Adjunctive non-pharmacological analgesia for invasive medical procedures: a randomised trial

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Summary

Background Non-pharmacological behavioural adjuncts have been suggested as efficient safe means in reducing discomfort and adverse effects during medical procedures. We tested this assumption for patients undergoing percutaneous vascular and renal procedures in a prospective, randomised, single-centre study.

Methods 241 patients were randomised to receive intraoperatively standard care (n=79), structured attention (n=80), or self-hypnotic relaxation (n=82). All had access to patient-controlled intravenous analgesia with fentanyl and midazolam. Patients rated their pain and anxiety on 0–10 scales before, every 15 min during and after the procedures.

Findings Pain increased linearly with procedure time in the standard group (slope 0·09 in pain score/15 min, p<0·0001), and the attention group (slope 0·04/15 min; p=0·0425), but remained flat in the hypnosis group. Anxiety decreased over time in all three groups with slopes of −0·04 (standard), −0·07 (attention), and −0·11 (hypnosis). Drug use in the standard group (1·9 units) was significantly higher than in the attention and hypnosis groups (0·8 and 0·9 units, respectively). One hypnosis patient became haemodynamically unstable compared with ten attention patients (p=0·0041), and 12 standard patients (p=0·0009). Procedure times were significantly shorter in the hypnosis group (61 min) than in the standard group (78 min, p=0·0016) with procedure duration of the attention group in between (67 min).

Interpretation Structured attention and self-hypnotic relaxation proved beneficial during invasive medical procedures. Hypnosis had more pronounced effects on pain and anxiety reduction, and is superior, in that it also improves haemodynamic stability.

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Introduction

Minimally invasive, image-guided, percutaneous medical procedures increasingly replace open surgery. Technical refinement minimises tissue injury and largely obviates the need for general anaesthesia, but patients may still experience distress, which can tax the coping mechanisms of even well-functioning individuals.[1] Most physicians rely on intravenous conscious sedation with narcotics and sedatives to manage pain and anxiety.[2] These drugs, however, can induce cardiovascular depression, hypoxia, apnoea, unconsciousness, and, rarely, death, even in dosages usually well tolerated.[3,4] The operator typically has to weigh the risks of medically induced oversedation against the risks of uncontrolled discomfort and restlessness. An approach that provides comfort while reducing or eliminating the need for intravenous drugs is, therefore, highly desirable.

Biobehavioural "non-pharmacological" analgesia in the form of imagery, relaxation training, and hypnosis has been used successfully to treat procedure pain.[5–10] Clinical practice guidelines for acute pain management, published by the US Public Health Service, mention relaxation exercises and cognitive approaches, but do not elaborate.[2] Behavioural methods still need testing in larger clinical studies. To address this need, we designed a prospective randomised trial comparing the standard approach of intravenous conscious sedation alone with the adjunctive use of two behavioural non-pharmacological interventions: structured attention and self-hypnotic relaxation. We tested the hypothesis that adjunctive non-pharmacological analgesia would reduce patients' perceived pain and anxiety during interventional radiological procedures, reduce the amount of intravenous conscious sedation needed and make the procedure safer. Since operating teams (and hospital administrators) are very sensitive to factors that could prolong the patient's stay in the procedure room, we also assessed how non-pharmacological analgesia adjuncts affect procedure time.

Methods

Selection and randomisation of patients

The study was approved by the Institutional Board for Human Subjects Review. Eligible individuals were adults referred for percutaneous transcatheter diagnostic and therapeutic peripheral vascular and renal interventions, who were able and willing to give written informed consent. Exclusion criteria were severe chronic obstructive pulmonary disease, psychosis, intolerance of midazolam or fentanyl, pregnancy, inability to hear or understand English. After one of the operators had obtained informed consent for the planned invasive medical procedure, a research assistant asked the patient to participate in a research study to assess whether a relaxation exercise would enhance comfort during invasive procedures. Patients were told that the chance of having this relaxation exercise would be one in three, and that, irrespective of whether they would have this relaxation exercise or not, they would have access to as much medication for comfort as they wanted within safe limits. Consenting patients were then screened

Characteristic	Standard group (n=79)	Attention group (n=80)	Hypnosis group (n=82)
Age*	57 (18–92)	57 (18–84)	54 (19–82)
Weight (kg)*	74 (44–118)	80 (40–143)	80 (45–147)
Male/female	36/43	40/40	38/44
Ethnicity			
White	74	75	78
Black	5	5	3
Native American	0	0	1
Procedure			
Arterial	48	55	51
Venous	19	17	17
Nephrostomy	12	8	14
Disease category			
1	24	34	25
2	41	37	44
3	12	8	10
4	2	1	3
Anaesthesia class (mean)	2·24	2·22	2·24
Previous procedures*	4 (0–17)	4 (0–18)	4 (0–47)
Mean baseline pain	2·1	1·8	1·9
Mean baseline anxiety	3·5	3·8	3·8

Disease categories: 1=benign, no threat to limb or life; 2=benign, threat to limb or organ, no threat to life; 3=malignant, 4=acutely life-threatening. Anaesthesia class=American Society of Anesthesiologists Physical Status Classification: 1=healthy patient, 2=mild systemic disease, 3=severe systemic disease, 4=threat to life.
* Median (range).

Table 1: **Patient characteristics**

with the Mini Mental-State Exam.[11] If they passed, patients were randomly assigned to received standard treatment ("standard group"), structured attention ("attention group"), or the self-hypnotic relaxation ("hypnosis group").

Random numbers generated a sequence of group assignments for consecutive patients. Group assignments were contained on a card in a sealed envelope. Envelopes were not opened until the patients were about to undergo surgery. Group attribution was based on the intent to treat so that a patient assigned to a group remained in that group irrespective of their reaction to the test treatments.

Test treatments

All test treatments were done during surgery. Standard-group patients received care typical for the institution; they were attended to by the department's special-procedure nurses, who were instructed to behave naturally, do their best to comfort the patient, but to abstain from induction of imagery and hypnosis. In the attention group, an additional provider displayed standardised structured attentive behaviour. In the hypnosis group, the additional provider displayed the same structured attention as in the attention group and in addition gave standardised guidance to self-hypnotic relaxation. The additional provider wore scrubs like the regular team members and, throughout the procedure, sat close to the patient's head separated from the imaging tower and operators by a mobile lead-glass shield. The surgical team worked on the opposite side of the imaging tower and behind another ceiling-mounted lead-glass shield, and could not hear what the provider said to the patient. There were no visual clues that would have permitted the operating team to distinguish between attention and hypnosis conditions.

Structured attentive behaviour included eight key components and guidance to self-hypnotic relaxation an additional three. These 11 key components were standardised in a treatment manual.[12] The components were: matching the patients' verbal and non-verbal communication patterns; attentive listening; provision of the perception of control ("Let us know at any time what we can do for you".); swift response to patient's requests; encouragement; use of emotionally neutral descriptors (such as "What are you experiencing?", focus on a sensation of fullness, numbness, coolness, or warmth when painful stimuli were imminent); avoidance of negatively loaded suggestions ("How bad is your pain?", "You will feel a sting and burn now"); reading a standardised hypnotic induction script; addressing anxiety and worries according to the script, if needed. For the first 29 hypnosis patients, a script was used that included progressive muscle relaxation and having patients count backwards from 100. Because procedure interruptions, particularly at the time of counting, made it awkward for the providers to restore the patient's state of concentration, we developed a script[12] that allowed a rapid restoration of a focused state with ease. It was used for the final 53 hypnosis patients. Patients were instructed to roll their eyes upwards, close their eyes, breathe deeply, and concentrate on a sensation of floating. Self-generated imagery was used to help patients focus on a safe and pleasant experience in this relaxed state.

Training of the providers was done anew to reflect what an average competent healthcare worker could do with specific training, not what experts in the field could achieve. Four providers (a nurse, two medical students, and a psychology graduate student) were trained in the structured attention and hypnosis interventions by 24 h classroom instruction and roleplay, study of the treatment manual and video, supervised clinical practice, and a second workshop lasting 8 h. Interactions with patients were videotaped and used for feedback. The trainees did not participate in the study until they were able to execute reliably all of the key components. Psychologists and physicians supervised throughout the training and study.

Fidelity of treatment administration

Our procedure followed recommendations by Moncher and Prinz[13] for achieving and monitoring fidelity of treatment administration. A standardised manual defined prescribed and proscribed techniques for each of the three treatments. Training in the intervention techniques was given to all providers. Adherence to the treatment protocol was ensured by analysis of videotaped sessions, consistent with previous research in health-care settings[6] and with recommendations by reviewers in the field.[14–16] All interventional procedures were videotaped and 55 (23%) tapes were randomly selected and rated for adherence. Two research assistants who were not otherwise involved in the study independently rated the videotapes with an inter-rater reliability of the manipulation check[17] of 0·81. Analysis of videotapes has been shown to be successful for assessing treatment fidelity.[13]

Pain, anxiety, and drug use

Pain and anxiety were assessed by self-certification on a scale of 0–10 before surgery and every 15 min during it. Since dimmed lights and immobilisation of patients in the radiography equipment made use of visual scales cumbersome, we used verbal scales with 0=no pain and 10=worst pain imaginable, and 0=no anxiety and 10=terrified. Such verbal pain scales have been validated for clinical research.[18,19] Reliability and validity of the verbally-administered anxiety rating has been shown previously.[20]

To reduce the possibility of unblinded experimenter bias and to ensure that patients in the three treatment groups had the same access to drugs, patient-controlled analgesia/sedation (PCA) was used. PCA is well suited for acute pain management during and after medical procedures and is felt to enhance comfort while providing patients with a means of control.[21,22] In a pilot trial before this study, use of a PCA pump was tested as a means of further blinding, but was found to be potentially hazardous. Drug-induced cardiorespiratory emergencies are treated differently from those of other origins, and rapid knowledge of the drug history becomes important. Entering the recording mechanism of a PCA pump, however, can cause undue delay. Therefore, patients were given a button to press to alert the attending nurse, rather than a machine, to deliver drugs through an indwelling intravenous access. The dose regimen was chosen within the standard of care for interventional procedures[2,23] as 0·5 mg of midazolam plus 25 μg of fentanyl per request up to four times with a lockout time of 5 min, then with a lockout time of 15 min. Medication was withheld during the lockout times and if systolic blood pressure was below 89 mm Hg, oxygen saturation fell below 89%, or the patient developed slurred speech or became difficult to arouse. In rare cases, fentanyl and midazolam were administered without the patient's request for reasons of safety, such as when systolic blood pressure exceeded 180 mm Hg and did not normalise after 20 mg

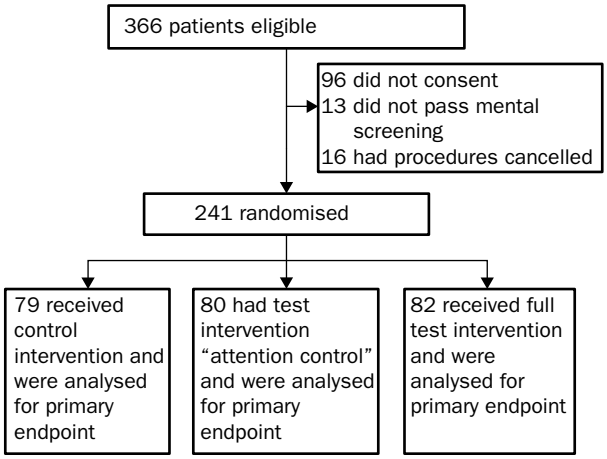

Figure 1: **Trial profile**

nifedipine, or if the patient was spontaneously distressed. Rules for overriding patient-determined analgesia were defined and agreed upon by the study and procedure personnel before the study. Periodic reviews found no deviations from the PCA protocol. Drug use was calculated in units of 1 mg of midazolam and 50 μg of fentanyl.

Procedural safety

Patients were monitored by ECG and pulse oximetry continuously during and after the procedure, and by automated blood-pressure measurements at least every 10 min during the procedure, and at least every 15 min during recovery. Haemodynamic instability was defined as any cardiovascular reaction that needed treatment or interruption of the procedure. Adverse effects in each of the three treatment groups were counted and included: oxygen desaturation less than 89%, need for placing oxygen tubing, prolonged hypoxaemia; haemodynamic instabilities such as prolonged new-onset bradycardia, new-onset hypertension, hypotension, or cardiac arrhythmia; rebleeding from puncture sites; oversedation with somnolence, unresponsiveness, disorientation; vomiting; patient behaviour prone to distract the operators such as crying, sobbing, talking to the operator, complaining loudly, and grabbing personnel.

Patients

The study was done over 11 months in the interventional radiology division of a single university medical centre with a mix of about 55% inpatients and 45% day patients. 336 consecutive patients, who presented during the regular working hours of the research assistant, were invited to enrol in this study. 66 declined to participate. Among the 270 consenting patients, 13 did not pass the Mini Mental-State Exam and 16 had their procedures cancelled. The study thus comprised 241 patients. Ages ranged from 18 to 92 years (median 56 years); 114/241 (47%) were men. Randomisation resulted in homogeneous groups of patients; there were no significant differences among the three groups in key characteristics including baseline pain and anxiety levels, type and technical complexity of procedures, disease status, and anaesthesia class (table 1). No patient withdrew from the study during the time of observation.

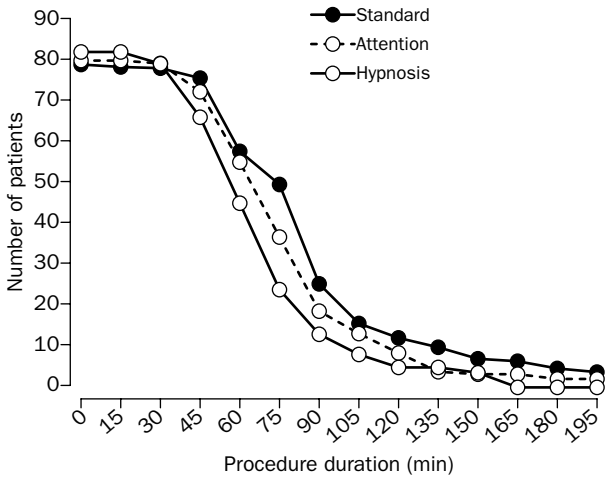

Figure 2: **Number of patients remaining in procedure as function of procedure-time interval for each group**

Statistical analysis

Effects of treatment on total units of drugs requested and administered, and on total procedure duration were assessed by univariate ANOVA with a between-patient factor for treatment group (standard, attention, hypnosis).[24] Before analysis, logarithmic transformations were applied to remove skewness from the data (ln[x+1], or ln[x] if x could not be 0); however, all results were presented in terms of the original scales.[24] Tukey tests were done to determine the pairs of treatment means that were significantly different from one another.[24]

The repeated-measures analysis of pain responses was designed to characterise and compare trends in pain ratings for the three treatment conditions over time.[25,26] The analysis used reports from as many as 13 successive 15 min intervals from 241 patients; the average number of reports from patients was 4·7 (median 3). The dependent variable for this analysis was ln(pain score+1) to correct skewness; residuals appeared normally distributed and no outliers were identified. For descriptive flexibility, the statistical model included separate parameters for intercepts, linear-order and higher-order trends. These latter quadratic and cubic trend components were not significant and were excluded from the model reported here. Correlations among residuals differed according to the time between observations, declining with increasing separation and reaching negligible levels after six intervals; there was a slight decrease in error variability in later intervals, but not enough to model. These linear mixed models were estimated by restricted maximum likelihood in BMDP, version 5, which provides unbiased estimates of the intercepts and slopes;[27] comparisons among slopes were done by two-tailed Wald statistics. A similar analysis was done for anxiety.

The frequencies of eight types of adverse effects in the three treatment groups were compared pairwise. One-tailed Fisher exact tests[28] tested the predictions that adverse effects would be more frequent in the standard group than either the attention or hypnosis group and more frequent in the attention than hypnosis group.

Since there were no differences in the outcomes for patients who had hypnosis script I and and those who had script II, the results are given for the entire hypnosis group.

Results

The trial profile is shown in figure 1. Figure 2 presents the number of patients remaining in their procedure as a function of duration (15-min intervals). The figure suggests procedures in the hypnosis group needed less time than procedures in the attention group, which in turn needed less time than those in the standard group. ANOVA confirmed the difference in groups' means (F_{2238}=6·60, p=0·0016). Average procedure duration was significantly shorter in the hypnosis group than in the standard group (61 *vs* 78 min). Procedure duration for the attention group was between, but not significantly different from, that of the other two groups (mean=67 min).

Groups differed from respect to medication received (F_{2238}=12·49, p<0·0001). Patients in the standard group had significantly higher drug use (1·8 drug units requested, 1·9 drug units received) than those in the attention group (0·8 units requested and received) and in the hypnosis group (0·9 units requested and received). Drug deliveries

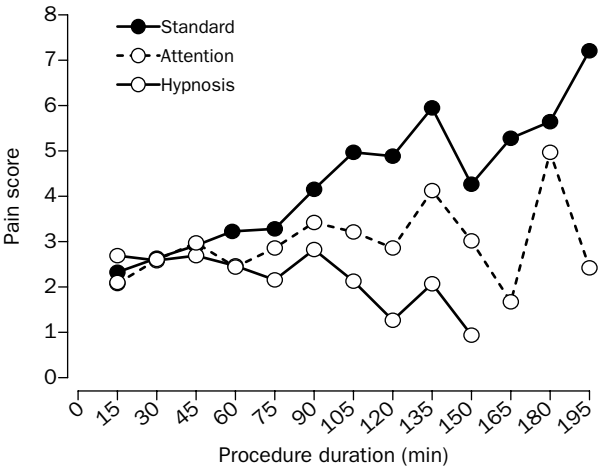

Figure 3: **Average pain score as a function of procedure-time interval for each group**

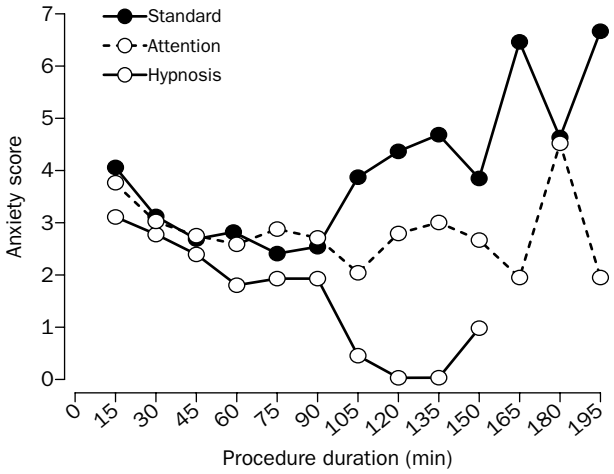

Figure 4: **Average anxiety score as a function of procedure-time interval for each group**

exceeded requests in ten patients (total 14 drug units) in the standard group, eight patients (total 9·5 drug units) in the attention group, and three patients (total 2 drug units) in the hypnosis groups. Drug deliveries were fewer than requested in five patients (6·5 drug units) in the standard group, in none in the attention group, and in one patient (3 drug units) in the hypnosis group.

Figures 3 and 4 present the average pain and anxiety scores as a function of procedure duration. Initially and for several 15-min periods, treatment groups did not differ in their levels of pain and anxiety. Subsequently, differences emerged with succeeding intervals. After an hour, absolute pain and anxiety were highest in the standard group, intermediate in the attention group, and lowest in the hypnosis group, and these relative positions stayed the same. All procedures for patients in the hypnosis group were completed by the tenth interval where that curve ends; the curves for the other conditions become somewhat erratic in the final intervals owing to the small number of cases (figure 2).

The repeated measures analysis of pain (raw data shown in figure 3) showed that pain increased linearly with procedure time in the standard group (slope=0·09 increase in pain score per 15 min, p<0·0001) and in the attention group (slope=0·04, p=0·0425, but not in the hypnosis group (slope=−0·03, p=0·234, a decrease in pain score over time, but not significantly different from 0, and hence interpreted as no change in pain over time, or flat). The flat trend of predicted pain as a function of procedure duration in the hypnosis group was significantly less than the positive trends in the standard (p<0·0001) and attention groups (p=0·0259). The difference in the trends of predicted pain as a function of procedure duration between the attention and standard group was not significant (p=0·0681).

The repeated measures analysis of anxiety (raw data in figure 4) showed that anxiety decreased linearly with procedure duration in all three groups: slopes were −0·04 in the standard group (p=0·0013), −0·07 in the attention group (p<0·0001), and −0·11 in the hypnosis group (p<0·0001). The difference in slope as compared with the standard group was significant for the hypnosis group (p=0·0022), and showed a trend towards, but did not reach significance for the attention group (p=0·0804). Adverse effects are listed in table 2.

Discussion

Non-pharmacological adjuncts have a positive effect on patients' comfort levels compared with standard conditions despite the use of half the analgesic and anti-anxiety medication. The trend towards less pain and anxiety over time, found with structured attention, reached significance with the addition of hypnosis. Whether less anxiety lessened the pain or vice versa, or whether anxiety and pain experience responded individually or interactively to the non-pharmacological intervention, remains unclear.

Pain perception increased with procedure time under standard care conditions. Similarly, Schutz and colleagues identified length of procedure as a negative predictor of satisfaction with pain management in a group of patients undergoing colonoscopy with intravenous conscious sedation.[29] These findings are consistent with laboratory research showing that exposure to acute pain makes individuals more attentive to external cues, such that they

Event	Standard group (n=79)	Attention group (n=80)	Hypnosis group (n=82)	Fisher's exact test S>A	Fisher's exact test S>H	Fisher's exact test A>H
Oxygen desaturation						
At least one occurrence	21	4	8	0·0001*	0·0047	0·1986
Oxygen tubing placed	17	5	6	0·0047	0·0088	0·5172
Prolonged hypoxaemia	6	2	1	..	..	..
Haemodynamic instability	12	10	1	0·3970	0·0009*	0·0041
Bleeding from puncture site	4	3	0	..	..	..
Oversedation	4	0	1	..	..	..
Distracting behaviour	10	10	4	0·5824	0·0697	0·0731
Vomiting	2	2	1	..	..	..

Admissions were due in one case to haemodynamic instability, and in one case to mental status change (somnolence). All five patients with mental status changes had received intravenous medication (one, four, four, five, and eight drug deliveries, respectively). S=Standard; A=Attention; H=Hypnosis.
*p<0·05/24=0·0021.

Table 2: **Adverse events**

report increasing pain over time even in the absence of a painful stimulus.[30] Pain scores in the standard group increased while anxiety scores decreased from baseline over time. This further complicates speculation about the impact of anxiety reduction on pain perception.[31]

Lower use of analgesics and anti-anxiety medication with adjunctive hypnosis compared with a control condition was also reported in clinical studies in which physicians, not the patients, controlled intravenous conscious sedation during invasive medical procedures.[6,8,9,32]

Reduced drug use in the attention and hypnosis groups resulted in a strong trend towards fewer overall and severe episodes of oxygen desaturation (significant for the comparison of standard and attention groups); only in the hypnosis group were there fewer episodes of haemodynamic instability. Thus, hypnosis has beneficial effects that cannot be explained solely by reduced drug use. These findings confirm the results of smaller scale studies showing a reduction of drug use and improved haemodynamic stability when adjunct hypnosis was used during invasive medical procedures.[9,32]

Self-hypnotic relaxation saved 17 min of theatre time despite the time invested in the hypnotic induction compared with standard care. Structured attention alone showed a strong trend towards savings (11 min) that might have reached significance in a study with more patients. It is likely that these savings resulted from lower frequencies of events diverting the surgical team's attention. When we took into account prolonged hypoxaemia, haemodynamic instability, rebleeding, oversedation, and vomiting (table 2) as such distractions, 34 events were counted in the standard group, 22 in the attention group, and eight in the hypnosis group.

The additional provider in the attention and hypnosis groups might possibly have changed patients' demand characteristics, thus contributing to the lower self-reports of pain and anxiety and fewer drug requests. Demand characteristics alone, however, would not explain why self-hypnotic relaxation had more profound effects on pain and anxiety reduction than structured attention. In particular, the greater haemodynamic stability in the hypnosis group would be difficult to explain based on a biased response. Since drug deliveries were nearly identical in the attention and hypnosis groups, medication can be excluded as a confounding factor.

Contributors

The original hypothesis and concept of the study was generated by E Lang. The experimental plan was elaborated by E Lang, E Benotsch, Susan Lutgendorf, Kevin Berbaum, Henrietta Logan, and David Spiegel. The hypnotic intervention use in the study was formulated for the study needs by D Spiegel, E Lang, Lauri Fick, and Susan Lutgendorf. The components of the study pertaining to psychological parameters and adherence checks were designed and supervised by E Benotsch, S Lutgendorf, and H Logan. The intervention was applied by Lauri Fick and E Benotsch. E Lang and L Fick were responsible for patient recruitment. K Berbaum and M Berbaum did the statistical analyses and wrote the statistical components of the paper. All authors were involved in writing and reviewing the paper.

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