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Intraoperative Music to Promote Patient Outcome (IMPROMPTU): A Double-Blind Randomized Controlled Trial

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ABSTRACT

Introduction: Perioperative music can have beneficial effects on postoperative pain, anxiety, opioid requirement, and the physiological stress response to surgery. The aim was to assess the effects of intraoperative music during general anesthesia in patients undergoing surgery for esophagogastric cancer.

Materials and methods: The IMPROMPTU study was a double-blind, placebo-controlled, randomized multicenter trial. Adult patients undergoing surgery for stage II-III esophagogastric cancer were eligible. Exclusion criteria were a hearing impairment, insufficient Dutch language knowledge, corticosteroids use, or objection to hearing unknown music. Patients wore active noise-cancelling headphones intraoperatively with preselected instrumental classical music (intervention) or no music (control). Computerized randomization with centralized allocation, stratified according to surgical procedure using variable block sizes, was employed. Primary endpoint was postoperative pain on the first postoperative day. Secondary endpoints were postoperative pain during the first postoperative week, postoperative opioid requirement, intraoperative medication requirement, the stress response to surgery, postoperative complication rate, length of stay, and mortality, with follow-up lasting 30 d.

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Results: From November 2018 to September 2020, 145 patients were assessed and 83 randomized. Seventy patients (music $n = 31$, control $n = 39$) were analyzed. Median age was 70 [IQR 63–70], and 48 patients (69%) were male. Music did not reduce postoperative pain (numeric rating scale 1.8 (SD0.94) *versus* 2.0 (1.0), mean difference −0.28 [95% CI -0.76–0.19], $P = 0.236$). No statistically significant differences were seen in medication requirement, stress response, complication rate, or length of stay.

Conclusions: Intraoperative, preselected, classical music during esophagogastric cancer surgery did not significantly improve postoperative outcome and recovery when compared to no music using noise-cancelling headphones.

Introduction

Esophageal and gastric cancers are among the most common cancers worldwide and rank high among the top ten of cancer-related mortality causes.[1] Multimodal treatment including surgery is the treatment of choice for stage II and III disease. Despite advancements in perioperative patient care and surgical techniques, postoperative morbidity remains relatively high.[2] Suboptimal pain management, leading to immobility and impairment of effective breathing can, contribute to the development of pulmonary complications and might impair postoperative recovery.[3] Moreover, postoperative pain levels are the predominant predictor of quality of life in the early postoperative period.[4,5] While epidural analgesia is effective and seen as the current standard for postoperative pain management after esophagogastric cancer surgery,[6,7] its use is associated with side-effects and impairment of postoperative patient mobility.[8,9] Furthermore, additional systemic opioid analgesics are required in almost half of the cases due to misplacement or displacement,[10] leading to potential opioid-related adverse effects.[11-13] Therefore, other ways of controlling postoperative pain have been evaluated as part of multimodal analgesia.[14]

Perioperative music can have beneficial effects on postoperative pain,[15] anxiety, intraoperative sedative medication requirement,[16] and postoperative opioid medication requirement.[16] Intraoperative music applied solely during general anesthesia can have significant beneficial effects on postoperative pain and opioid requirement within the first 24 h after surgery as well.[17] This is implied by the finding that the auditory sensory system is still activated by auditory stimuli on functional magnetic resonance imaging during deep propofol sedation.[18] Furthermore, intraoperative music might also attenuate the physiological stress response to surgery, with lower levels of cortisol and cytokines in studies employing locoregional anesthesia with sedation.[19] This could prove beneficial in major surgical procedures with a vigorous stress response, like esophagogastric cancer surgery. To date, the effects of music on clinical outcomes have only been assessed sparingly.[19] Intraoperative music is relatively cheap, easily applicable, and can increase patient satisfaction.[20] Hence, it may be useful as part of multimodal analgesia. The aim of this double-blind, randomized multicenter trial is to investigate the effect of intraoperative music during general anesthesia on postoperative pain, medication requirement the physiological stress response to surgery, and the postoperative clinical outcome and recovery in patients undergoing surgery for esophagogastric cancer.

Materials and Methods

Trial design

This two-arm parallel, double-blind, multicenter, randomized controlled trial was conducted at three Dutch hospitals (Erasmus University Medical Center, Rotterdam; Maasstad Hospital, Rotterdam; and Elisabeth-Tweesteden Hospital, Tilburg). Institutional medical research ethics committee approval was obtained (MEC-2018-127, NL64875.078.18). Two substantial study protocol amendments were approved in order to facilitate participation at the latter two hospital sites, without any change regarding trial design, eligibility criteria, or outcome assessment. The study was registered with the Netherlands Trial Register (NTR 7546) and followed the CONSORT guidelines (Appendix A).

Participants

Eligible patients were informed by the surgeon about the study preoperatively. All adult patients ≥18 y old undergoing elective, curative esophageal, or gastric cancer resection surgery were eligible for this study. All patients were discussed in a multidisciplinary session in order to assess the perioperative treatment strategy and receive preoperative chemoradiation (esophageal cancer) or perioperative chemotherapy (gastric cancer) according to the Dutch national guidelines. The exclusion criteria were a known hearing impairment or usage of a hearing aid, insufficient knowledge of the Dutch language, or objection to hearing any unknown music. As systemic steroids, immunosuppressant, and cytotoxic medication affect the physiological stress response to surgery, patients using these medications were also excluded.[21] In cases of unresectable esophageal or gastric cancer during surgery or distant metastases found intraoperatively with no surgical resection performed, the participating patient and collected data were excluded from the final analysis and the patient was replaced.

Interventions

A custom four-item questionnaire on music preferences and the importance of music in daily life was filled out by all participating patients (Appendix B). The music intervention consisted of a 5 -h long playlist of popular instrumental, nonlyrical, classical music, selected by an expert panel of five research physicians (Appendix C). When the operation lasted more than 5 h, the playlist was repeated automatically. Consent was obtained from the Buma Association (Dutch: Vereniging Buma) and Stemra Foundation (Dutch: Stichting Stemra), who manage music copyright in the Netherlands, to use music for research purposes in this study. The control group wore the same over-ear, active noise-cancelling headphones as the music intervention group, but a blank file without sounds was played continuously.

After induction of general anesthesia and before skin incision, active noise-cancelling, Bose QuietComfort 35 II over-ear headphones connected to a Sandisk Sansa Clip Sport MP3-player were applied to all patients from incision start until wound closure. Depending on the group allocation, the allocated playlist with either preselected music or silence was selected by a member of the research team. While the research team was not blinded to the intervention, it was not possible for the perioperative care team to distinguish which auditory file was played. At the end of the surgical procedure, the elapsed playing time was noted to denote the duration of the intervention. Intraoperative opioid, sedative and catecholamine requirement were recorded, starting from placement of headphones until removing of the headphones at the moment of wound closure. Blood samples for physiological stress response to surgery assessment were drawn preoperatively before incision (baseline sample), with the second blood sample being drawn exactly 8 h later. Peak stress response levels in major surgical procedures are observed after 8 h.[21-23] Blood samples were centrifuged with 2000g during 10 min within 2 h after blood drawing and stored at −80°C.

Perioperative care

A standardized anesthesia protocol was used consisting of bispectral-index (BIS) guided, total intravenous propofol anesthesia. All patients undergoing esophagectomy received an epidural catheter, or a patient-controlled analgesia (PCA) pump, as well as a central venous line and arterial line. Patients undergoing gastrectomy received PCA and an arterial line if deemed necessary by the perioperative care team. In the Netherlands, esophagogastric surgery is centralized in dedicated hospitals that perform at least 20 esophagectomies and/or 20 gastrectomies per year. Therefore, surgery was performed by a limited number of dedicated upper-gastrointestinal surgeons who had performed more than one hundred procedures, with an experienced surgical and perioperative care team. Minimally invasive gastrectomy was performed as previously described.[24] The preferred surgical approach for the esophagus was left to the discretion of the surgeon and involved transthoracic and transhiatal totally minimally invasive esophagectomy with an anastomosis in the chest (Ivor lewis) or neck (Mc Keown). Also hybrid (laparoscopy and open chest) and totally open resections were allowed.

Postoperatively, the pain team of the anesthesiology department was responsible for the epidural or PCA pump and analgesic medication regimen during the first postoperative days until removal of the epidural and PCA pump. Pain scores were assessed daily by the nursing staff, with analgesic medication administered accordingly if needed. Mobilization was encouraged as early as possible, directly after surgery, following the Enhanced Recovery After Surgery protocols. All patients that underwent esophagectomy were admitted to the intensive care unit postoperatively for at least 24 h. Patients that underwent gastrectomy were only admitted to the intensive care unit if deemed necessary. Patients were kept on a nil-per-os regimen for the first postoperative days until the nasogastric tube was removed after esophagectomy, while the jejunostomy catheter was used for feeding during the first postoperative month. After gastrectomy, patients were allowed liquid oral feeding from the first postoperative day onward.

Outcome measures

The primary outcome was postoperative pain on the first postoperative day. This was assessed using an 11-point numeric rating scale (NRS) during the first postoperative week, with 0 being defined as no pain and 10 as the worst pain imaginable. Postoperative pain was calculated by averaging the pain scores of the morning, afternoon, and evening on each postoperative day, including the additional pain score by the pain team responsible for the epidural catheter and PCA pump during the first few postoperative days. Both the mean pain score of each postoperative day per group as well as the average of the entire first postoperative week per group were analyzed. Pain scores were assessed as part of standard care by patients and the nursing staff, who were blinded to the intervention.

Secondary outcome measures were postoperative pain during the first postoperative week, the physiological stress response to surgery, intraoperative medication requirement (opioid, sedatives, inotropes, and vasopressors), postoperative opioid medication requirement during the first postoperative week, postoperative complication rate (classified according to the Clavien-Dindo classification), hospital and intensive care length of stay, and 30-d mortality. All outcome measures, except the physiological stress response to surgery, were part of standard patient care, assessed by health care providers blinded to the intervention, and documented in the electronic patient database. The physiological stress response to surgery was assessed by measuring serum cortisol levels as a derivative of neurohormonal stress response activity using a Siemens Immulite 2000XPi immunoassay. For the immunological stress response activity, measurement of interleukin-6 levels using the Genprobe Diaclone ELISA immunoassay, tumor necrosis factor alpha (TNF-α) levels using R&D Systems ELISA immunoassay, and C-reactive protein (CRP) levels using Roche cobas assay were conducted. Opioid requirement was converted using universal formulas to calculate milligrams (mg) of morphine equivalent (ME) dosage, with 1 mg ME being the equivalent of 1 mg parenteral administered morphine.[16]

Fentanyl 0.1 mg parenteral was considered to be equipotent to 10 mg ME,[25] oxycodone 20 mg oral to be 10 mg ME,[25] tramadol 100 mg oral to be 6.7 mg ME,[26] fentanyl transdermal 12.5 mcg/h to be 8.3 mg ME,[27] sufentanil 0.1 mg to be 100 mg ME,[28] and piritramide 15 mg parenteral to be 10 mg ME.[29] As remifentanil does not have a reliable conversion factor, this was reported separately. Continuous opioid infusion through epidural catheters and PCA pumps combined with the amount of administered bolus injections were converted to mg ME as well.

Participants were followed during the first 30 d after surgery. Postoperative complications and mortality were recorded during a 30-d follow-up period.

Randomization and blinding

Patients fulfilling eligibility criteria and providing written informed consent were randomly allocated in a 1:1 ratio to either the intervention (intraoperative music) or control group. Centralized allocation concealment was present by using a computer-generated randomization sequence through the web-based software ALEA.[30] The randomization was stratified according to the surgical procedure (esophagectomy or gastrectomy) and planned surgical approach (esophagectomy: minimally invasive, hybrid or open; gastrectomy: minimally invasive or open). Variable block sizes of 4 or 6 designed by a statistician not involved in study procedures or data analysis were used. Computerized randomization revealed the allocated intervention to the coordinating research physician, who implemented allocation with the research team during surgery by applying the noise-cancelling headphones and selecting the correct playlist (music or silence). These nonblinded research team members were not involved in patient care. As all participating patients received general anesthesia and wore active noise-cancelling headphones during the surgical procedure, the patients and perioperative care team were blinded to the intervention. All outcome measures were assessed by perioperative care team members blinded to the intervention. The laboratory technicians conducting the blood sample measurements for the stress response to surgery were blinded to the group allocation as well. Postoperative complications were assessed by physicians conducting the primary patient care and if needed discussed with the supervising surgeons by the coordinating research physician. Statistical analysis was encoded and performed by a member of the research team blinded to the group allocation. Data collection, recording of perioperative complications and additional quality measures followed the proposed system by the Esophagectomy Complications Consensus Group.[2] Deblinding was performed after finalization of the data analysis.

Sample size calculation

A retrospective analysis of 24 esophagogastric cancer patients who underwent surgery in the 6 mo prior to study approval revealed a mean postoperative pain score of 2.6 and a standard deviation of 1.92. A reduction of 1.3 points on an 11 point scale was deemed clinically relevant. A previous meta-analysis observed an average reduction of 1.0 points when evaluating perioperative music, that is music before, during and after surgery, in a wide range of surgical procedures.[15] Comparable studies in regards to the surgical procedure severity with major abdominal surgery and intraoperative music were scarce, but in major visceral abdominal surgical procedures, a similar effect was observed.[20] Sample size calculation resulted in each study arm requiring 35 patients in order to obtain a power of 80% with alpha of 5% and planned two-sided testing.

Statistical analysis

Descriptive analysis was performed in order to report outcome measures for both the music and control group. The mean and standard deviation (SD), in case of parametric data, or the median and interquartile range [IQR], in case of nonparametric data, was reported. Statistical significance of difference was tested using a student's t-test or Mann–Whitney U-test, as appropriate. Mean differences with 95% confidence interval (95% CI) were presented. Percentile confidence intervals for differences in medians were obtained using 2000 bootstrap samples. Except for the percentile confidence intervals for differences in medians which were performed using R, all data analyses were performed using IBM SPSS version 20.0. Statistical significance was set at $P < 0.05$.

Results

Patients

From November 1, 2018 to September 16, 2020, 145 patients undergoing surgery for esophagogastric cancer were assessed for eligibility. Due to varying reasons, 35 patients were not approached. This included logistical reasons such as three procedures in the different hospitals at the same time. Furthermore, due to the COVID pandemic, cancer surgeries were still performed but all nonessential personnel and activities were reduced to a minimum. Twenty-one patients were not eligible due to use of corticosteroids ($n = 8$), insufficient knowledge of the Dutch language ($n = 5$), hearing impairment ($n = 2$), or planned palliative surgery ($n = 6$). Six patients (6.7%) refused to participate. Eighty-three patients were randomized (41 patients in the music and 42 in the control group). Thirteen patients were excluded according to the protocol due to the administration of corticosteroids intraoperatively ($n = 1$), no resection performed ($n = 9$), or change in scheduling ($n = 3$). Of the remaining 70 patients (31 patients in the music and 39 in the control group), all completed follow-up and were included for data analysis (Fig.).

Patient characteristics are shown in Table 1 and Appendix D. Median age was 70 [IQR 63-70] and 48 of the 70 patients (69%) were male. Approximately 80% of participants listened to music every day, with the importance of music in daily life being rated as 8 and 7 out of 10 in the music and control group, respectively (Table 2). The majority of participants had never played a musical instrument.

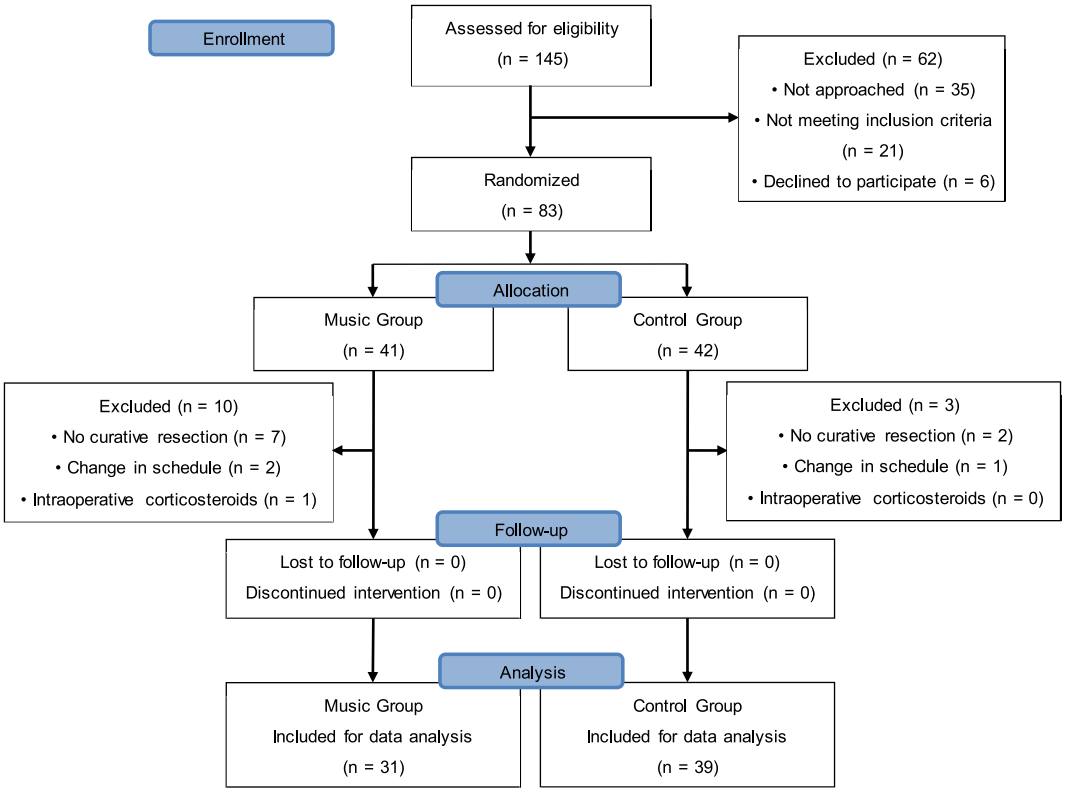

Fig. – CONSORT flow diagram. *n* = number of patients.

Treatment characteristics

Perioperative treatment characteristics are shown in Table 1. Forty-eight patients (69%) underwent esophagectomy and 22 patients (31%) underwent laparoscopic gastrectomy. In six patients (8.6%), conversion to open resection was required for technical reasons. No statistically significant differences between groups were present regarding duration of surgery, duration of anesthesia, and total procedural time. All participating patients received BIS-guided, total propofol anesthesia. In 13 of the 70 patients (19%), ketamine was administered intraoperatively, which was in most cases due to lack of an epidural and equally divided among the music ($n = 7$) and control ($n = 6$) group.

Postoperative pain and perioperative medication requirement

The effects of intraoperative music on postoperative pain levels and perioperative medication requirement are presented in Table 3. Mean (SD) postoperative pain levels were not statistically significant different between the music and control group on the first postoperative day (NRS 1.8 (1.6) *versus* 2.2 (1.5), mean difference −0.44 (95% CI -1.2 to 0.31), $P = 0.249$), nor did it differ during the first week after surgery (NRS 1.8 (0.94) *versus* 2.0 (1.0), mean difference −0.28 (95% CI -0.76 to 0.19), $P = 0.236$). Postoperative opioid requirement was also not statistically significant different during the first week after surgery between the music and control group (median 379 mg ME [IQR 121-800] *versus* 407 [37.5-982], median difference −28 (95% CI -434 to 144), $P = 0.718$). There were also no statistically significant differences between both treatment arms for mean NRS and mg ME for each postoperative day.

Mean (SD) intraoperative propofol requirement did not differ significantly between the music and control group (2900 mg (1692) *versus* 2929 (1844), mean difference −28.75 (95% CI 882.6 to 825.1), $P = 0.874$). Post-hoc sensitivity analysis excluding the 13 patients that received ketamine, which can have contradictory effects on BIS values,[31] did not change the results. Three patients, one in the music group and two in the control group, required additional intraoperative midazolam. Intraoperative opioid requirement was comparable for both groups (median 50 mg ME [IQR 25-87] *versus* 51 [35-93], median difference 1.0 (95% CI -25 to 26), $P = 0.901$), nor did remifentanil requirement (4.3 mg (SD 3.4) *versus* 3.6 (2.4), median difference 0.79 (95% CI -0.60 to 2.2) $P = 0.260$) differ. Mean (SD) intraoperative noradrenaline requirement did not differ significantly between the music and control group (59 mg (69) *versus* 70 mg (96), mean difference −11 (95% CI -52 to 30), $P = 0.590$). Twenty-one patients required additional intraoperative inotropes or vasopressors, of which ten had been allocated to the music group and 11 to the control group.

Physiological stress response to surgery

The effects of intraoperative music on the physiological stress response to surgery are presented in Table 4. All preoperative blood samples for stress response assessment were drawn before incision and all postoperative blood samples 8 h after the preoperative samples. All the second samples were drawn after wound closure. No statistically significant differences in preoperative levels of cortisol, IL-6, or TNF-α were observed

Table 1 – Baseline and treatment characteristics of the study groups.

Baseline and treatment characteristic	Music group ($n = 31$)	Control group ($n = 39$)
Age (years)	70 [63-73]	70 [62-75]
Sex (*n*)		
Female	10	12
Male	21	27
American Society of Anesthesiologists classification (*n*)		
1	2 (6.5%)	2 (5.1%)
2	15 (48%)	24 (62%)
3	14 (45%)	11 (28%)
4	0 (0%)	2 (5.1%)
Body mass index	27 (4.5)	27 (6.2)
Charlson comorbidity index	5 [3-9]	5 [2-9]
WHO performance score (*n*)		
0	9 (29%)	18 (46%)
1	20 (65%)	16 (41%)
2	1 (3.2%)	3 (7.7%)
Missing	1 (3.2%)	2 (5.1%)
Neoadjuvant therapy (*n*)		
Full course	26 (84%)	29 (74%)
Incomplete (<100% of planned)	2 (6.5%)	3 (7.7%)
No	3 (9.7%)	7 (18%)
Esophageal cancer resection (*n*)		
Open	2 (6.5%)	1 (2.6%)
Hybrid	6 (19%)	9 (23%)
Minimally invasive	14 (45%)	16 (41%)
Stomach cancer resection (*n*)		
Open	0 (0%)	0 (0%)
Minimally invasive	9 (29%)	13 (33%)
Conversion (*n*)	3 (9.7%)	3 (7.7%)
Duration of surgery (minutes)	306 (122)	299 (102)
Duration of anesthesia (minutes)	373 (142)	364 (113)
Duration of intervention (minutes)	280 (117)	287 (95.0)

Baseline and perioperative treatment characteristics. For categorical variables, absolute numbers (percentage of allocated study group) are presented. For continuous variables, medians [interquartile ranges] or means (standard deviations) are presented, as appropriate. No statistical significant differences between groups were observed.
n = number of patients; WHO = World Health Organization.

Table 2 – Music preferences and importance of music in daily life.

Outcome measure	Music group		Control group	
	n	hours	*n*	hours
How often do you listen to music in your daily life?				
Almost the entire day	11 (36%)	-	12 (31%)	-
A couple of hours every day	13 (42%)	3.0 (1.8)	19 (49%)	3.4 (1.6)
A couple of hours every week	6 (19%)	5.2 (4.4)	8 (21%)	3.9 (2.0)
Almost never	1 (3.2%)	-	0 (0.0%)	-
Importance of music in daily life (NRS)	8 [7-8]		7 [7-9]	

	Genre	*n*	Genre	*n*
Top three preferred music genre	Dutch	12 (18%)	Rock	14 (16%)
	Pop	10 (15%)	Classical	12 (14%)
	Country	9 (13%)	Country	11 (13%)
Plays a musical instrument				
Yes		6 (19%)		3 (7.7%)
Used to		5 (16%)		12 (31%)
No		20 (65%)		24 (62%)

Custom questionnaire on music preferences and importance of music in daily life. For categorical variables, absolute numbers (percentage of allocated study group) are presented. For continuous variables, medians [interquartile ranges] are presented.
n = Number of patients; NRS = Numeric Rating Scale with range 0 to 10.

between the groups. Mean (SD) postoperative levels of cortisol (880 nmol/L (445) *versus* 939 (365), mean difference −58.4 (95% CI -252 to 135), $P = 0.549$), IL-6 (median 277 pg/mL [IQR 135-427] *versus* 165 [94-440], median difference 110 (95% CI -33.0 to 206), $P = 0.221$], and TNF-α (median 10 pg/mL [IQR 10-21] *versus* 16 [10-27], median difference −4.8 (−15 to 4.5), $P = 0.178$] did not differ statistically significant between groups. Mean CRP levels were statistically significantly higher in the music group compared to the control group on the first (108 mg/L (27.3) *versus* 89.9 (31.1), mean difference 18.4 [95% CI 2.82 to 33.9], $P = 0.021$) and third postoperative day (231 (113) *versus* 127 (70.2), mean difference 104 [95% CI 7.71 to 200], $P = 0.036$).

Postoperative complications and length of stay

The effects of intraoperative music on postoperative complications and length of stay are presented in Table 5. There was no statistically significant difference in the number of patients with postoperative complications, with 19 patients (61%) in the music group and 26 (67%) in the control group having at least 1 postoperative complication ($P = 0.641$). Also, no difference in complication severity according to the Clavien-Dindo classification was observed.

Mean (SD) hospital length of stay was comparable (15.5 d (11.7) *versus* 14.7 (10.7), mean difference 0.817 (95% CI -4.52 to 1.16), $P = 0.671$). Four patients were readmitted to the intensive care unit, two in each group (6.5% *versus* 5.1%, $P = 0.780$). None of the participating patients remembered hearing music during surgery when assessed postoperatively during the drawing of the second blood sample, while no reported

Table 3 – Postoperative pain and perioperative medication requirement.

Outcome measure	Music group		Control group		Mean or median difference (95%CI)	P-value
	n	M (SD) or [IQR]	n	M (SD) or [IQR]		
Postoperative pain (NRS)						
Postoperative day 1	30	1.8 (1.6)	38	2.2 (1.5)	−0.44 (−1.2 to 0.31)	0.249
Postoperative day 2	31	1.7 (1.5)	39	1.9 (1.5)	−0.19 (−0.91 to 0.53)	0.608
Postoperative day 3	29	1.4 (1.1)	38	1.8 (1.4)	−0.38 (−1.0 to 0.25)	0.231
Postoperative day 4	28	1.7 (1.7)	35	1.6 (1.3)	0.069 (−0.67 to 0.80)	0.852
Postoperative day 5	28	1.9 (1.4)	31	2.4 (1.9)	−0.48 (−1.4 to 0.40)	0.278
Week 1 average	31	1.8 (0.94)	39	2.0 (1.0)	−0.28 (−0.76 to 0.19)	0.236
Postoperative opioid requirement (mg ME)						
Postoperative day 1	31	90.0 [46.0-192]	39	96.0 [10.2-176]	−6.0 [−55 to 89]	0.331
Postoperative day 2	31	86.5 [10.0-168]	39	96.0 [5.00-168]	−9.5 [−64 to 108]	0.590
Postoperative day 3	29	66.0 [5.00-159]	38	74.3 [9.38-153]	−8.3 [−59 to 63]	0.970
Postoperative day 4	28	25.3 [1.25-115]	37	63.0 [5.00-138]	−38 [−89 to 22]	0.209
Postoperative day 5	27	80.1 [0.00-71.5]	33	26.0 [0.50-61.0]	54.1 [−41 to 14]	0.393
Week 1 average	31	379 [121-800]	39	407 [37.5-982]	−28 [−434 to 144]	0.718
Intraoperative opioid requirement (mg ME)	31	50 [25-87]	39	51 [35-93]	1.0 [−25 to 26]	0.901
Intraoperative remifentanil requirement (mg)	31	4.3 (3.4)	39	3.6 (2.4)	0.79 (−0.60 to 2.2)	0.260
Intraoperative propofol requirement (mg)	31	2900 (1692)	39	2929 (1844)	−28.75 (−882.6 to 825.1)	0.947
Intraoperative noradrenaline requirement (mg)	31	59 (69)	39	70 (96)	−11 (−52 to 30)	0.590

Postoperative pain and perioperative medication requirement. Data presented as mean (standard deviation) or median [interquartile range], as appropriate. Opioids were converted to milligrams of parenteral Morphine Equivalent (mg ME). Median differences with 95% confidence interval were calculated using 2000 bootstrap samples for postoperative and intraoperative opioid requirement.
95% CI = 95% confidence interval; IQR = interquartile range; M = mean or median; mg = milligram; n = number of patients; SD = standard deviation.

adverse side effects were observed due to the music intervention or headphones employed.

Discussion

This double-blind, multicenter, randomized controlled trial investigated the effects of intraoperative, preselected, instrumental classical music compared to active noise canceling headphones with silence during general anesthesia on the postoperative outcome and recovery in patients that underwent esophagogastric cancer surgery. We chose to study intraoperative application of music as it is easy to perform in all patients and can be well controlled. However, no statistically significant beneficial effects regarding postoperative pain, intraoperative medication requirement, postoperative opioid requirement, stress response to surgery, postoperative complication rate or length of stay were observed. Recently, it has been observed that auditory sensory information including music can still be processed in propofol-sedated subjects.[18] Furthermore, several studies have reported beneficial effects on postoperative pain and opioid requirement after exposure to intraoperative music during general anesthesia.[17,32-34] Our results contradict other studies that reported less postoperative pain and opioid requirement in patients that were exposed to intraoperative music during general anesthesia.[17,35] Several reasons may explain this discrepancy.

No participant-preferred choice concerning the music intervention was taken into account in this study. This was in part due to practical reasons. Music selected preoperatively by the patient should be transferred to the study audio equipment in order to maintain blinding. The devoted time to assemble a playlist of sufficient length would add an additional burden to patients with cancer, while there is a realistic chance that they do not get to hear it if randomized to the control group. Off course, it could be argued to use readily available playlists based on genre. However, in any given music genre, there is a huge range of different music pieces and this could still not be the preferred music of the patient. In previous studies evaluating the effect of intraoperative music during general anesthesia, preselected music by the research team was used.[17,32-34,36,37] No studies assessing intraoperative music used the preferred music list of the patient,[17] although two offered patients a choice to select from a limited preselected music list.[17,20,38] It is unclear which music was chosen and therefore preferred by the patients in these two studies. A previously published meta-analysis of 85

Table 4 – Physiological stress response to surgery.

Physiological stress response to surgery parameter	Music group		Control group		Mean or median difference (95%CI)	P-value
	n	M (SD) or [IQR]	*n*	M (SD) or [IQR]		
Cortisol						
Preoperative	31	338 (126)	39	351 (139)	−13.0 (−77.1 to 51.1)	0.687
Postoperative	31	880 (445)	39	939 (365)	−58.4 (−252 to 135)	0.549
IL-6						
Preoperative	31	9.00 [9.00-13.0]	39	9.00 [9.00-11.0]	0.00 (−1.00 to 1.00)	0.484
Postoperative	31	277 [135-427]	39	165 [94.0-440]	110 (−33.0 to 206)	0.221
Tumor necrosis factor-alpha						
Preoperative	31	10 [10-23]	39	10 [10-28]	0.0 (−10 to 0.0)	0.248
Postoperative	31	10 [10-21]	39	16 [10-27]	−4.8 (−15 to 4.5)	0.178
CRP						
CRP POD 1	24	108 (27.3)	37	89.9 (31.1)	18.4 (2.82 to 33.9)	0.021
CRP POD 2	22	225 (86.8)	19	198 (75.3)	27.4 (−24.3 to 79.2)	0.290
CRP POD 3	4	231 (113)	14	127 (70.2)	104 (7.71 to 200)	0.036

Effect of intraoperative music during esophageal and stomach cancer surgery on the physiological stress response to surgery. Data presented as mean (standard deviation) or median [interquartile range], as appropriate. Cortisol, interleukin-6, and tumor necrosis factor-alpha were assessed before incision (preoperative) and 8 h later (postoperative). C-reactive protein was assessed on the first three postoperative days in light of standard perioperative care. Median differences with 95% confidence interval were calculated using 2000 bootstrap samples.
95% CI = 95% Confidence interval; CRP = C-reactive protein; IQR = interquartile range; M = mean or median; POD = postoperative day; SD = standard deviation.

randomized controlled trials identified nonlyrical instrumental music as the only characteristic described sufficiently for analysis with a beneficial effect and acceptable heterogeneity.[39] Even less is known about intraoperative music during general anesthesia, with the majority using preselected, soft, instrumental music.[17,20,32-34,36] Based on these previously conducted studies combined with the practical barriers, a preselected list of soft, classical, instrumental music was chosen. Of interest is that the employed music in our study did not rank among the top three favorite music genres of the

Table 5 – Postoperative complications and length of stay.

	Music group (*n* = 31)	Control group (*n* = 39)	*P*-value
Postoperative complications (*n*, %)	19 (61%)	26 (67%)	0.641
Clavien-Dindo classification (*n*)			
Grade I	8	14	0.796
Grade II	26	34	0.468
Grade IIIa	9	16	0.740
Grade IIIb	1	6	0.249
Grade IVa	3	0	0.110
Grade IVb	0	0	
Anastomotic leak (*n*, %)	5 (16%)	7 (18%)	0.841
Chyle leak (*n*, %)	2 (6.5%)	4 (10%)	0.572
Intensive care length of stay (days)	2.0 [1.0-3.0]	2.0 [1.0-3.0]	0.773
Hospital length of stay (days)	15.5 (11.7)	14.7 (10.7)	0.761
Readmission to intensive care (*n*, %)	2 (6.5%)	2 (5.1%)	0.780
Discharge to home (*n*, %)	28 (90%)	35 (90%)	0.936
30-d mortality (*n*, %)	0 (0%)	0 (0%)	

Effect of intraoperative music on postoperative complication rate and length of stay. For categorical variables, absolute numbers (percentage of allocated study group) are presented. For continuous variables, medians [interquartile ranges] or means (standard deviations) are presented, as appropriate.
n = number of patients.

music group, as revealed in our questionnaire. In regards to perioperative music applied before, during and after the surgical procedure, a larger beneficial effect of preselected music offering a choice seemed present when compared to no choice.[15] It is unclear whether the favorite genre of the patient or offering a choice would yield different results, especially during general anesthesia with unconscious perception. This warrants further investigation.

Other factors could also have influenced the different outcomes compared to previous studies. In our study, the control group consisted of patients wearing noise-cancelling headphones in order to assess the effect of music itself. Several previously conducted studies used recorded operation room noise mimicking standard patient care or white noise as an auditory control factor.[20,32,36,37] Noise is recognized universally as a stressor and seems to have negative effects on patient outcome.[40] Therefore, it could be that the music intervention effect is smaller due to the effect being partly caused by noise reduction. However, music itself does seem to have a beneficial effect, given that earlier conducted studies employing both a standard patient care and headphones without music control group did still observe a beneficial effect of music.[19,41] No beneficial effect on intraoperative medication requirement was observed. It has been speculated that the reduced need for intraoperative medication requirement while maintaining similar sedation depth due to music is through its anxiolytic effects,[16] as higher anxiety levels can require an increased dosage to induce and maintain anesthesia.[42] To date, a beneficial effect on anxiety by solely intraoperative music has not been observed.[15] No attenuating effect of intraoperative music was observed on the physiological stress response to surgery. The severity of this response is partly dependent on tissue damage by the invasiveness of the surgical procedure. Given the major surgical procedures investigated in this study, compared to previously conducted studies in patients who underwent less invasive procedures (laparoscopic cholecystectomy, elective hip replacement, caesarean section, and inguinal hernia repair), it could well be possible that the influence of music on the stress response is too small to be measured. While postoperative CRP levels were significantly higher in the music group on the first and third postoperative day, the clinical relevance is unclear as postoperative complication rate did not differ between groups. Although CRP assessment was part of standard postoperative care, in 23% of the music group, no CRP was assessed on the first postoperative day, with only 5% missing in the control group. This was unlike the other parameters of the physiological stress response to surgery, that is cortisol, interleukin-6 and TNF-α, which were assessed specifically for this trial by drawing additional vials of blood perioperatively. The effect of music on the postoperative complication rate reported only rarely been assessed. One study on varicose vein surgery reported an insignificant ratio of complications in both music and control group. As it would be difficult to find a difference when no complications (i.e., events) occurred, we chose an operation with a rather high complication rate but did not observe a statistically significant difference. Finally, it seems that the administration of benzodiazepines preoperatively may influence intraoperative auditory perception during general anesthesia.[17] This only became known to us recently after patient inclusion was completed, and at least 20% of patients in our study received benzodiazepines before surgery.

Strengths of the present study were the prespecified, BIS-guided, total intravenous propofol anesthesia regimen, in order to ensure adequate sedation levels and reduce potential influence on implicit auditory perception by the employed drug regimen. The patients and entire perioperative care team were blinded to the intervention, with centralized allocation concealment and statistical analysis performed by a statistician unaware of patient allocation. Care was taken to ensure that the research team could not influence the study results, as outcomes were assessed by health-care staff blinded to the intervention.

A limitation was the relatively small sample size combined with the relatively low mean pain levels. The observed mean NRS for pain under 2.0 was approximately 25% lower than expected, based on which the sample size was calculated. In general, all patients who underwent esophagectomy with gastric tube reconstruction received an epidural or PCA pump, with continuous infusion, potentially clouding the effects of music on opioid requirement. Additional assessment moments on pain, for example 3, 6, and 12 h after surgery, could have increased the chance of finding a difference, but whether it has clinical relevance if one specific time point in the first 24 h after surgery is different, is unclear. Adhering to our standard perioperative care protocols minimized the impact of the study and additional outcome measures increases the risk of a false positive statistical results. This study also included different surgical approaches (hybrid and laparoscopic) and procedures (esophageal and gastric cancer surgery). Although baseline characteristics, including the aforementioned factors, did not differ statistically and stratified randomization was used, the heterogenous patient cohort may be reflected in the outcome measures, showing fairly wide confidence intervals makinginterpretation of study results difficult. While ideally a single surgical procedure might have been chosen, this study does reflect clinical practice of patients with esophagogastric cancer undergoing surgery.

Based on the present study, it is not likely that intraoperative music can improve postoperative patient outcome and recovery in esophagogastric cancer surgery. Future studies should consider focusing on one specific type of surgery with a large sample size, given the observed broad confidence intervals in this study. Furthermore, more attention should be diverted to assess whether music preference could make a difference.

Conclusion

Intraoperative, research-selected, classical instrumental music played during esophageal and gastric cancer surgery did not reduce postoperative pain and perioperative medication requirement, attenuate the physiological stress response, or improve postoperative patient outcome.

Trial Registry

Dutch Trial Registry (NTR7546).

Supplementary Materials

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2024.01.006.

CRediT authorship contribution statement

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Availability of Data

Study data and syntax are available on request.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65:5–29.
2. Low DE, Alderson D, Cecconello I, et al. International Consensus on Standardization of data collection for complications associated with esophagectomy: esophagectomy complications Consensus group (ECCG). *Ann Surg*. 2015;262:286–294.
3. Weijs TJ, Ruurda JP, Nieuwenhuijzen GA, van Hillegersberg R, Luyer MD. Strategies to reduce pulmonary complications after esophagectomy. *World J Gastroenterol*. 2013;19:6509–6514.
4. Ali M, Winter DC, Hanly AM, O'Hagan C, Keaveny J, Broe P. Prospective, randomized, controlled trial of thoracic epidural or patient-controlled opiate analgesia on perioperative quality of life. *Br J Anaesth*. 2010;104:292–297.
5. Scarpa M, Saadeh LM, Fasolo A, et al. Health-related quality of life in patients with oesophageal cancer: analysis at different steps of the treatment pathway. *J Gastrointest Surg*. 2013;17:421–433.
6. Flisberg P, Tornebrandt K, Walther B, Lundberg J. Pain relief after esophagectomy: thoracic epidural analgesia is better than parenteral opioids. *J Cardiothorac Vasc Anesth*. 2001;15:282–287.
7. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy: enhanced Recovery after Surgery (ERAS(R)) Society recommendations. *Br J Surg*. 2014;101:1209–1229.
8. Allen MS, Blackmon SH, Nichols 3rd FC, et al. Optimal timing of urinary catheter removal after thoracic operations: a randomized controlled study. *Ann Thorac Surg*. 2016;102:925–930.
9. Al-Rawi OY, Pennefather SH, Page RD, Dave I, Russell GN. The effect of thoracic epidural bupivacaine and an intravenous adrenaline infusion on gastric tube blood flow during esophagectomy. *Anesth Analg*. 2008;106:884–887. table of contents.
10. Kingma BF, Visser E, Marsman M, Ruurda JP, van Hillegersberg R. Epidural analgesia after minimally invasive esophagectomy: efficacy and complication profile. *Dis Esophagus*. 2019;32:doy116.
11. Barletta JF. Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. *Pharmacotherapy*. 2012;32:12S–18S.
12. Barletta JF, Asgeirsson T, Senagore AJ. Influence of intravenous opioid dose on postoperative ileus. *Ann Pharmacother*. 2011;45:916–923.
13. Gupta K, Nagappa M, Prasad A, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. *BMJ Open*. 2018;8:1–10.
14. Donohoe CL, Phillips AW, Flynn E, et al. Multimodal analgesia using intrathecal diamorphine, and paravertebral and rectus sheath catheters are as effective as thoracic epidural for

analgesia post-open two-phase esophagectomy within an enhanced recovery program. *Dis Esophagus*. 2018;31:1–8.
15. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. 2018;105:773–783.
16. Fu VX, Oomens P, Klimek M, Verhofstad MHJ, Jeekel J. The effect of perioperative music on medication requirement and hospital length of stay: a meta-analysis. *Ann Surg*. 2020;272:961–972.
17. Fu VX, Sleurink KJ, Janssen JC, Wijnhoven BPL, Jeekel J, Klimek M. Perception of auditory stimuli during general anesthesia and its effects on patient outcomes: a systematic review and meta-analysis. *Can J Anaesth*. 2021;68:1231–1253.
18. Gross WL, Lauer KK, Liu X, et al. Propofol sedation alters perceptual and cognitive functions in healthy volunteers as revealed by functional magnetic resonance imaging. *Anesthesiology*. 2019;131:254–265.
19. Fu VX, Oomens P, Sneiders D, et al. The effect of perioperative music on the stress response to surgery: a meta-analysis. *J Surg Res*. 2019;244:444–455.
20. Kahloul M, Mhamdi S, Nakhli MS, et al. Effects of music therapy under general anesthesia in patients undergoing abdominal surgery. *Libyan J Med*. 2017;12:1–6.
21. Khoo B, Boshier PR, Freethy A, et al. Redefining the stress cortisol response to surgery. *Clin Endocrinol*. 2017;87:451–458.
22. Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci (Lond)*. 1990;79:161–165.
23. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg*. 1992;79:757–760.
24. Haverkamp L, Brenkman HJ, Seesing MF, et al. Laparoscopic versus open gastrectomy for gastric cancer, a multicenter prospectively randomized controlled trial (LOGICA-trial). *BMC Cancer*. 2015;15:1–7.
25. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage*. 2001;22:672–687.
26. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43:879–923.
27. Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. *Oncology (Williston Park)*. 2000;14:695–705, 709-617.
28. Joshi GP. Sufentanil for chronic pain management. *Future Neurol*. 2010;5:791–796.
29. Döpfmer UR, Schenk MR, Kuscic S, Beck DH, Döpfmer S, Kox WJ. A randomized controlled double-blind trial comparing piritramide and morphine for analgesia after hysterectomy. *Eur J Anaesthesiol*. 2001;18:389–393.
30. ALEA | Tools for clinical trials. Available at: https://www.aleaclinical.eu/. Accessed November 17, 2019.
31. Faraoni D, Salengros JC, Engelman E, Ickx B, Barvais L. Ketamine has no effect on bispectral index during stable propofol-remifentanil anaesthesia. *Br J Anaesth*. 2009;102:336–339.
32. Nilsson U, Rawal N, Uneståhl LE, Zetterberg C, Unosson M. Improved recovery after music and therapeutic suggestions during general anaesthesia: a double-blind randomised controlled trial. *Acta Anaesthesiol Scand*. 2001;45:812–817.
33. Nilsson U, Rawal N, Unosson M. A comparison of intra-operative or postoperative exposure to music - a controlled trial of the effects on postoperative pain. *Anaesthesia*. 2003;58:699–703.
34. Nilsson U, Unosson M, Rawal N. Stress reduction and analgesia in patients exposed to calming music postoperatively: a randomized controlled trial. *Eur J Anaesthesiol*. 2005;22:96–102.
35. Fu VX, Sleurink KJ, Janssen JC, Wijnhoven BPL, Jeekel J, Klimek M. Perception of auditory stimuli during general anesthesia and its effect on patient outcome: a meta-analysis. *Can J Anesth*. 2021;68:1231–1253.
36. Reza N, Ali SM, Saeed K, Abul-Qasim A, Reza TH. The impact of music on postoperative pain and anxiety following cesarean section. *Middle East J Anesthiol*. 2007;19:573–586.
37. Simcock XC, Yoon RS, Chalmers P, Geller JA, Kiernan HA, Macaulay W. Intraoperative music reduces perceived pain after total knee arthroplasty: a blinded, prospective, randomized, placebo-controlled clinical trial. *J Knee Surg*. 2008;21:275–278.
38. Migneault B, Girard F, Albert C, et al. The effect of music on the neurohormonal stress response to surgery under general anesthesia. *Anesth Analg*. 2004;98:527–532. table of contents.
39. Martin-Saavedra JS, Vergara-Mendez LD, Pradilla I, Vélez-van-Meerbeke A, Talero-Gutiérrez C. Standardizing music characteristics for the management of pain: a systematic review and meta-analysis of clinical trials. *Complement Ther Med*. 2018;41:81–89.
40. Fu VX, Oomens P, Merkus N, Jeekel J. The perception and attitude toward noise and music in the operation room: a systematic review. *J Surg Res*. 2021;263:193–206.
41. Tabrizi EM, Sahraei H, Rad SM, Hajizadeh E, Lak M. The effect of music on the level of cortisol, blood glucose and physiological variables in patients undergoing spinal anesthesia. *EXCLI J*. 2012;11:556–565.
42. Kil HK, Kim WO, Chung WY, Kim GH, Seo H, Hong JY. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. *Br J Anaesth*. 2012;108:119–125.