in respiratory parameters (respiratory rate, transcutaneous oxygen saturation, exhaled tidal volume) and the changes in cardiovascular parameters during NIV sessions (heart rate, arterial pressure) were evaluated before the initiation of the NIV session, after 5 and 30 minutes, and at 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hours depending on the length of each NIV session and at the end of the session. Quality of life was determined by Hospital Anxiety and Depression Scale (HADS) questionnaire [4] and Short Form-36 (SF-36) [5]. Both questionnaires were administered by the research team, to the patient or to a proxy if the patient was not able to answer, at baseline and day-90.

Sample size calculation

The sample size was a priori calculated. We assumed a difference of 2 units of respiratory discomfort for comparison of SD group and MI group, with a standard deviation of 2.5 [6]. Seventy-eight participants (26 participants per arm) had therefore to be included to obtain a power of 80% to demonstrate such a difference between the two groups, with an alpha risk of 5% (bilateral formulation). We planned to perform three comparisons to assess the primary endpoint: the comparison between MI and SD; the comparison between MI and CG; and the comparison between SD and CG. To maintain an overall type I error rate of 5% in a strong sense, we applied a non-parametric Bonferroni-based chain procedure [7] for the analysis, which implied to reduce the significance level of two comparisons at 2.5%. In order to maintain a power of 80%, the number of planned participants was increased to 93 in total (31 per arm). To take into account a potential loss to follow-up of about 5% rate for the primary endpoint, it was expected to randomize a total of 99 participants (33 per arm).

Analysis of the primary endpoint

The primary endpoint (*i.e*. the change in respiratory discomfort at initiation and after 30 minutes of the first NIV session after randomization) was calculated for each subject, and compared between the treatment groups based on a Student test. We performed a pre-established hierarchical test procedure. The comparisons of MI vs CG and SD vs CG were performed at 2.5% (bilateral) alpha risk, as described elsewhere [3].

Several sensitivity analyses of the primary endpoint were performed. First, the analysis of the primary endpoint was adjusted on the stratification factors (centres and underlying

chronic respiratory disease) and on potential confounders (a PaO_2/FiO_2<200 mmHg and a prior psychiatric disease) using a multivariate analysis (linear regression model). Moreover, Multiple imputations of missing values were performed with the expectation-maximization with bootstrapping (EMB) algorithm, using the R package Amelia [8]. Five imputed datasets were created. Results from each imputed datasets were pooled using Rubin's rules [9]. Finally, a per-protocol analysis of the primary outcome was performed in subjects having complied with the protocol.

Analyze of respiratory discomfort and physiological variables

Respiratory discomfort and physiological variables measured over time (respiratory rate, oxygen saturation, exhaled tidal volume, heart rate, systolic arterial pressure, and arterial pressure) were analyzed with a linear mixed effects model (including fixed and random effects) to model the effect of the three interventions on the evolution of these parameters during NIV sessions. Two separate analyses were performed, first using only data from the first NIV session, second using data from all NIV sessions.

Results

Secondary outcomes

No difference was evidenced when considering the number of patients requiring physical restraint, sedative or anxiolytic treatments.

The adequacy of the prescribed NIV sessions duration and their actual duration did not differ in-between treatments arms, nor did the number of interrupted sessions before the end of the prescribed time per patient.

The overall assessment of NIV at ICU discharge and day-90, in terms of discomfort and trauma did not significantly differ in-between randomization arms. NIV satisfaction at ICU discharge did not significantly differ, but was poorer at day-90 in the sensory deprivation group.

Other outcomes (Table 2)

Median duration of the first NIV session were 70 minutes [60-140] in the CG, 60 minutes [50-

75] in the SD group and 82.5 minutes [60-145] in the MI group (p=0.21). The number of NIV sessions in which an attempt to remove the NIV interface occurred did not differ significantly between the 3 arms (32 in CG, 26 in SD and 19 in the MI group; p=0.9). The relative risk of premature interruption of NIV sessions was of 1.56 [1.03-2.38] in SD arm, (p=0.037 compared to CG). RASS variation was not significant, with agitation (RASS>1) at least once during NIV sessions in 6 (15.4%), 7 (18.4%) and 4 (11.1%) respectively for CG, SD and MI arms.

Patients received NIV for a median duration of 3 [2-5], 3 [2-4], and 3 [2-3.5] days, respectively for NIV, SD and MI-groups. Median number of NIV sessions per patients did not differ between groups (respectively 7 [3-17], 6.5 [4-10], 5.5 [2-8.5] for NIV, SD and MI-groups). ICU survival was 94.7% (respectively 92.3; 100; 91.7% for NIV, SD and MI-groups), with a D90 survival of 59.6% (respectively 66.7; 57.8; 55.6% for NIV, SD and MI-groups).

Discussion

Stress and anxiety are common in NIV treated patients [10], and lead in some instances to a premature interruption of the technique with subsequent tracheal intubation [11–13]. This premature interruption of the technique is associated with increased mortality. Hence, the search for techniques aiming to improve NIV tolerance has to be encouraged. Several interventions have been studied to improve NIV tolerance. Light sedation and analgesia have been shown to be effective by some [14–16]. Nevertheless, in a recent large international multicenter observational study [17], analgesia was applied to 10% of patients, sedation in 5% and both in 4%. This study failed to evidence any benefit of sedation or analgesia during NIV, but an increased risk for NIV failure when sedation and analgesia were combined. Among non-pharmacological ones, sophrology may also be of interest [6]. This behavioral and relational technique relies on cognitive, emotional and somatic aspects of consciousness [18]. When performed during a 30-minute session, sophrology may significantly improve respiratory comfort of patients with ARF treated with NIV [6]. It is however a time-consuming technique, largely dependent on the availability of a skilled sophrologist, and on the patients' receptive state, and therefore scarcely used.

Table S1. Baseline data

	Control Group (n=39)	**Sensory Deprivation (n=38)**	**Musical Intervention (n=36)**
Charlson score, median [IQR]	5.00 [3.00-6.00]	5.00 [4.00-7.00]	5.00 [4.00-7.00]
Home treatment, No (%)			
- Long term oxygen therapy	5 (12.8%)	6 (15.8%)	10 (27.8%)
- Neuroleptic	0	1 (2.6%)	2 (5.6%)
- Benzodiazepines	8 (20.5%)	7 (18.4%)	9 (25%)
- Anti-depressants	10 (25.6%)	9 (23.7%)	10 (27.8%)
Obstructive sleep apnea	6 (15.4%)	10 (26.3%)	6 (16.7%)
History of non-invasive ventilation			
- at home	4 (10.3%)	4 (10.5%)	2 (5.6%)
- in the ICU	7 (17.9%)	5 (13.2%)	6 (16.7%)
ICU admission diagnosis, No (%)			
- Acute respiratory failure	37 (94.8%)	33 (86.9%)	33 (91.7%)
- Acute circulatory failure	0	2 (5.3%)	1 (2.8%)
- Post-operative	2 (5.3%)	2 (5.3%)	2 (5.6%)
- Trauma	0	1 (2.3%)	0
SOFA score at enrolment, median [IQR]	4 [2-5]	3 [2-4]	4 [2.5-5]
RASS at enrolment, median [IQR]	0 [0-0]	0 [0-0]	0 [0-0]
-5, n (%)	0	0	1 (2.8%)
-3	0	0	1 (2.8%)
-1	5 (12.8%)	2 (5.3%)	5 (13.9%)
0	29 (74.4%)	35 (92.1%)	27 (75.0%)
1	4 (10.3%)	1 (2.6%)	2 (5.6%)
3	1 (2.6%)	0	0

Abbreviations: ICU, Intensive Care Unit; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment.

Demographic characteristics and comorbid conditions were recorded at study inclusion.

The Charlson comorbidity index categorizes the comorbidity burden. Comorbidity categories are based on the International Classification of Diseases. Each category is weighted, from 1 to 6, depending on the adjusted risk of mortality or resource use, and the sum of all the weights produces a single comorbidity score for the patient. A score of 0 indicates that no comorbidities were found. Higher scores predict a higher risk of mortality and greater resource use.

SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multiorgan failure).

The RASS is a 10-points scale, ranging from -5 to +4, the lowest for the deeper sedation (-5: unarousable) and the highest indicating a major agitation (+4: combative).

Table S2. Sensitivity analyses of the primary outcome: T0 to T30 change in respiratory discomfort during the first NIV session

	P-value	
	Comparison of musical-intervention group *versus* the control-group	Comparison of sensory deprivation *versus* the control-group
Per protocol analysis[a] (median [IQR])	0.21	0.47
Multiple imputation of missing values	0.72	0.85
Adjustment on stratification factors and potential confounders[b]	0.63	0.57

P-values are provided for the comparison of Musical Intervention group *versus* the Control Group, and for the comparison of Sensory Deprivation *versus* the Control Group. As both tests were non-significant, the comparison of Musical Intervention group *versus* the Sensory Deprivation group was not performed.

[a] During the first NIV session:

- 15 subjects (39,5%) of the Sensory Deprivation group have accepted the intervention. Nine (9) subjects refused the visual deprivation only, 2 subjects refused the sound isolation only, 9 subjects refused both visual and sound deprivation, and 4 subjects had missing values.
- 14 subjects (38,9%) of the Musical Intervention group have accepted the intervention; 19 (52.8%) subjects refused the visual deprivation only, and 3 subjects had missing values.

[b] Stratification factors were centres and underlying chronic respiratory disease, and potential confounders were a PaO2/FiO2<200 mmHg and a prior psychiatric disease

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