BMJ Open

Examining the effects of enhanced provider-patient communication on post-operative pain; Protocol of a Randomized Controlled Trial performed in daily clinical care

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015505
Article Type:	Protocol
Date Submitted by the Author:	09-Dec-2016
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Primary Subject Heading:	Communication
Secondary Subject Heading:	Anaesthesia
Keywords:	communication, plaebo-effects, Pain management < ANAESTHETICS, tonsillectomy, randomized controlled trial

Title page

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Word count: 4856
Number of Figures: 1
Number of Tables: 1
Number of References: 25

Key words: Communication, placebo-effects, pain management, tonsillectomy, randomized controlled trial

Abstract

Introduction: Placebo effects (true biopsychological effects not attributable to the active ingredients of medical technical interventions) can be attributed to several mechanisms, such as expectancy manipulation and empathy manipulation elicited by a provider's communication. So far, effects have primarily been shown in laboratory settings. The aim of this study is to determine the separate and combined effects of expectancy manipulation and empathy manipulation during pre- and post-operative tonsillectomy analgesia care on clinical adult patients' outcomes.

Methods and analysis: Using a two by two randomized controlled trial 128 adult tonsillectomy patients will be randomly assigned to one out of four conditions differing in the level of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced). Daycare ward nurses are trained to deliver the intervention, while patients are treated via the standard analgesia protocol and hospital routines. The primary outcome, perceived pain, is measured via hospital routine by a Numeric Rating Scale, and additional pre-, peri- and post-hospitalization questionnaires are completed (until day 3, i.e. 2 days after the operation). The manipulation is checked using audio-recordings of nurse-patient interactions.

Ethics and dissemination: Although communication is manipulated, the manipulations do not cross norms or values of acceptable behavior. Standard medical care is provided. The ethical committee of the UMC Utrecht and the local OLVG hospital committee approved the study. Results will be published via (inter)national peer-reviewed journals and a lay publication.

Registration details: NTR5994 (Dutch Trial Register)

Strengths:

- This study is a RCT on the (placebo) effects of communication on top of standard medical care, building the evidence-base of communication.

Limitations:

- The success of the intervention will depend on the ability of nurses to carry out the different communication styles successfully

INTRODUCTION

In clinical care, patients' outcomes are not only influenced by the active ingredients of drugs or other medical technical interventions, but also by the context in which care is delivered. Such biopsychosocial effects on patients' outcomes that are not attributable to the active ingredients of treatments or interventions are called 'non-specific' or 'placebo-effects'[1 2]. They are real and robust, occurring on top of natural history and regression to the mean[3], and can be observed alongside 'sham-treatments' as well as 'real treatments'.

Several mechanisms underlie the generation of placebo-effects on patient outcomes such as pain[4]. A well-understood mechanism is the manipulation of expectations. According to a recent systematic review of our research group, manipulating patients' expectations seems capable of influencing clinical patients' pain perceptions[5]. For example, the verbal suggestion that a drug is an active pain killer is more effective than receiving the same dosage medication without such a suggestion[6]. A less-well understood mechanism is the communication of empathy in health care professional-patient encounters. Only few scholars have pointed out the potential role of the professional-patient relationship in explaining placebo-effects[7-9]. In our systematic review, we found that empathy had a less strong effect on pain compared to expectations[5]; but studies used different empathy operationalization and empathy was often manipulated together with other elements of the clinical encounter, making it difficult to draw strong conclusions from empathy[5].

When looking at these mechanisms, it seems reasonable that health care professionals' communication can influence them, and can thus produce placebo-effects. Until recently, however, the entities of communication and placebo-effects have hardly been integrated[9]. Communication is traditionally associated with 'art, not science' and placebos with 'evidence-based medicine' in which their effects are typically ruled out by the study design of randomized controlled trials (RCTs).

The tide is changing. A landmark-study led by Kaptchuk et al 2008[8] found that placebo-acupuncture delivered with high outcome expectations and an empathic approach led to

statistically and clinically significant improvements in the functioning of patients with irritable bowel syndrome compared to placebo-acupuncture delivered without expectations and empathy. The distinct and combined effects of both mechanism, and the effects alongside an active treatment remain, however, unknown from this study.

Our research group has started to unravel the potential separate and combined effects of both expectancy manipulation and empathy manipulation in highly controlled settings. Using scripted video-vignettes and role-play studies, we found that expectancy mainly influences cognitive outcomes (e.g. expected treatment effect) and empathy mainly affective outcomes (e.g. anxiety). The largest positive effects were found when the two elements were combined and a physician raised high expectations meanwhile communicating in a warm, empathic manner[10] (van Osch et al, 2016, *submitted*). However, whether these distinct and combined effects also translate to the clinical setting, alongside an active intervention remains, as yet, an unanswered question.

Study objective

This study therefore aims to disentangle the role of communication in eliciting placebo-effects in the clinical setting within the context of standard medical care. More specifically, the objective is to determine the separate and combined effects of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced) during pre- and post-operative tonsillectomy analgesia care on clinical adult patients' outcomes (main outcome measure is pain perception). This will be studied using a 2 by 2 RCT design. By following this approach the evidence base on the effects of expressed outcome expectancy and conveyed empathy will be built in clinical care.

Accompanying the study objective, the goals of this study are in subsequent order:

1. To examine whether adult patients following tonsillectomy in the enhanced outcome expectancy condition will experience less pain (and other outcomes), compared to patients in the standard condition.

2. To examine whether adult patients following tonsillectomy in the enhanced empathy communication condition will experience less pain (and other outcomes) compared to patients in the standard empathy communication condition.
3. To examine the interaction effects of the different levels of outcome expectancy and empathy on adult patients' experiences of pain (and other outcomes).

METHODS AND ANALYSIS

Design and setting

A four-arm (2 by 2 design) single-blind randomized controlled trial will be conducted at the daycare nursing wards on two locations of a Dutch general hospital (OLVG Amsterdam), in which adult tonsillectomy patients are pre- and postoperatively monitored and treated by nurses. Patients will be randomly assigned to one out of 4 arms, which vary in the induction of expectations (standard vs enhanced), and (the level of) nurses' communication of empathy (standard vs enhanced). Depending on the patient's allocation, nurses will express a standard or enhanced outcome expectation of patients' pain, and provide care in a standard or enhanced empathic manner. See figure 1 for the study design. All patients will be treated according to the usual analgesic treatment protocol and daily routine care of the hospital. Recruitment started in August 2016 and will presumably continue until early 2017.

Patients

This study focusses on adult tonsillectomy patients. This population was carefully selected as it is a homogeneous population. These patients are young adults, generally aged 18-35, without complex comorbidity (ASA 1) and lack a history of chronic pain. Moreover, tonsillectomy is generally accepted as a strong confound nociceptive trigger resulting into high levels of postoperative pain that only lasts for a relatively short period of time (1-2 weeks).

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet the following criteria:

- Scheduled for tonsillectomy in day care
- ≥18 years of age
- Speaking and understanding of the Dutch language
- Having mental capacity

Exclusion criteria

A potential patient who meets the following criteria will be excluded from participation in this study:

At study start (during inclusion process):

- Not scheduled for tonsillectomy in day care
- <18 years of age
- Not speaking and understanding of the Dutch language
- Lacking mental capacity (cognitive decline, dementia)

During the course of the study:

- Patients who experience a post-operative bleeding will be excluded.
- The health care professionals involved and research team can decide to withdraw a patient from the study for urgent medical reasons (e.g. if patients are not discharged on the day of operation due to complications).

If a patient drops-out, data until exclusion will be included in the analyses unless the patient objects to this (this will be asked upon exclusion).

Sample size

The sample size calculation is based on the primary outcome, i.e. pain. This calculation is based on a previous similar study[6], in which an open versus hidden administration of analgesic showed a difference of 1.2 and a total variance of 2.18. Based on a power of .80 and alpha of .05, and including an interaction-effect (with a within variance of 1.92), this results in a needed sample size of 32 patients per arm and 4x32=128 patients in total.

Recruitment

The recruitment of patients occurs in several steps:

i) Patients are approached for the study while discussing the operation with their consulting ear nose and throat specialist (i.e. ENT doctor). All eligible and interested patients are provided with a Patient Information Folder (PIF) and informed consent form. The PIF omits specific study aims, but mentions that communication will be manipulated. It is stressed that participation is free of choice and will not affect usual medical care.

ii) During the pre-operative examination, which is mostly conducted within a few days of the ENT consultation, the anestheasiology clinician asks whether the patient is informed about the study. If not, they will provide them the PIF and consent form. They will ask whether the patient is interested in participation and whether the research team can call the patient to provide them with more information. This response is noted in the electronic record and transferred to the researchers via an (automated) email.

iii) The research team will call the patient, explain the study in more detail and ask the patient to return the informed consent form.

Patients who are already planned for surgery when the study opens (the normal time between ENT consultation and the operation is 6-8 weeks) will be called by involved health care practitioners (from the ENT/Anaesthesiology department). They are informed about the study via telephone. In case they are interested, their name and telephone number are transferred to the researchers. The researchers will call the patient, and send them an information letter and consent form which participants can return in case they are willing to participate.

Randomization

Upon providing informed consent patients are randomized using a random number generator (1:1:1:1: allocation rate). Assignments will be provided via sequentially numbered opaque sealed envelopes. A secretary not otherwise involved in the study will open the assignment envelopes.

After patients are randomized, the research team will inform the health care professionals about their inclusion. They will insert this information in the medical records of the hospital system (EPIC). Moreover, they will inform the day care administrators and key contact persons about the patients that are scheduled in the upcoming week or days and which condition they are randomized to. On the day of admission, the researchers will ensure that all appropriate systems (e.g. the ward lists and the hard copy patient records) are adequately signposted with the patients' condition. We will use color codes for this to avoid unblinding patients. Only one patient per room is included at any time point.

Intervention

The intervention consists of a (protocolled) communication manipulation on top of standard analgesic treatment. Nurses at the day care ward will incorporate an (protocolled) expectancy manipulation (standard versus enhanced) related to the effects of the pain medication and empathy manipulation (standard versus enhanced) into their communication. The communication intervention will be provided during patients' stay at the day care ward (pre- and post-operation, day 1, the daycare wards are open between 7AM-6PM and 6.45AM-7PM respectively), and during the nurses' telephone consultation with patients the day post-discharge (day 2).

All nurses will receive training to ensure their ability to perform the different communication manipulations. We will make use of a professional trainer and comprehensive training protocol including scripts (i.e. written examples), video-examples, and role-play. Moreover, posters are placed in the communal spaces for nurses with information about the study; e.g. examples of the manipulations and study procedures. Pocket cards with examples of the manipulations are provided.

Expectancy manipulation

In the standard condition nurses do not aim to create the expectation that the pain medication will work very well. They might use sentences such as "The medications attempt to reduce your pain ever so slightly", or "This is your pain medication".

In the enhanced condition nurses aim to create the expectation that the pain medication will work very well. They might use sentences such as: "The medications I am giving you now will lead to a strong decrease of your pain", or "This pain medication is known for working very well".

Empathy manipulation

In the standard condition nurses aim to create a neutral atmosphere which is standard. They will be trained to (amongst other behavior) keep standing when communicating with patients, react with standard empathy to patients' cues and concerns, not explore concerns in detail, to not express extra interest in the patient as a person, to not pay extra attention to not interrupting patients, and to not make extra eye contact.

In the enhanced condition, nurses aim to create an atmosphere, which is extra warm and extra friendly. They will be trained to (amongst other behavior) introduce themselves properly, sit while communicating with patients, react extra empathically to patients' cues and concerns (verbal and nonverbal) and take their concerns seriously, to show extra interest in the patient as a person, to not interrupt the patient, and to make adequate eye contact.

It should be noted that the communication manipulation does not cross important norms or values of acceptable behavior and that the psychological integrity of patients will not be harmed. An observational study among clinical postsurgical patients showed that nurse-patient interactions are often subject to interruptions related to other tasks e.g. searching for equipment, answering telephone calls, or being interrupted by other professionals[11]. The interruptions and nurses' attempts to address competing demands impact on the time and attention spent with patients. It can therefore be assumed that variations in communication are inherently due to clinical encounters. This was also confirmed by field observations conducted by the research team before study start. The aforementioned developed scripts/examples which are used in the training have been commented upon by nurses and researchers in a pilot study to ensure they are realistic

and do not trespass ethical boundaries and have been finalized in collaboration with involved clinicians.

Standardizing of communication

The communication patients receive from other clinicians involved during their hospitalization (e.g. from the OK team and recovery team) will be standardized as much as possible. Also the communication during the pre-operative ENT and Anaesthesiology visit will be standardized as much as possible. Involved health care professionals will be informed of the study aims and the importance to keep their communication neutral (if possible) (i.e. to not provide extra empathy or raise extra expectations about pain) for included patients. This is feasible, as the ENT and anesthesiology team are involved in the study, and it is uncommon for patients to ask about pain medication during their time at the OK recovery.

Blinding

Patients will be blinded to the specific study aims and treatment allocation.

The involved health care personnel cannot be blinded. All health care personnel involved will receive clear and specific instructions about informing and including patients to preserve experimental control. Besides, all interactions within the study between nurses and patients will be audio-recorded to evaluate the fidelity of the communication manipulation.

Study procedure

After receiving informed consent, the research team will send a baseline questionnaire to the patient. Completion of this questionnaire will be done at home and will take no more than 20 minutes. Post-surgery (at daycare, day 1) a short (5-minute) questionnaire is administered. As part of routine care, pre- and post- surgery, patients rate their level of pain. At day 2 (the day after discharge) patients will complete another questionnaire about their pain and medication use. At day 3 a last questionnaire will be completed which will take 20 minutes. Patients are given the choice between paper and pencil and online completion of questionnaires.

Moreover, the interactions between involved nurses and included patients will be recorded. Nurses will be provided with a portable audio-recording device with microphone. During every visit, the nurses will mention patient's identification number by means of reference, to protect patients' privacy. At day 4 (3 days after discharge) patients will receive a debriefing letter by postal mail which will inform them about the study aims and their assigned condition. If they wish to receive more information they can contact the research team.

Withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The health care professionals involved and research team can decide to withdraw a patient from the study for urgent medical reasons (e.g. a bleeding after operation). If a patient drops-out, the research team is informed of this. Patients will continue to receive standard medical care and communication.

Informed consent nurses

Nurses involved in the study will be asked to participate as participants using an information sheet and a consent form. They will be asked to complete the consent form and a questionnaire about their background characteristics. We will offer them, at study end, participation in a (accredited) communication training to thank them for their participation in this project.

Outcomes

Main study outcome:

- Pain perception/intensity

As part of routine care, during hospitalization and post-hospitalization patients' pain will be assessed on the basis of a Numeric Rating Scale (NRS) (0-10), ranging from 'no pain' to 'worst imaginable pain' [12 13]. Pain is rated preoperatively at daycare ward, at recovery, postoperatively at daycare ward. On study day 2, one day after discharge, daycare ward

nurses will contact the patients by telephone and again assess their pain. On top of this standard routine, pain is assessed at home on day 2 and day 3 (study end).

Secondary study outcome

In the patient questionnaires, the following secondary outcomes will be assessed:

- Pain expectations

Patients' pain expectations are measured using two items (both measured using a self-created VAS scale); i) Patients' pain expectations for the few days following the operation (VAS ranging from 'no pain' to 'the most intense pain imaginable', ranging from 0-10, adapted from Petersen et al., 2014[14]); ii) Patients' expectations of improvement in pain following receiving pain medication (VAS ranging from '0% improvement' (no improvement) to '100% improvement' (most improvement imaginable), adapted from the Credibility and Expectancy Questionnaire (CEQ)[15]. These questions will be assessed post-operatively (during hospitalization).

- Overall benefit of analgesia

The overall benefit of analgesia score (OBAS) will be assessed[16]. The OBAS is a multidimensional 7-item instrument in which patients indicate (on a 0-4 scale, ranging from 'not at all' to 'very much') the level of current pain and distress arising from several symptoms such as itch. The OBAS is measured post-hospitalization (at home) at day 2 and 3 (study end).

- Analgesic dosage

The total dosage of administered analgesics will be assessed during hospital stay and noted in the medical record. The total dosage of administered analgesic at home post-operation will be assessed at day 2 and 3 (study end) by asking patients to indicate which pain medication they use/have used.

- Analgesic request by a patient

Analgesic request will be assessed during hospital stay and noted in the medical record.

- Perceived empathy

Perceived empathy will be determined using the Consultation and Relational Empathy Measure (CARE)[17] in which the term 'doctor' is replaced with 'nurse' and 'consultation' is replaced with 'contact' (10 items, 1-5 scale ranging from 'poor' to 'excellent' (and 'not

relevant'), e.g. "How was the nurse at showing care and compassion"). Perceived empathy is measured at day 3 (study end).

- Perceived expectation

We will measure the extent to which participants thought nurses had induced the expectation that medication would be effective to decrease their pain. This will be assessed using a 1-item self-created VAS scale ('no effect at all' to 'a lot of effect', ranging from 0-10). Perceived expectation will be measured at day 3 (study end).

- State anxiety

Patients' level of anxiety will be measured by the Dutch 10-item State measure of the State-Trait Anxiety Inventory (STAI-State)[18](1-4 scale ranging 'not at all' to 'very much'). Patients' anxiety is assessed pre-hospitalization, and at day 3 (study end).

- Mood

Mood will be measured using the Positive and Negative Affect Schedule (PANAS)[19] (20-items, 1-5 scale ranging from 'not at all' to 'very much' e.g. "I am exited" or "I am upset"). Mood is measured pre-hospitalization, and at day 3 (study end).

- Satisfaction

Participants' satisfaction with the provided care by the nurses during daycare will be assessed using a 1-item self-created VAS scale ('not at all' to 'very much', 0-10 range). Satisfaction will be measured at day 3 (study end).

- General pain evaluation

Whether the pain following the operation has been better or worse than expected, will be measured using a 1-item self-created VAS scale (ranging from 'much worse than expected' to 'much better than expected', 0-10 range). Pain evaluation is measured at day 3 (study end).

- General evaluations regarding hospitalization

Patients' evaluations of their hospitalization are measured using two items i) How likely it is that the patient would recommend this hospital to other tonsillectomy patients (using an adapted item from the CQ Index[20] (0-10 scale 'would definitely not recommend' to 'would definitely recommend'); ii) Their overall rating of the quality of care provided by the hospital during hospitalization, using an adapted item from the CQ Index[20](0-10 scale, 'very poor care' to 'extremely good care'). This is measured at day 3 (study end) .

Other outcomes

The following background characteristics of patients are measured pre-hospitalization;

- Socio-demographics

E.g. date of birth, gender, marital status, education, ethnicity, societal position, and date of operation.

- Functional health status

Measured using the COOP-WONCA; 7-item scale assessing several health status elements, e.g. physical fitness, on a 1-5 scale ranging from ''not limited at all' to 'severely limited'[21 22].

- General experiences/expectations/attitudes medications

We will measure the extent to which patients generally i) benefit from, ii) have positive expectations towards the effect of, iii) have objections against taking medicines. This will be done using self-created VAS scales (ranging from 'not at all' to 'very much', 0-10 range).

- General reporting of pain

We will measure whether patients generally are inclined to report their pain using a self-created VAS scale (ranging from 'never' to 'always', 0-10 range)

- Attitudes towards operation

The extent to which participants i) are dreading, and ii) are afraid of the operation will be measured using two self-created VAS scales (ranging from 'not at all' to 'very much', 0-10 range).

In addition, we will measure:

- Data medical record

We will ask patients' permissions to access the medical record. We will routinely use medical background data (diagnosis, weight, prescribed medication) and analgesic information (as aforementioned). If needed, additional data will be screened for (e.g. in cases of outlier data the medical record might provide useful information).

Background measures for nurses

The following nurses' characteristics will be measured pre-hospitalization

- Socio-demographics

E.g. date of birth, gender, and type of nurse.

- Empathy personality trait:

We will measure nurses' empathic abilities using the Interactive Reactivity Index (IRI)[23]. The IRI consists of 28 items (e.g. "I often feel sorry for people who are less fortunate than me") which are scored on a 1-5 scale (ranging from 'describes me not at all' to 'describes me very well).

An overview of the measured outcomes at different time points is provided in Table 1.

Domain	Measure	Collected	Pre-hospitalization	Post-operation (at day care, day 1)	During hospitalization (pre-peri-post operative, day 1)	Post-hospitalization (at home, day 2)	Post-hospitalization/study end (at home, day 3)
Pain perception/ intensity	Standard hospital	Patient			x	x	x
Pain Expectations	Adapted VAS scale	Patient		x			
Overall benefit of analgesia	OBAS	Patient				x	x
Analgesic Dosage		medical record/patient			x	x	x
Analgesic Request		medical record			x		
Perceived empathy	CARE	Patient					x
Perceived expectation	Self-created VAS	Patient					x
Anxiety	State-anxiety (Stai state)	Patient	X				x
Mood	PANAS	Patient	X				x

Satisfaction	Self-created VAS scale	Patient					x
General pain evaluation	Self-created VAS Scale	Patient					x
General evaluation about hospitalization	Adapted CQ Index items	Patient					x
Socio demographics		Patient	X				
Functional health status	COOP-WONCA	Patient	X				
General Experiences/Expectations/Attitudes	Self-created VAS scales	Patient	X				
General reporting of pain	Self-created VAS scale	Patient	X				
Attitudes towards operation	Self-created VAS scale	Patient	X				
Data medical record	e.g. Diagnosis, weight, prescribed medication	Medical record	X		X		
Nurse – socio demographics		Nurse	X				
Nurse - empathy	IRI	Nurse	X				

Table 1 – Overview measured outcomes at different time points

Adherence to the communication manipulation protocol:

To verify the fidelity of the communication manipulation, the interaction between nurses and patients will be audio-recorded. The adherence will be verified by listening back to a random sample (10% of the sample) of audio-recorded visits and to determine the adherence to the protocol (as is comparably done by[8]). Two research assistants who are not otherwise involved in the study will independently evaluate the audio-recordings on adherence to the protocol.

Data analysis plan

All data will be analysed using STATA 13.0 with two-sided significance testing at p <.05. All available data from patients will be included in the analysis and missing data might be imputed. An intention to treat (ITT) analysis will be performed, thereby also examining selective attrition.

Primary outcomes

Descriptive statistics will be calculated for patients' reported pain intensity (main outcome measure) for the different time points during and post- hospitalization. Since our design consists of a 2 (expectancy: enhanced vs. standard) by 2 (empathy: enhanced vs. standard) design all outcomes will be analysed using either analyses of variance (if focussed on a specific time point) or multilevel repeated measures regression analyses (if focused on different time points which means that several ratings are included for one person). Both communication elements (i.e. expectancy and empathy) are dummy coded. Main effects and interaction effects will be explored. New insights gathered during the analysing process might be examined (if feasible).

Secondary outcomes

Descriptive statistics will be calculated for secondary outcome measures. The effect of our manipulated variables will be analysed using analyses of variance.

Other outcomes

Frequencies and means will be calculated for the demographics. The four groups will be checked on equality by using chi-squared tests or analyses of variance (ANOVA). If groups differ on specific variables, these variables might be used as control variables in the multilevel analysis.

Adherence to communication protocol

Data of the audio-recordings are observed by trained coders on adherence to the protocol to verify fidelity. First, 10% of the audio-recordings are independently checked on adherence to the protocol. For this purpose, the main features of the four conditions are described and rated when listening to the audio-recordings. Second, inter-rater reliability between the coders of the outcomes will be assessed by calculating Cohen's kappa. Values ranging between 0.21 and 0.41 are considered fair, values between 0.41 and 0.60 moderate and values greater than 0.61 are considered good (i.e. substantial/almost perfect). We consider values as reliable if Cohen's kappa is greater than 0.41[24 25].

ETHICS AND DISSEMINATION

Risks and burden for participants

All participating patients receive usual care with regard to surgery, analgesia and pre- and post-operative treatment. There are no risks associated with this clinical study. The communication manipulation will be provided on top of standard care and is designed in such a way that there will be no harmful effects for patients. Although practitioners' communication is deliberately manipulated and associated with both positive and less positive effects, the communication manipulation does not cross important norms or values of acceptable behavior nor will it affect the psychological integrity of patients. Variations in nurse-patient interactions occur naturally within clinical settings, justifying our approach. Moreover, although patients are informed about the study by their treating clinicians, informed consent will be gathered by the research team. The clinical and research team will stress that participation is voluntary and will not affect standard clinical care. Patients are always free to withdraw their participation in the study. Last, it

can be a burden for patients to complete a few additional questionnaires. We attempt to decrease the burden by using short questionnaires. Results, ultimately, will provide more insight into the effect of communication on patient outcomes.

Adverse and serious adverse events

All adverse events reported spontaneously by the patient or observed by the clinical or research team will be recorded. All serious adverse events will be reported to the ethical committee who has approved the study and the online database. This will be done within 15 days (7 days for the first reporting if an SAE resulted in death or was life threatening). Due to the content of the intervention, we do not expect SAE's to happen. The research team, supported by the clinical team will regularly check the medical records for the occurrence of any adverse events and serious adverse events.

Confidentiality

Patients' data will be anonymized using an identification number. This code will be safeguarded by an independent contact person at NIVEL and this information will be kept on a protected drive using a protected file independently of the research data. The researchers involved in this study will have access to the research data. The audio-recordings will not be destroyed after the research, but will be added to the NIVEL audio/video database. At present, NIVEL has a database of around 18,000 (digitized) video-recorded and audio-recorded healthcare visits and a well-equipped infrastructure with computerized observation units.

Ethical approval

This study has received ethical approval from the ethical committee of the UMC Utrecht (number 16/144, NL55225.041) and the institutional review board of the participating hospital (number WO 16.506). All amendments will be notified to the ethical committee that gave a favorable opinion.

Trial registration

The study is registered at the Dutch Trial Register (Registration number NTR5994) which is the Primary Registry in the Netherlands.

Dissemination

At the minimum, the results of this study will be published in international peer-reviewed scientific journals. A lay summary of the results will be published as well and send to participants if they are interested.

DISCUSSION

This innovative study aims to manipulate communication to determine how expectations and empathy can lead to placebo-effects and help minimize patients' post-operative pain (among other outcomes). The results can help to shed more light on how communication can be used alongside medical care to enhance patients' outcomes for the better.

That being said, manipulating communication in clinical care poses methodological, ethical and logistical challenges. The success of the study will depend on the success of the manipulation. To ensure communication differs between the various groups, and to avoid contamination, all nurses have been trained and the research team is available (on and offsite) for questions, practice, and feedback. On most intervention days, a member of the research team is present at the daycare ward. This is much appreciated by nurses, and ensures that the appropriate manipulation is often practiced before a patient is admitted. Throughout an intervention day, the signposting of all systems (ward lists/hardcopy patient records) and the appropriate pocket cards with examples also serve as a constant reminder of the group allocation. The success of the manipulation is checked using the audio-recordings of nursing interactions. While varying communication, the ethical boundaries of not providing any suboptimal communication are and will be clearly adhered to and are stressed in contacts with involved health care professionals. Last, patients come in contact with many clinicians before and during hospitalization. Informing all clinicians and ensuring all but the daycare ward nurses will standardize their communication is crucial to ensure causal effects of the manipulated communication can be determined. Therefore, both the research and clinical team involved have ensured

many contact moments with clinicians to personally inform them about the study and appropriate information material has been circulated at study start.

Despite these challenges, we believe this study is of utmost importance to bring the field of communication and pain research forward. Without conducting controlled studies into the effect of communication, communication will always remain a soft-sided add-on. We hope this study and detailed protocol will provide an impetus for further work in this important area turning communication from 'art to science'.

Authors' contributions

JB is the Chief Investigator.

JB developed the initial concept of the study, supported by SvD and LV

LV, JB, SvD, and SI led on the protocol development, while all authors provided input for the trial design and protocol.

MG, BT, and GvD led on the standardization of hospital routine, pain protocol and medical content.

LV and SI (as of August 2016 also supported by MK) lead on the daily management of the trial, supported by MG, BT, GvD, SvD and JB

All authors have read, contributed and approved the final manuscript.

Acknowledgements

We thank Peter Spreeuwenberg for his help with the data analysis plan and power calculation. We thank the clinicians from the daycare ward, recovery and operation room, ENT and Anesthesia department for their help in facilitating the study logistics.

Funding

The study is funded by the Spinoza Prize from the Dutch Research Council awarded to Prof. dr. Jozien M. Bensing.

The funder had no role in the study design and decision to submit the report for publication. The funder will have no role in the collection, management, analysis and interpretation of data or writing and publication of future publications.

Competing interest

None declared

Legends

Figure 1. Study design.

Reference list

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Figure 1. Study design.

		Expectancy	
		enhanced	standard
Empathy	enhanced	Group 1	Group 2
	standard	Group 3	Group 4

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_NA-registered at the Dutch Trial Register _
Protocol version	3	Date and version identifier	_ NA, Not in article, we currently use protocol V4.0 16-08-2016__
Funding	4	Sources and types of financial, material, and other support	__23_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1-2_____
	5b	Name and contact information for the trial sponsor	___23_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__23_____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____NA, a collaboration agreement between the hospital (OLVG) and NIVEL has been created_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__4-6_____
	6b	Explanation for choice of comparators	__4-6_____
Objectives	7	Specific objectives or hypotheses	__5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_6-7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-11_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_12,7_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_9,11,19,20____

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__20,6,_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_12-20_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_8,9,11,12-19___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___7_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__11, 9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__12_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_11-19_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__21,7_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_21_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_19_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_20_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_19_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_NA, no DMC has been set up_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__NA, no interim analyses are performed_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___21_____

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__NA_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___21_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__21_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___8,12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__21_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__24_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___21_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___12_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__22_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__NA – ICMJE criteria will be used___

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not provided in article____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Examining the effects of enhanced provider-patient communication on post-operative tonsillectomy pain; Protocol of a Randomized Controlled Trial performed by nurses in daily clinical care.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015505.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Aug-2017
Complete List of Authors:	van Vliet, Liesbeth; Nederlands Instituut voor Onderzoek van de Gezondheidszorg van Dulmen, Sandra; NIVEL; Radboud University Medical Center , Department of Primary and Community Care Thiel , B; Onze Lieve Vrouwe Gasthuis, Department of Aneasthesiology van Deelen, G; Onze Lieve Vrouwe Gasthuis, Department of ENT Immerzeel, S; Nederlands Instituut voor Onderzoek van de Gezondheidszorg, Communication Godfried, M; Onze Lieve Vrouwe Gasthuis, Department of Anesthesiology Bensing, Jozien; NIVEL, Netherlands Institute for Health Services Res
Primary Subject Heading:	Communication
Secondary Subject Heading:	Anaesthesia
Keywords:	communication, plaebo-effects, Pain management < ANAESTHETICS, tonsillectomy, randomized controlled trial

Title page

Title: Examining the effects of enhanced provider-patient communication on post-operative tonsillectomy pain; Protocol of a Randomized Controlled Trial performed by nurses in daily clinical care.

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Word count: 5317
Number of Figures: 1
Number of Tables: 1
Number of References: 28

Key words: Communication, placebo-effects, pain management, tonsillectomy, randomized controlled trial

Abstract

Introduction: Placebo effects (true biopsychological effects not attributable to the active ingredients of medical technical interventions) can be attributed to several mechanisms, such as expectancy manipulation and empathy manipulation elicited by a provider's communication. So far, effects have primarily been shown in laboratory settings. The aim of this study is to determine the separate and combined effects of expectancy manipulation and empathy manipulation during pre- and post-operative tonsillectomy analgesia care on clinical adult patients' outcomes.

Methods and analysis: Using a two by two randomized controlled trial 128 adult tonsillectomy patients will be randomly assigned to one out of four conditions differing in the level of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced). Daycare ward nurses are trained to deliver the intervention, while patients are treated via the standard analgesia protocol and hospital routines. The primary outcome, perceived pain, is measured via hospital routine by a Numeric Rating Scale, and additional pre-, peri- and post-hospitalization questionnaires are completed (until day 3, i.e. 2 days after the operation). The manipulation is checked using audio-recordings of nurse-patient interactions.

Ethics and dissemination: Although communication is manipulated, the manipulations do not cross norms or values of acceptable behavior. Standard medical care is provided. The ethical committee of the UMC Utrecht and the local OLVG hospital committee approved the study. Results will be published via (inter)national peer-reviewed journals and a lay publication.

Registration details: NTR5994 (Dutch Trial Register)

Strengths:

- This study is a RCT on the (placebo) effects of communication on top of standard medical care, building the evidence-base of communication.

Limitations:

- The success of the intervention will depend on the ability of nurses to carry out the different communication styles successfully.

INTRODUCTION

In clinical care, patients' outcomes are not only influenced by the active ingredients of drugs or other medical technical interventions, but also by the context in which care is delivered. Such biopsychosocial effects on patients' outcomes that are not attributable to the active ingredients of treatments or interventions are called 'non-specific' or 'placebo-effects'[1 2]. They are real and robust, occurring on top of natural history and regression to the mean[3], and can be observed alongside 'sham-treatments' as well as 'real treatments'[4].

Several mechanisms underlie the generation of placebo-effects on patient outcomes such as pain[5]. A well-understood mechanism is the manipulation of expectations. According to a recent systematic review of our research group, manipulating patients' expectations seems capable of influencing clinical patients' pain perceptions[6]. For example, the verbal suggestion that a drug is an active pain killer is more effective than receiving the same dosage medication without such a suggestion[7]. Manipulating expectations also contribute to the recent described positive effects of open-label placebos (inert treatments being described as such)[8]. A less-well understood mechanism is the communication of empathy in health care professional-patient encounters. Only few scholars have pointed out the potential role of the professional-patient relationship in explaining placebo-effects[9-11]. In our systematic review, we found that empathy had a less strong effect on pain compared to expectations[6]; but studies used different empathy operationalization and empathy was often manipulated together with other elements of the clinical encounter, making it difficult to draw strong conclusions from empathy[6].

When looking at these mechanisms, it seems reasonable that health care professionals' communication can influence them, and can thus produce placebo-effects. Until recently, however, the entities of communication and placebo-effects have hardly been integrated[11]. Communication is traditionally associated with 'art, not science' and placebos with 'evidence-based medicine' in which their effects are typically ruled out by the study design of randomized controlled trials (RCTs).

The tide is changing. A landmark-study led by Kaptchuk et al 2008[10] found that placebo-acupuncture delivered with high outcome expectations and an empathic approach led to statistically and clinically significant improvements in the functioning of patients with irritable bowel syndrome compared to placebo-acupuncture delivered without expectations and empathy. The distinct and combined effects of both mechanism, and the effects alongside an active treatment remain, however, unknown from this study.

Our research group has started to unravel the potential separate and combined effects of both expectancy manipulation and empathy manipulation in highly controlled settings. Using scripted video-vignettes and role-play studies, we found that expectancy mainly influences cognitive outcomes (e.g. expected treatment effect) and empathy mainly affective outcomes (e.g. anxiety). The largest positive effects were found when the two elements were combined and a physician raised high expectations meanwhile communicating in a warm, empathic manner[12 13]. However, whether these distinct and combined effects also translate to the clinical setting, alongside an active intervention remains, as yet, an unanswered question. Answering this question is important, as it will provide insight into how specific communication elements can influence specific health outcomes.

Study objective

This study therefore aims to disentangle the role of communication in eliciting placebo-effects in the clinical setting within the context of standard medical care. More specifically, the objective is to determine the separate and combined effects of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced) during pre- and post-operative tonsillectomy analgesia care on clinical adult patients' outcomes (main outcome measure is pain perception). This will be studied using a 2 by 2 RCT design. By following this approach the evidence base on the effects of expressed outcome expectancy and conveyed empathy will be built in clinical care.

Accompanying the study objective, the goals of this study are in subsequent order:

1. To examine whether adult patients following tonsillectomy in the enhanced outcome expectancy condition will experience less pain (and other outcomes), compared to patients in the standard condition.
2. To examine whether adult patients following tonsillectomy in the enhanced empathy communication condition will experience less pain (and other outcomes) compared to patients in the standard empathy communication condition.
3. To examine the interaction effects of the different levels of outcome expectancy and empathy on adult patients' experiences of pain (and other outcomes).

METHODS AND ANALYSIS

Design and setting

A four-arm (2 by 2 design) single-blind randomized controlled trial will be conducted at the daycare nursing wards on two locations of a Dutch general hospital (OLVG Amsterdam), in which adult tonsillectomy patients are pre- and postoperatively monitored and treated by nurses. Patients will be randomly assigned to one out of 4 arms, which vary in the induction of expectations (standard vs enhanced), and (the level of) nurses' communication of empathy (standard vs enhanced). Depending on the patient's allocation, nurses will express a standard or enhanced outcome expectation of patients' pain, and provide care in a standard or enhanced empathic manner. See figure 1 for the study design. All patients will be treated according to the usual analgesic treatment protocol and daily routine care of the hospital. Recruitment started in August 2016 and will presumably continue until early 2018.

Patients

This study focuses on adult tonsillectomy patients. This population was carefully selected as it is a homogeneous population. These patients are young adults, generally aged 18-35, without complex comorbidity (ASA 1) and lack a history of chronic pain. Moreover, tonsillectomy is generally accepted as a strong confound nociceptive trigger resulting into high levels of postoperative pain that only lasts for a relatively short period of time (1-2 weeks).

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet the following criteria:

- Scheduled for tonsillectomy in daycare
- ≥18 years of age
- Speaking and understanding of the Dutch language
- Having mental capacity

Exclusion criteria

A potential patient who meets the following criteria will be excluded from participation in this study:

At study start (during inclusion process):

- Not scheduled for tonsillectomy in day care
- <18 years of age
- Not speaking and understanding of the Dutch language
- Lacking mental capacity (cognitive decline, dementia)

During the course of the study:

- Patients who experience a post-operative bleeding will be excluded.
- The health care professionals involved and research team can decide to withdraw a patient from the study for urgent medical reasons (e.g. if patients are not discharged on the day of operation due to complications).

If a patient drops-out, data until exclusion will be included in the analyses unless the patient objects to this (this will be asked upon exclusion).

Sample size

The sample size calculation is based on the primary outcome, i.e. pain. This calculation is based on a previous similar study[7], in which an open versus hidden administration of analgesic showed a difference of 1.2 and a total variance of 2.18. Based on a power of .80

and alpha of .05, and including an interaction-effect (with a within variance of 1.92), this results in a needed sample size of 32 patients per arm and 4x32=128 patients in total.

Recruitment

The recruitment of patients occurs in several steps:

i) Patients are approached for the study while discussing the operation with their consulting ear nose and throat specialist (i.e. ENT doctor). All eligible and interested patients are provided with a Patient Information Folder (PIF) and informed consent form. The PIF omits specific study aims, but mentions that communication will be manipulated. It is stressed that participation is free of choice and will not affect usual medical care.

ii) During the pre-operative examination, which is mostly conducted within a few days of the ENT consultation, the anesthesiology clinician asks whether the patient is informed about the study. If not, they will provide them the PIF and consent form. They will ask whether the patient is interested in participation and whether the research team can call the patient to provide them with more information. This response is noted in the electronic record and transferred to the researchers via an (automated) email.

iii) The research team will call the patient, explain the study in more detail and ask the patient to return the completed informed consent form.

Patients who are already planned for surgery when the study opens (the normal time between ENT consultation and the operation is 6-8 weeks) will be called by involved health care practitioners (from the ENT/Anaesthesiology department). They are informed about the study via telephone. In case they are interested, their name and telephone number are transferred to the researchers. The researchers will call the patient, and send them an information letter and consent form which participants can complete and return in case they are willing to participate.

Randomization

Upon providing informed consent patients are randomized using a random number generator (1:1:1:1: allocation rate). Assignments will be provided via sequentially

numbered opaque sealed envelopes. A secretary not otherwise involved in the study will open the assignment envelopes.

After patients are randomized, the research team will inform the health care professionals about their inclusion. They will insert this information in the medical records of the hospital system (EPIC). Moreover, they will inform the day care administrators and key contact persons about the patients that are scheduled in the upcoming week or days and which condition they are randomized to. On the day of admission, the researchers will ensure that all appropriate systems (e.g. the ward lists and the hard copy patient records) are adequately signposted with the patients' condition. We will use color codes for this to avoid unblinding patients. Only one patient per room is included at any time point.

Intervention

The intervention consists of a (protocolled) communication manipulation on top of standard analgesic treatment. Nurses at the day care ward will incorporate an (protocolled) expectancy manipulation (standard versus enhanced) related to the effects of the pain medication and empathy manipulation (standard versus enhanced) into their communication. The communication intervention will be provided at all nurse-patient communication moments during patients' stay at the day care ward (pre- and post-operation, day 1, the daycare wards are open between 7AM-6PM and 6.45AM-7PM respectively), and during the nurses' telephone consultation with patients the day post-discharge (day 2). In practice, this means that all communication patients receive from daycare ward nurses during this time frame will be according to patients' assigned condition. This includes interactions during intake, pain assessments, medication allocation, and transferal to the operation theater and from the post anesthesia care unit (PACU), discharge, and all other interactions due to patients' questions or medical need.

All nurses will receive training to ensure their ability to perform the different communication manipulations. We will make use of a professional trainer and comprehensive training protocol including scripts (i.e. written examples), video-examples, and role-play. Moreover, posters are placed in the communal spaces for nurses with

information about the study; e.g. examples of the manipulations and study procedures. Pocket cards with examples of the manipulations are provided. To ensure the communication differs between the 4 conditions and to minimize carry-over effects (e.g. nurses' stressing enhanced expectations display automatically an enhanced empathy style), the 4 conditions are trained separately and the posters and pockets cards focus on the 4 different conditions. The importance of the manipulations being successful in order to draw conclusions from the found results is stressed during the training day.

Expectancy manipulation

In the standard condition nurses do not aim to create the expectation that the pain medication will work very well. They might use sentences such as "The medications attempt to reduce your pain ever so slightly", or "This is your pain medication".

In the enhanced condition nurses aim to create the expectation that the pain medication will work very well. They might use sentences such as: "The medications I am giving you now will lead to a strong decrease of your pain", or "This pain medication is known for working very well".

Empathy manipulation

In the standard condition nurses aim to create a neutral atmosphere which is standard. They will be trained to (amongst other behavior) keep standing when communicating with patients, react with standard empathy to patients' cues and concerns, not explore concerns in detail, to not express extra interest in the patient as a person, to not pay extra attention to not interrupting patients, and to not make extra eye contact.

In the enhanced condition, nurses aim to create an atmosphere, which is extra warm and extra friendly. They will be trained to (amongst other behavior) introduce themselves properly, sit while communicating with patients, react extra empathically to patients' cues and concerns (verbal and nonverbal) and take their concerns seriously, to show extra interest in the patient as a person, to not interrupt the patient, and to make adequate eye contact.

It should be noted that the communication manipulation does not cross important norms or values of acceptable behavior and that the psychological integrity of patients will not be harmed. An observational study among clinical postsurgical patients showed that nurse-patient interactions are often subject to interruptions related to other tasks e.g. searching for equipment, answering telephone calls, or being interrupted by other professionals[14]. The interruptions and nurses' attempts to address competing demands impact on the time and attention spent with patients. It can therefore be assumed that variations in communication are inherently due to clinical encounters. This was also confirmed by field observations conducted by the research team before study start. The aforementioned developed scripts/examples which are used in the training have been commented upon by nurses and researchers in a pilot study to ensure they are realistic and do not trespass ethical boundaries and have been finalized in collaboration with involved clinicians.

Standardizing of communication

The communication patients receive from other clinicians involved during their hospitalization (e.g. from the surgical team working in the operation theater and the clinical team working in the PACU) will be standardized as much as possible. Also the communication during the pre-operative ENT and Anaesthesiology visit will be standardized as much as possible. Involved health care professionals will be informed of the study aims and the importance to keep their communication neutral (if possible) (i.e. to not provide extra empathy or raise extra expectations about pain) for included patients. This is feasible, as the ENT and anesthesiology team are involved in the study, and it is uncommon for patients to ask about pain medication during their time at the PACU.

Blinding

Patients will be blinded to the specific study aims and treatment allocation.

The involved health care personnel cannot be blinded. All health care personnel involved will receive clear and specific instructions about informing and including patients to preserve experimental control. Besides, all interactions within the study between nurses

and patients will be audio-recorded to evaluate the fidelity of the communication manipulation.

Study procedure

After receiving informed consent, the research team will send a baseline questionnaire to the patient. Completion of this questionnaire will be done at home and will take no more than 20 minutes. Post-operatively (at daycare, day 1) a short (5-minute) questionnaire is administered. As part of routine care, pre- and post- operatively, patients rate their level of pain. At day 2 (the day after discharge) patients will complete another questionnaire about their pain and medication use. At day 3 a last questionnaire will be completed which will take 20 minutes. Patients are given the choice between paper and pencil and online completion of questionnaires. This timeframe of follow-up is chosen as we expect the effect of the intervention (delivered within a few hours by daycare ward nurses solely) to wane within a few days.

Moreover, the interactions between involved nurses and included patients will be recorded. Nurses will be provided with a portable audio-recording device with microphone. During every visit, the nurses will mention patient's identification number by means of reference, to protect patients' privacy. At day 4 (3 days after discharge) patients will receive a debriefing letter by postal mail which will inform them about the study aims and their assigned condition. If they wish to receive more information they can contact the research team.

Withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The health care professionals involved and research team can decide to withdraw a patient from the study for urgent medical reasons (e.g. a bleeding after operation). If a patient drops-out, the research team is informed of this. Patients will continue to receive standard medical care and communication.

Informed consent nurses

Nurses involved in the study will be asked to participate as participants using an information sheet and a consent form. They will be asked to complete the consent form and a questionnaire about their background characteristics. We will offer them, at study end, participation in a (accredited) communication training to thank them for their participation in this project.

Outcomes

Main study outcome:

- Pain perception/intensity

As part of routine care, during hospitalization and post-hospitalization patients' pain will be assessed on the basis of a Numeric Rating Scale (NRS) (0-10), ranging from 'no pain' to 'worst imaginable pain' [15 16]. Pain is rated preoperatively at daycare ward, at the PACU , and postoperatively at daycare ward. On study day 2, one day after discharge, daycare ward nurses will contact the patients by telephone and again assess their pain. On top of this standard routine, pain is assessed at home on day 2 and day 3 (study end).

Secondary study outcome

In the patient questionnaires, the following secondary outcomes will be assessed:

- Pain expectations

Patients' pain expectations are measured using two items (both measured using a self-created Visual Analogue Scale (VAS); i) Patients' pain expectations for the few days following the operation (VAS ranging from 'no pain' to 'the most intense pain imaginable', ranging from 0-10, adapted from Petersen et al., 2014[17]); ii) Patients' expectations of improvement in pain following receiving pain medication (VAS ranging from '0% improvement' (no improvement) to '100% improvement' (most improvement imaginable), adapted from the Credibility and Expectancy Questionnaire (CEQ)[18]. These questions will be assessed post-operatively (during hospitalization).

- Overall benefit of analgesia

The overall benefit of analgesia score (OBAS) will be assessed[19]. The OBAS is a multidimensional 7-item instrument in which patients indicate (on a 0-4 scale, ranging from 'not at all' to 'very much') the level of current pain and distress arising from several

symptoms such as itch. The OBAS is measured post-hospitalization (at home) at day 2 and 3 (study end).

- Analgesic dosage

The total dosage of administered analgesics will be assessed during hospital stay and noted in the medical record. The total dosage of administered analgesic at home post-operation will be assessed at day 2 and 3 (study end) by asking patients to indicate which pain medication they use/have used.

- Analgesic request by a patient

Analgesic request will be assessed during hospital stay and noted in the medical record.

- Perceived empathy

Perceived empathy will be determined using the Consultation and Relational Empathy Measure (CARE)[20] in which the term 'doctor' is replaced with 'nurse' and 'consultation' is replaced with 'contact' (10 items, 1-5 scale ranging from 'poor' to 'excellent' (and 'not relevant'), e.g. "How was the nurse at showing care and compassion"). Perceived empathy is measured at day 3 (study end).

- Perceived expectation

We will measure the extent to which participants thought nurses had induced the expectation that medication would be effective to decrease their pain. This will be assessed using a 1-item self-created VAS scale ('no effect at all' to 'a lot of effect', ranging from 0-10). Perceived expectation will be measured at day 3 (study end).

- State anxiety

Patients' level of anxiety will be measured by the Dutch 10-item State measure of the State-Trait Anxiety Inventory (STAI-State)[21](1-4 scale ranging 'not at all' to 'very much'). Patients' anxiety is assessed pre-hospitalization, and at day 3 (study end).

- Mood

Mood will be measured using the Positive and Negative Affect Schedule (PANAS)[22] (20-items, 1-5 scale ranging from 'not at all' to 'very much' e.g. "I am exited" or "I am upset"). Mood is measured pre-hospitalization, and at day 3 (study end).

- Satisfaction

Participants' satisfaction with the provided care by the nurses during daycare will be assessed using a 1-item self-created VAS scale ('not at all' to 'very much', 0-10 range). Satisfaction will be measured at day 3 (study end).

- General pain evaluation

Whether the pain following the operation has been better or worse than expected, will be measured using a 1-item self-created VAS scale (ranging from 'much worse than expected' to 'much better than expected', 0-10 range). Pain evaluation is measured at day 3 (study end).

- General evaluations regarding hospitalization

Patients' evaluations of their hospitalization are measured using two items i) How likely it is that the patient would recommend this hospital to other tonsillectomy patients (using an adapted item from the CQ Index[23] (0-10 scale 'would definitely not recommend' to 'would definitely recommend'); ii) Their overall rating of the quality of care provided by the hospital during hospitalization, using an adapted item from the CQ Index[23](0-10 scale, 'very poor care' to 'extremely good care'). This is measured at day 3 (study end).

Other outcomes

The following background characteristics of patients are measured pre-hospitalization;

- Socio-demographics

E.g. date of birth, gender, marital status, education, ethnicity, societal position, and date of operation.

- Functional health status

Measured using the COOP-WONCA; 7-item scale assessing several health status elements, e.g. physical fitness, on a 1-5 scale ranging from ''not limited at all' to 'severely limited'[24 25].

- General experiences/expectations/attitudes medications

We will measure the extent to which patients generally i) benefit from, ii) have positive expectations towards the effect of, iii) have objections against taking medicines. This will be done using self-created VAS scales (ranging from 'not at all' to 'very much', 0-10 range).

- General reporting of pain

We will measure whether patients generally are inclined to report their pain using a self-created VAS scale (ranging from 'never' to 'always', 0-10 range)

- Attitudes towards operation

The extent to which participants i) are dreading, and ii) are afraid of the operation will be measured using two self-created VAS scales (ranging from 'not at all' to 'very much', 0-10 range).

In addition, we will measure:

- Data medical record

We will ask patients' permissions to access the medical record. We will routinely use medical background data (diagnosis, weight, prescribed medication) and analgesic information (as aforementioned). If needed, additional data will be screened for (e.g. in cases of outlier data the medical record might provide useful information).

Background measures for nurses

The following nurses' characteristics will be measured at study start.

- Socio-demographics

E.g. date of birth, gender, and type of nurse (i.e. nurse in training, regular nurse, specialized nurse).

- Empathy personality trait:

We will measure nurses' empathic abilities using the Interactive Reactivity Index (IRI)[26]. The IRI consists of 28 items (e.g. "I often feel sorry for people who are less fortunate than me") which are scored on a 1-5 scale (ranging from 'describes me not at all' to 'describes me very well).

An overview of the measured outcomes at different time points is provided in Table 1.

Domain	Measure	Collected	Pre-hospitalization	Post-operation (at day care, day 1)	During hospitalization (pre-peri-post operative, day 1)	Post-hospitalization (at home, day 2)	Post-hospitalization/study end (at home, day 3)
Pain perception/ intensity	Standard hospital NRS	Patient			x	x	x
Pain Expectations	Adapted VAS scale	Patient		x			
Overall benefit of analgesia	OBAS	Patient				x	x
Analgesic Dosage		medical record/patient			x	x	x
Analgesic Request		medical record			x		
Perceived empathy	CARE	Patient					x
Perceived expectation	Self-created VAS	Patient					x
Anxiety	State-anxiety (Stai state)	Patient	X				x
Mood	PANAS	Patient	X				x

Satisfaction	Self-created VAS scale	Patient					x
General pain evaluation	Self-created VAS Scale	Patient					x
General evaluation about hospitalization	Adapted CQ Index items	Patient					x
Socio demographics		Patient	X				
Functional health status	COOP-WONCA	Patient	X				
General Experiences/Expectations/Attitudes	Self-created VAS scales	Patient	X				
General reporting of pain	Self-created VAS scale	Patient	X				
Attitudes towards operation	Self-created VAS scale	Patient	X				
Data medical record	e.g. Diagnosis, weight, prescribed medication	Medical record	X		X		
Nurse – socio demographics		Nurse	At study start				
Nurse - empathy	IRI	Nurse	At study start				

Table 1 – Overview measured outcomes at different time points

Adherence to the communication manipulation protocol:

To verify the fidelity of the communication manipulation, the interaction between nurses and patients will be audio-recorded. The adherence will be verified by listening back to a random sample (10% of the sample) of audio-recorded visits and to determine the adherence to the protocol (as is comparably done by[10]). Two research assistants who are not otherwise involved in the study will independently evaluate the audio-recordings on adherence to the protocol.

Data analysis plan

All data will be analysed using STATA 13.0 with two-sided significance testing at p <.05. All available data from patients will be included in the analysis and missing data might be imputed. An intention to treat (ITT) analysis will be performed, thereby also examining selective attrition.

Primary outcomes

Descriptive statistics will be calculated for patients' reported pain intensity (main outcome measure) for the different time points during and post- hospitalization. Since our design consists of a 2 (expectancy: enhanced vs. standard) by 2 (empathy: enhanced vs. standard) design all outcomes will be analysed using either analyses of variance (if focussed on a specific time point) or multilevel repeated measures regression analyses (if focused on different time points which means that several ratings are included for one person). Both communication elements (i.e. expectancy and empathy) are dummy coded. Main effects and interaction effects of expectancy and empathy will be explored. New insights gathered during the analysing process might be examined (if feasible).

Secondary outcomes

Descriptive statistics will be calculated for secondary outcome measures. The effect of our manipulated variables will be analysed using analyses of variance.

Other outcomes

Frequencies and means will be calculated for the demographics. The four groups will be checked on equality by using chi-squared tests or analyses of variance (ANOVA). If groups differ on specific variables, these variables might be used as control variables in the multilevel analysis.

Adherence to communication protocol

Data of the audio-recordings are observed by trained coders on adherence to the protocol to verify fidelity. First, 10% of the audio-recordings are independently checked on adherence to the protocol. For this purpose, the aforementioned main (verbal) features of the manipulations (see p10) are described and rated for their occurrence when listening to the audio-recordings. Using this it is determined to which of the 4 conditions the audio recording belongs to. Second, inter-rater reliability between the coders of the outcomes will be assessed by calculating Cohen's kappa. Values ranging between 0.21 and 0.41 are considered fair, values between 0.41 and 0.60 moderate and values greater than 0.61 are considered good (i.e. substantial/almost perfect). We consider values as reliable if Cohen's kappa is greater than 0.41[27 28].

ETHICS AND DISSEMINATION

Risks and burden for participants

All participating patients receive usual care with regard to surgery, analgesia and pre- and post-operative treatment. There are no risks associated with this clinical study. The communication manipulation will be provided on top of standard care and is designed in such a way that there will be no harmful effects for patients. Although practitioners' communication is deliberately manipulated and associated with both positive and less positive effects, the communication manipulation does not cross important norms or values of acceptable behavior nor will it affect the psychological integrity of patients. Variations in nurse-patient interactions occur naturally within clinical settings, justifying our approach. Moreover, although patients are informed about the study by their treating clinicians, informed consent will be gathered by the research team. The clinical and

research team will stress that participation is voluntary and will not affect standard clinical care. Patients are always free to withdraw their participation in the study. Last, it can be a burden for patients to complete a few additional questionnaires. We attempt to decrease the burden by using short questionnaires and limiting follow-up to 3 days. Results, ultimately, will provide more insight into the effect of communication on patient outcomes.

Adverse and serious adverse events

All adverse events reported spontaneously by the patient or observed by the clinical or research team will be recorded. All serious adverse events will be reported to the ethical committee who has approved the study and the online database. This will be done within 15 days (7 days for the first reporting if an SAE resulted in death or was life threatening). Due to the content of the intervention, we do not expect SAE's to happen. The research team, supported by the clinical team will regularly check the medical records for the occurrence of any adverse events and serious adverse events.

Confidentiality

Patients' data will be anonymized using an identification number. This code will be safeguarded by an independent contact person at NIVEL and this information will be kept on a protected drive using a protected file independently of the research data. The researchers involved in this study will have access to the research data. The audio-recordings will not be destroyed after the research, but will be added to the NIVEL audio/video database. At present, NIVEL has a database of around 18,000 (digitized) video-recorded and audio-recorded healthcare visits and a well-equipped infrastructure with computerized observation units.

Ethical approval

This study has received ethical approval from the ethical committee of the UMC Utrecht (number 16/144, NL55225.041) and the institutional review board of the participating hospital (number WO 16.506). All amendments will be notified to the ethical committee that gave a favorable opinion.

Trial registration

The study is registered at the Dutch Trial Register (Registration number NTR5994) which is the Primary Registry in the Netherlands.

Dissemination

At the minimum, the results of this study will be published in international peer-reviewed scientific journals. A lay summary of the results will be published as well and send to participants if they are interested.

DISCUSSION

This innovative study aims to manipulate communication to determine how expectations and empathy can lead to placebo-effects and help minimize patients' post-operative pain (among other outcomes). The results can help to shed more light on how communication can be used alongside medical care to enhance patients' outcomes for the better.

That being said, manipulating communication in clinical care poses methodological, ethical and logistical challenges. The success of the study will depend on the success of the delivery of the manipulations. To ensure communication differs between the various groups, and to avoid contamination, all nurses have been trained and the research team is available (on and offsite) for questions, practice, and feedback. On most intervention days, a member of the research team is present at the daycare ward. This is much appreciated by nurses, and ensures that the appropriate manipulation is often practiced before a patient is admitted. Throughout an intervention day, the signposting of all systems (ward lists/hardcopy patient records) and the appropriate pocket cards with examples also serve as a constant reminder of the group allocation. The success of the manipulation is checked using the audio-recordings of nursing interactions and will assist in interpreting our results. While varying communication, the ethical boundaries of not providing any suboptimal communication are and will be clearly adhered to and are stressed in contacts with involved health care professionals. Last, patients come in contact with many clinicians before and during hospitalization. Informing all clinicians and ensuring all but

the daycare ward nurses will standardize their communication is crucial to ensure causal effects of the manipulated communication can be determined. Therefore, both the research and clinical team involved have ensured many contact moments with clinicians to personally inform them about the study and appropriate information material has been circulated at study start.

Of course, this study is beforehand not without limitations. Most importantly, due to the clinical nature of the study it is impossible to standardize communication elements beyond expectancy and empathy. We did, however, instruct nurses to vary only the manipulated communication and keep the remaining care and communication standard. We therefore believe these elements to not differ widely, but if evenly, between conditions. Moreover, time-differences between the conditions could potentially occur. We did, however, tried to ensure that the manipulations differed as minimally as possible in time (e.g. enhanced empathy consists of little time-consuming behaviors such as sitting opposed to standing) and all interventions need to be delivered within nurses' standard work time. We therefore believe to have minimized the risk for time-differences to occur between conditions. That being said, we acknowledge it remains a limitation of this complex clinical study that due to focus- and power-constraints we will not measure or control for all variables beyond, and time-differences between, the manipulations. A last limitation is that nonverbal behavior (e.g. eye contact) cannot be taken into account when determining adherence to the protocol using the audiotapes.

Despite these challenges and limitations, we believe this study is of utmost importance to bring the field of communication and pain research forward. Without conducting controlled studies into the effect of communication, communication will always remain a soft-sided add-on. In order to overcome this, we would recommend future studies to also include biological and clinical outcomes. Most importantly, we hope this study and detailed protocol will provide an impetus for further work in this important area turning communication from 'art to science'.

Authors' contributions

JB is the Chief Investigator.

JB developed the initial concept of the study, supported by SvD and LV

LV, JB, SvD, and SI led on the protocol development, while all authors provided input for the trial design and protocol.

MG, BT, and GvD led on the standardization of hospital routine, pain protocol and medical content.

LV and SI (as of August 2016 also supported by MK, while SI left the project in 2017) lead on the daily management of the trial, supported by MG, BT, GvD, SvD and JB

All authors have read, contributed and approved the final manuscript.

Acknowledgements

We thank Peter Spreeuwenberg for his help with the data analysis plan and power calculation. We thank the clinicians working at the daycare ward, the operation theater, the PACU and at the ENT and Anesthesia department for their help in facilitating the study logistics. We especially thank the daycare ward nurses for delivering the intervention.

Funding

The study is funded by the Spinoza Prize from the Dutch Research Council awarded to Prof. dr. Jozien M. Bensing.

LV is partly funded by a grant from the Foundation for the Science of the Therapeutic Encounter (F-STE).

The funder had no role in the study design and decision to submit the report for publication. The funder will have no role in the collection, management, analysis and interpretation of data or writing and publication of future publications.

Competing interest

None declared

Legends

Figure 1. Study design.

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Figure 1. Study design.

		Expectancy	
		enhanced	standard
Empathy	enhanced	Group 1	Group 2
	standard	Group 3	Group 4

209x296mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_NA-registered at the Dutch Trial Register _
Protocol version	3	Date and version identifier	_ NA, Not in article, __
Funding	4	Sources and types of financial, material, and other support	__24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1-2_____
	5b	Name and contact information for the trial sponsor	___24_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__24_____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____NA, a collaboration agreement between the hospital (OLVG) and NIVEL has been created_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__4-6_____
	6b	Explanation for choice of comparators	__4-6_____
Objectives	7	Specific objectives or hypotheses	__5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-12_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_12,7_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_9-12 19,20____

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__20,21, 6,_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_12-20_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_8,9,11,12-19___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___7-8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__8-9_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8-9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____8-9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__11-12, 9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__12_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_12-20_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__21,7_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_21_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_19_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_20_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_19_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_NA, no DMC has been set up_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__NA, no interim analyses are performed_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___21_____

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__NA_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___21_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__21_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___8,12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__21_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__24-25_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___21_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___12_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__22_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__NA – ICMJE criteria will be used___

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not provided in article____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Examining the effects of enhanced provider-patient communication on post-operative tonsillectomy pain: protocol of a Randomized Controlled Trial performed by nurses in daily clinical care.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015505.R2
Article Type:	Protocol
Date Submitted by the Author:	25-Sep-2017
Complete List of Authors:	van Vliet, Liesbeth; NIVEL (Netherlands Institute for Health Services Research), Department of Communication van Dulmen, Sandra; NIVEL, Department of Communication; Radboud University Medical Center , Department of Primary and Community Care Thiel , B; OLVG Hospital , Department of Anesthesiology van Deelen, G; OLVG Hospital , Department of ENT Immerzeel, S; NIVEL, Department of Communication Godfried, M; OLVG Hospital , Department of Anesthesiology Bensing, Jozien; NIVEL, Department of Communication
Primary Subject Heading:	Communication
Secondary Subject Heading:	Anaesthesia
Keywords:	communication, plaebo-effects, Pain management < ANAESTHETICS, tonsillectomy, randomized controlled trial

Title page

Title: Examining the effects of enhanced provider-patient communication on post-operative tonsillectomy pain; Protocol of a Randomized Controlled Trial performed by nurses in daily clinical care.

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Word count: 5390
Number of Figures: 1
Number of Tables: 1
Number of References: 28

Key words: Communication, placebo-effects, pain management, tonsillectomy, randomized controlled trial

Abstract

Introduction: Placebo effects (true biopsychological effects not attributable to the active ingredients of medical technical interventions) can be attributed to several mechanisms, such as expectancy manipulation and empathy manipulation elicited by a provider's communication. So far, effects have primarily been shown in laboratory settings. The aim of this study is to determine the separate and combined effects of expectancy manipulation and empathy manipulation during pre- and post-operative tonsillectomy analgesia care on clinical adult patients' outcomes.

Methods and analysis: Using a two by two randomized controlled trial 128 adult tonsillectomy patients will be randomly assigned to one out of four conditions differing in the level of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced). Daycare ward nurses are trained to deliver the intervention, while patients are treated via the standard analgesia protocol and hospital routines. The primary outcome, perceived pain, is measured via hospital routine by a Numeric Rating Scale, and additional pre-, peri- and post-hospitalization questionnaires are completed (until day 3, i.e. 2 days after the operation). The manipulation is checked using audio-recordings of nurse-patient interactions.

Ethics and dissemination: Although communication is manipulated, the manipulations do not cross norms or values of acceptable behavior. Standard medical care is provided. The ethical committee of the UMC Utrecht and the local OLVG hospital committee approved the study. Results will be published via (inter)national peer-reviewed journals and a lay publication.

Registration details: NTR5994 (Dutch Trial Register)

Strengths:

- This study is a RCT on the (placebo) effects of communication on top of standard medical care, building the evidence-base of communication.

Limitations:

- The success of the intervention will depend on the ability of nurses to carry out the different communication styles successfully.

INTRODUCTION

In clinical care, patients' outcomes are not only influenced by the active ingredients of drugs or other medical technical interventions, but also by the context in which care is delivered. Such biopsychosocial effects on patients' outcomes that are not attributable to the active ingredients of treatments or interventions are called 'non-specific' or 'placebo-effects'[1 2]. They are real and robust, occurring on top of natural history and regression to the mean[3], and can be observed alongside 'sham-treatments' as well as 'real treatments'[4].

Several mechanisms underlie the generation of placebo-effects on patient outcomes such as pain[5]. A well-understood mechanism is the manipulation of expectations. According to a recent systematic review of our research group, manipulating patients' expectations seems capable of influencing clinical patients' pain perceptions[6]. For example, the verbal suggestion that a drug is an active pain killer is more effective than receiving the same dosage medication without such a suggestion[7]. Manipulating expectations also contribute to the recent described positive effects of open-label placebos (inert treatments being described as such)[8]. A less-well understood mechanism is the communication of empathy in health care professional-patient encounters. Only few scholars have pointed out the potential role of the professional-patient relationship in explaining placebo-effects[9-11]. In our systematic review, we found that empathy had a less strong effect on pain compared to expectations[6]; but studies used different empathy operationalization and empathy was often manipulated together with other elements of the clinical encounter, making it difficult to draw strong conclusions from empathy[6].

When looking at these mechanisms, it seems reasonable that health care professionals' communication can influence them, and can thus produce placebo-effects. Until recently, however, the entities of communication and placebo-effects have hardly been integrated[11]. Communication is traditionally associated with 'art, not science' and placebos with 'evidence-based medicine' in which their effects are typically ruled out by the study design of randomized controlled trials (RCTs).

The tide is changing. A landmark-study led by Kaptchuk et al 2008[10] found that placebo-acupuncture delivered with high outcome expectations and an empathic approach led to statistically and clinically significant improvements in the functioning of patients with irritable bowel syndrome compared to placebo-acupuncture delivered without expectations and empathy. The distinct and combined effects of both mechanism, and the effects alongside an active treatment remain, however, unknown from this study.

Our research group has started to unravel the potential separate and combined effects of both expectancy manipulation and empathy manipulation in highly controlled settings. Using scripted video-vignettes and role-play studies, we found that expectancy mainly influences cognitive outcomes (e.g. expected treatment effect) and empathy mainly affective outcomes (e.g. anxiety). The largest positive effects were found when the two elements were combined and a physician raised high expectations meanwhile communicating in a warm, empathic manner[12 13]. However, whether these distinct and combined effects also translate to the clinical setting, alongside an active intervention remains, as yet, an unanswered question. Answering this question is important, as it will provide insight into how specific communication elements can influence specific health outcomes.

Study objective

This study therefore aims to disentangle the role of communication in eliciting placebo-effects in the clinical setting within the context of standard medical care. More specifically, the objective is to determine the separate and combined effects of expectancy manipulation (standard versus enhanced) and empathy manipulation (standard versus enhanced) during pre- and post-operative tonsillectomy analgesia care on clinical adult patients' outcomes (main outcome measure is pain perception). This will be studied using a 2 by 2 RCT design. By following this approach the evidence base on the effects of expressed outcome expectancy and conveyed empathy will be built in clinical care.

Accompanying the study objective, the goals of this study are in subsequent order:

1. To examine whether adult patients following tonsillectomy in the enhanced outcome expectancy condition will experience less pain (and other outcomes), compared to patients in the standard condition.
2. To examine whether adult patients following tonsillectomy in the enhanced empathy communication condition will experience less pain (and other outcomes) compared to patients in the standard empathy communication condition.
3. To examine the interaction effects of the different levels of outcome expectancy and empathy on adult patients' experiences of pain (and other outcomes).

METHODS AND ANALYSIS

Design and setting

A four-arm (2 by 2 design) single-blind randomized controlled trial will be conducted at the daycare nursing wards on two locations of a Dutch general hospital (OLVG Amsterdam), in which adult tonsillectomy patients are pre- and postoperatively monitored and treated by nurses. Patients will be randomly assigned to one out of 4 arms, which vary in the induction of expectations (standard vs enhanced), and (the level of) nurses' communication of empathy (standard vs enhanced). Depending on the patient's allocation, nurses will express a standard or enhanced outcome expectation of patients' pain, and provide care in a standard or enhanced empathic manner. See figure 1 for the study design. All patients will be treated according to the usual analgesic treatment protocol and daily routine care of the hospital. Recruitment started in August 2016 and will presumably continue until early 2018.

Patients

This study focuses on adult tonsillectomy patients. This population was carefully selected as it is a homogeneous population. These patients are young adults, generally aged 18-35, without complex comorbidity (ASA 1) and lack a history of chronic pain. Moreover, tonsillectomy is generally accepted as a strong confound nociceptive trigger resulting into high levels of postoperative pain that only lasts for a relatively short period of time (1-2 weeks).

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet the following criteria:

- Scheduled for tonsillectomy in daycare
- ≥18 years of age
- Speaking and understanding of the Dutch language
- Having mental capacity

Exclusion criteria

A potential patient who meets the following criteria will be excluded from participation in this study:

At study start (during inclusion process):

- Not scheduled for tonsillectomy in day care
- <18 years of age
- Not speaking and understanding of the Dutch language
- Lacking mental capacity (cognitive decline, dementia)

During the course of the study:

- Patients who experience a post-operative bleeding will be excluded.
- The health care professionals involved and research team can decide to withdraw a patient from the study for urgent medical reasons (e.g. if patients are not discharged on the day of operation due to complications).

If a patient drops-out, data until exclusion will be included in the analyses unless the patient objects to this (this will be asked upon exclusion).

Sample size

The sample size calculation is based on the primary outcome, i.e. pain. This calculation is based on a previous similar study[7], in which an open versus hidden administration of analgesic showed a difference of 1.2 and a total variance of 2.18. Based on a power of .80

and alpha of .05, and including an interaction-effect (with a within variance of 1.92), this results in a needed sample size of 32 patients per arm and 4x32=128 patients in total.

Recruitment

The recruitment of patients occurs in several steps:

i) Patients are approached for the study while discussing the operation with their consulting ear nose and throat specialist (i.e. ENT doctor). All eligible and interested patients are provided with a Patient Information Folder (PIF) and informed consent form. The PIF omits specific study aims, but mentions that communication will be manipulated. It is stressed that participation is free of choice and will not affect usual medical care.

ii) During the pre-operative examination, which is mostly conducted within a few days of the ENT consultation, the anesthesiology clinician asks whether the patient is informed about the study. If not, they will provide them the PIF and consent form. They will ask whether the patient is interested in participation and whether the research team can call the patient to provide them with more information. This response is noted in the electronic record and transferred to the researchers via an (automated) email.

iii) The research team will call the patient, explain the study in more detail and ask the patient to return the completed informed consent form.

Patients who are already planned for surgery when the study opens (the normal time between ENT consultation and the operation is 6-8 weeks) will be called by involved health care practitioners (from the ENT/Anaesthesiology department). They are informed about the study via telephone. In case they are interested, their name and telephone number are transferred to the researchers. The researchers will call the patient, and send them an information letter and consent form which participants can complete and return in case they are willing to participate.

Randomization

Upon providing informed consent patients are randomized using a random number generator (1:1:1:1: allocation rate). Assignments will be provided via sequentially

numbered opaque sealed envelopes. A secretary not otherwise involved in the study will open the assignment envelopes.

After patients are randomized, the research team will inform the health care professionals about their inclusion. They will insert this information in the medical records of the hospital system (EPIC). Moreover, they will inform the day care administrators and key contact persons about the patients that are scheduled in the upcoming week or days and which condition they are randomized to. On the day of admission, the researchers will ensure that all appropriate systems (e.g. the ward lists and the hard copy patient records) are adequately signposted with the patients' condition. We will use color codes for this to avoid unblinding patients. Only one patient per room is included at any time point.

Intervention

The intervention consists of a (protocolled) communication manipulation on top of standard analgesic treatment. Nurses at the day care ward will incorporate an (protocolled) expectancy manipulation (standard versus enhanced) related to the effects of the pain medication and empathy manipulation (standard versus enhanced) into their communication. The communication intervention will be provided at all nurse-patient communication moments during patients' stay at the day care ward (pre- and post-operation, day 1, the daycare wards are open between 7AM-6PM and 6.45AM-7PM respectively), and during the nurses' telephone consultation with patients the day post-discharge (day 2). In practice, this means that all communication patients receive from daycare ward nurses during this time frame will be according to patients' assigned condition. This includes interactions during intake, pain assessments, medication allocation, and transferal to the operation theater and from the post anesthesia care unit (PACU), discharge, and all other interactions due to patients' questions or medical need.

All nurses will receive training to ensure their ability to perform the different communication manipulations. We will make use of a professional trainer and comprehensive training protocol including scripts (i.e. written examples), video-examples, and role-play. Moreover, posters are placed in the communal spaces for nurses with

information about the study; e.g. examples of the manipulations and study procedures. Pocket cards with examples of the manipulations are provided. To ensure the communication differs between the 4 conditions and to minimize carry-over effects (e.g. nurses' stressing enhanced expectations display automatically an enhanced empathy style), the 4 conditions are trained separately and the posters and pockets cards focus on the 4 different conditions. The importance of the manipulations being successful in order to draw conclusions from the found results is stressed during the training day.

Expectancy manipulation

In the standard condition nurses do not aim to create the expectation that the pain medication will work very well. They might use sentences such as "The medications attempt to reduce your pain ever so slightly", or "This is your pain medication".

In the enhanced condition nurses aim to create the expectation that the pain medication will work very well. They might use sentences such as: "The medications I am giving you now will lead to a strong decrease of your pain", or "This pain medication is known for working very well".

Empathy manipulation

In the standard condition nurses aim to create a neutral atmosphere which is standard. They will be trained to (amongst other behavior) keep standing when communicating with patients, react with standard empathy to patients' cues and concerns, not explore concerns in detail, to not express extra interest in the patient as a person, to not pay extra attention to not interrupting patients, and to not make extra eye contact.

In the enhanced condition, nurses aim to create an atmosphere, which is extra warm and extra friendly. They will be trained to (amongst other behavior) introduce themselves properly, sit while communicating with patients, react extra empathically to patients' cues and concerns (verbal and nonverbal) and take their concerns seriously, to show extra interest in the patient as a person, to not interrupt the patient, and to make adequate eye contact.

It should be noted that the communication manipulation does not cross important norms or values of acceptable behavior and that the psychological integrity of patients will not be harmed. An observational study among clinical postsurgical patients showed that nurse-patient interactions are often subject to interruptions related to other tasks e.g. searching for equipment, answering telephone calls, or being interrupted by other professionals[14]. The interruptions and nurses' attempts to address competing demands impact on the time and attention spent with patients. It can therefore be assumed that variations in communication are inherently due to clinical encounters. This was also confirmed by field observations conducted by the research team before study start. The aforementioned developed scripts/examples which are used in the training have been commented upon by nurses and researchers in a pilot study to ensure they are realistic and do not trespass ethical boundaries and have been finalized in collaboration with involved clinicians.

Standardizing of communication

The communication patients receive from other clinicians involved during their hospitalization (e.g. from the surgical team working in the operation theater and the clinical team working in the PACU) will be standardized as much as possible. Also the communication during the pre-operative ENT and Anaesthesiology visit will be standardized as much as possible. Involved health care professionals will be informed of the study aims and the importance to keep their communication neutral (if possible) (i.e. to not provide extra empathy or raise extra expectations about pain) for included patients. This is feasible, as the ENT and anesthesiology team are involved in the study, and it is uncommon for patients to ask about pain medication during their time at the PACU.

Blinding

Patients will be blinded to the specific study aims and treatment allocation.

The involved health care personnel cannot be blinded. All health care personnel involved will receive clear and specific instructions about informing and including patients to preserve experimental control. Besides, all interactions within the study between nurses

and patients will be audio-recorded to evaluate the fidelity of the communication manipulation.

Study procedure

After receiving informed consent, the research team will send a baseline questionnaire to the patient. Completion of this questionnaire will be done at home and will take no more than 20 minutes. Post-operatively (at daycare, day 1) a short (5-minute) questionnaire is administered. As part of routine care, pre- and post- operatively, patients rate their level of pain. At day 2 (the day after discharge) patients will complete another questionnaire about their pain and medication use. At day 3 a last questionnaire will be completed which will take 20 minutes. Patients are given the choice between paper and pencil and online completion of questionnaires. This timeframe of follow-up is chosen as we expect the effect of the intervention (delivered within a few hours by daycare ward nurses solely) to wane within a few days.

Moreover, the interactions between involved nurses and included patients will be recorded. Nurses will be provided with a portable audio-recording device with microphone. During every visit, the nurses will mention patient's identification number by means of reference, to protect patients' privacy. At day 4 (3 days after discharge) patients will receive a debriefing letter by postal mail which will inform them about the study aims and their assigned condition. If they wish to receive more information they can contact the research team.

Withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The health care professionals involved and research team can decide to withdraw a patient from the study for urgent medical reasons (e.g. a bleeding after operation). If a patient drops-out, the research team is informed of this. Patients will continue to receive standard medical care and communication.

Informed consent nurses

Nurses involved in the study will be asked to participate as participants using an information sheet and a consent form. They will be asked to complete the consent form and a questionnaire about their background characteristics. We will offer them, at study end, participation in a (accredited) communication training to thank them for their participation in this project.

Outcomes

Main study outcome:

- Pain perception/intensity

As part of routine care, during hospitalization and post-hospitalization patients' pain will be assessed on the basis of a Numeric Rating Scale (NRS) (0-10), ranging from 'no pain' to 'worst imaginable pain' [15 16]. Pain is rated preoperatively at daycare ward, at the PACU , and postoperatively at daycare ward. On study day 2, one day after discharge, daycare ward nurses will contact the patients by telephone and again assess their pain. On top of this standard routine, pain is assessed at home on day 2 and day 3 (study end).

Secondary study outcome

In the patient questionnaires, the following secondary outcomes will be assessed:

- Pain expectations

Patients' pain expectations are measured using two items (both measured using a self-created Visual Analogue Scale (VAS); i) Patients' pain expectations for the few days following the operation (VAS ranging from 'no pain' to 'the most intense pain imaginable', ranging from 0-10, adapted from Petersen et al., 2014[17]); ii) Patients' expectations of improvement in pain following receiving pain medication (VAS ranging from '0% improvement' (no improvement) to '100% improvement' (most improvement imaginable), adapted from the Credibility and Expectancy Questionnaire (CEQ)[18]. These questions will be assessed post-operatively (during hospitalization).

- Overall benefit of analgesia

The overall benefit of analgesia score (OBAS) will be assessed[19]. The OBAS is a multidimensional 7-item instrument in which patients indicate (on a 0-4 scale, ranging from 'not at all' to 'very much') the level of current pain and distress arising from several

symptoms such as itch. The OBAS is measured post-hospitalization (at home) at day 2 and 3 (study end).

- Analgesic dosage

The total dosage of administered analgesics will be assessed during hospital stay and noted in the medical record. The total dosage of administered analgesic at home post-operation will be assessed at day 2 and 3 (study end) by asking patients to indicate which pain medication they use/have used.

- Analgesic request by a patient

Analgesic request will be assessed during hospital stay and noted in the medical record.

- Perceived empathy

Perceived empathy will be determined using the Consultation and Relational Empathy Measure (CARE)[20] in which the term 'doctor' is replaced with 'nurse' and 'consultation' is replaced with 'contact' (10 items, 1-5 scale ranging from 'poor' to 'excellent' (and 'not relevant'), e.g. "How was the nurse at showing care and compassion"). Perceived empathy is measured at day 3 (study end).

- Perceived expectation

We will measure the extent to which participants thought nurses had induced the expectation that medication would be effective to decrease their pain. This will be assessed using a 1-item self-created VAS scale ('no effect at all' to 'a lot of effect', ranging from 0-10). Perceived expectation will be measured at day 3 (study end).

- State anxiety

Patients' level of anxiety will be measured by the Dutch 10-item State measure of the State-Trait Anxiety Inventory (STAI-State)[21](1-4 scale ranging 'not at all' to 'very much'). Patients' anxiety is assessed pre-hospitalization, and at day 3 (study end).

- Mood

Mood will be measured using the Positive and Negative Affect Schedule (PANAS)[22] (20-items, 1-5 scale ranging from 'not at all' to 'very much' e.g. "I am exited" or "I am upset"). Mood is measured pre-hospitalization, and at day 3 (study end).

- Satisfaction

Participants' satisfaction with the provided care by the nurses during daycare will be assessed using a 1-item self-created VAS scale ('not at all' to 'very much', 0-10 range). Satisfaction will be measured at day 3 (study end).

- General pain evaluation

Whether the pain following the operation has been better or worse than expected, will be measured using a 1-item self-created VAS scale (ranging from 'much worse than expected' to 'much better than expected', 0-10 range). Pain evaluation is measured at day 3 (study end).

- General evaluations regarding hospitalization

Patients' evaluations of their hospitalization are measured using two items i) How likely it is that the patient would recommend this hospital to other tonsillectomy patients (using an adapted item from the CQ Index[23] (0-10 scale 'would definitely not recommend' to 'would definitely recommend'); ii) Their overall rating of the quality of care provided by the hospital during hospitalization, using an adapted item from the CQ Index[23](0-10 scale, 'very poor care' to 'extremely good care'). This is measured at day 3 (study end).

Other outcomes

The following background characteristics of patients are measured pre-hospitalization;

- Socio-demographics

E.g. date of birth, gender, marital status, education, ethnicity, societal position, and date of operation.

- Functional health status

Measured using the COOP-WONCA; 7-item scale assessing several health status elements, e.g. physical fitness, on a 1-5 scale ranging from ''not limited at all' to 'severely limited'[24 25].

- General experiences/expectations/attitudes medications

We will measure the extent to which patients generally i) benefit from, ii) have positive expectations towards the effect of, iii) have objections against taking medicines. This will be done using self-created VAS scales (ranging from 'not at all' to 'very much', 0-10 range).

- General reporting of pain

We will measure whether patients generally are inclined to report their pain using a self-created VAS scale (ranging from 'never' to 'always', 0-10 range)

- Attitudes towards operation

The extent to which participants i) are dreading, and ii) are afraid of the operation will be measured using two self-created VAS scales (ranging from 'not at all' to 'very much', 0-10 range).

In addition, we will measure:

- Data medical record

We will ask patients' permissions to access the medical record. We will routinely use medical background data (diagnosis, weight, prescribed medication) and analgesic information (as aforementioned). If needed, additional data will be screened for (e.g. in cases of outlier data the medical record might provide useful information).

Background measures for nurses

The following nurses' characteristics will be measured at study start.

- Socio-demographics

E.g. date of birth, gender, and type of nurse (i.e. nurse in training, regular nurse, specialized nurse).

- Empathy personality trait:

We will measure nurses' empathic abilities using the Interactive Reactivity Index (IRI)[26]. The IRI consists of 28 items (e.g. "I often feel sorry for people who are less fortunate than me") which are scored on a 1-5 scale (ranging from 'describes me not at all' to 'describes me very well).

An overview of the measured outcomes at different time points is provided in Table 1.

Domain	Measure	Collected	Pre-hospitalization	Post-operation (at day care, day 1)	During hospitalization (pre-peri-post operative, day 1)	Post-hospitalization (at home, day 2)	Post-hospitalization/study end (at home, day 3)
Pain perception/ intensity	Standard hospital NRS	Patient			x	x	x
Pain Expectations	Adapted VAS scale	Patient		x			
Overall benefit of analgesia	OBAS	Patient				x	x
Analgesic Dosage		medical record/patient			x	x	x
Analgesic Request		medical record			x		
Perceived empathy	CARE	Patient					x
Perceived expectation	Self-created VAS	Patient					x
Anxiety	State-anxiety (Stai state)	Patient	X				x
Mood	PANAS	Patient	X				x

Satisfaction	Self-created VAS scale	Patient					x
General pain evaluation	Self-created VAS Scale	Patient					x
General evaluation about hospitalization	Adapted CQ Index items	Patient					x
Socio demographics		Patient	X				
Functional health status	COOP-WONCA	Patient	X				
General Experiences/Expectations/Attitudes	Self-created VAS scales	Patient	X				
General reporting of pain	Self-created VAS scale	Patient	X				
Attitudes towards operation	Self-created VAS scale	Patient	X				
Data medical record	e.g. Diagnosis, weight, prescribed medication	Medical record	X		X		
Nurse – socio demographics		Nurse	At study start				
Nurse - empathy	IRI	Nurse	At study start				

Table 1 – Overview measured outcomes at different time points

Adherence to the communication manipulation protocol:

To verify the fidelity of the communication manipulation, the interaction between nurses and patients will be audio-recorded. The adherence will be verified by listening back to a random sample (10% of the sample) of audio-recorded visits and to determine the adherence to the protocol (as is comparably done by[10]). Two research assistants who are not otherwise involved in the study will independently evaluate the audio-recordings on adherence to the protocol.

Data analysis plan

All data will be analysed using STATA 13.0 with two-sided significance testing at $p < .05$. All available data from patients will be included in the analysis and missing data might be imputed. An intention to treat (ITT) analysis will be performed, thereby also examining selective attrition.

Primary outcomes

Descriptive statistics will be calculated for patients' reported pain intensity (main outcome measure) for the different time points during and post- hospitalization. Since our design consists of a 2 (expectancy: enhanced vs. standard) by 2 (empathy: enhanced vs. standard) design all outcomes will be analysed using either analyses of variance (if focussed on a specific time point) or multilevel repeated measures regression analyses (if focused on different time points which means that several ratings are included for one person). Both communication elements (i.e. expectancy and empathy) are dummy coded. Main effects and interaction effects of expectancy and empathy will be explored. New insights gathered during the analysing process might be examined (if feasible).

Secondary outcomes

Descriptive statistics will be calculated for secondary outcome measures. The effect of our manipulated variables will be analysed using analyses of variance.

Other outcomes

Frequencies and means will be calculated for the demographics. The four groups will be checked on equality by using chi-squared tests or analyses of variance (ANOVA). If groups differ on specific variables, these variables might be used as control variables in the multilevel analysis.

Adherence to communication protocol

Data of the audio-recordings are observed by trained coders on adherence to the protocol to verify fidelity. First, 10% of the audio-recordings are independently checked on adherence to the protocol. For this purpose, the aforementioned main (verbal) features of the manipulations (see p10) are described and rated for their occurrence when listening to the audio-recordings. Using this it is determined to which of the 4 conditions the audio recording belongs to. Second, inter-rater reliability between the coders of the outcomes will be assessed by calculating Cohen's kappa. Values ranging between 0.21 and 0.41 are considered fair, values between 0.41 and 0.60 moderate and values greater than 0.61 are considered good (i.e. substantial/almost perfect). We consider values as reliable if Cohen's kappa is greater than 0.41[27 28]. Moreover, the number of nurse-patient interactions and duration of interactions is measured for each audio-recording.

ETHICS AND DISSEMINATION

Risks and burden for participants

All participating patients receive usual care with regard to surgery, analgesia and pre- and post-operative treatment. There are no risks associated with this clinical study. The communication manipulation will be provided on top of standard care and is designed in such a way that there will be no harmful effects for patients. Although practitioners' communication is deliberately manipulated and associated with both positive and less positive effects, the communication manipulation does not cross important norms or values of acceptable behavior nor will it affect the psychological integrity of patients. Variations in nurse-patient interactions occur naturally within clinical settings, justifying our approach. Moreover, although patients are informed about the study by their treating

clinicians, informed consent will be gathered by the research team. The clinical and research team will stress that participation is voluntary and will not affect standard clinical care. Patients are always free to withdraw their participation in the study. Last, it can be a burden for patients to complete a few additional questionnaires. We attempt to decrease the burden by using short questionnaires and limiting follow-up to 3 days. Results, ultimately, will provide more insight into the effect of communication on patient outcomes.

Adverse and serious adverse events

All adverse events reported spontaneously by the patient or observed by the clinical or research team will be recorded. All serious adverse events will be reported to the ethical committee who has approved the study and the online database. This will be done within 15 days (7 days for the first reporting if an SAE resulted in death or was life threatening). Due to the content of the intervention, we do not expect SAE's to happen. The research team, supported by the clinical team will regularly check the medical records for the occurrence of any adverse events and serious adverse events.

Confidentiality

Patients' data will be anonymized using an identification number. This code will be safeguarded by an independent contact person at NIVEL and this information will be kept on a protected drive using a protected file independently of the research data. The researchers involved in this study will have access to the research data. The audio-recordings will not be destroyed after the research, but will be added to the NIVEL audio/video database. At present, NIVEL has a database of around 18,000 (digitized) video-recorded and audio-recorded healthcare visits and a well-equipped infrastructure with computerized observation units.

Ethical approval

This study has received ethical approval from the ethical committee of the UMC Utrecht (number 16/144, NL55225.041) and the institutional review board of the participating

hospital (number WO 16.506). All amendments will be notified to the ethical committee that gave a favorable opinion.

Trial registration

The study is registered at the Dutch Trial Register (Registration number NTR5994) which is the Primary Registry in the Netherlands.

Dissemination

At the minimum, the results of this study will be published in international peer-reviewed scientific journals. A lay summary of the results will be published as well and send to participants if they are interested.

DISCUSSION

This innovative study aims to manipulate communication to determine how expectations and empathy can lead to placebo-effects and help minimize patients' post-operative pain (among other outcomes). The results can help to shed more light on how communication can be used alongside medical care to enhance patients' outcomes for the better.

That being said, manipulating communication in clinical care poses methodological, ethical and logistical challenges. The success of the study will depend on the success of the delivery of the manipulations. To ensure communication differs between the various groups, and to avoid contamination, all nurses have been trained and the research team is available (on and offsite) for questions, practice, and feedback. On most intervention days, a member of the research team is present at the daycare ward. This is much appreciated by nurses, and ensures that the appropriate manipulation is often practiced before a patient is admitted. Throughout an intervention day, the signposting of all systems (ward lists/hardcopy patient records) and the appropriate pocket cards with examples also serve as a constant reminder of the group allocation. The success of the manipulation is checked using the audio-recordings of nursing interactions and will assist in interpreting our results. While varying communication, the ethical boundaries of not providing any suboptimal communication are and will be clearly adhered to and are stressed in contacts

with involved health care professionals. Last, patients come in contact with many clinicians before and during hospitalization. Informing all clinicians and ensuring all but the daycare ward nurses will standardize their communication is crucial to ensure causal effects of the manipulated communication can be determined. Therefore, both the research and clinical team involved have ensured many contact moments with clinicians to personally inform them about the study and appropriate information material has been circulated at study start.

Of course, this study is beforehand not without limitations. Most importantly, due to the clinical nature of the study it is impossible to standardize communication elements beyond expectancy and empathy. We did, however, instruct nurses to vary only the manipulated communication and keep the remaining care and communication standard. We therefore believe these elements to not differ widely, but if evenly, between conditions. Moreover, time-differences and differences in the number of nurse-patient interactions between the conditions could potentially occur. We did, however, tried to ensure that the manipulations differed as minimally as possible in time (e.g. enhanced empathy consists of little time-consuming behaviors such as sitting opposed to standing) and all interventions need to be delivered within nurses' standard work time. Moreover, we instructed nurses to display the manipulations during all their standard interactions, and did not instruct them to have extra interactions in the enhanced conditions. We therefore believe to have minimized the risk for time-differences and interaction-differences to occur between conditions. For the 10% checked audio-recordings consultation time and the number of nurse-patient interactions are measured, which might help us in interpreting the findings. Still, we acknowledge it remains a limitation of this complex clinical study that due to focus- and power-constraints we will not completely measure or control for all variables beyond, and time-/interaction-differences between, the manipulations. A last limitation is that nonverbal behavior (e.g. eye contact) cannot be taken into account when determining adherence to the protocol using the audiotapes.

Despite these challenges and limitations, we believe this study is of utmost importance to bring the field of communication and pain research forward. Without conducting controlled studies into the effect of communication, communication will always remain a soft-sided add-on. In order to overcome this, we would recommend future studies to also include biological and clinical outcomes. Most importantly, we hope this study and detailed protocol will provide an impetus for further work in this important area turning communication from 'art to science'.

Authors' contributions

JB is the Chief Investigator.

JB developed the initial concept of the study, supported by SvD and LV

LV, JB, SvD, and SI led on the protocol development, while all authors provided input for the trial design and protocol.

MG, BT, and GvD led on the standardization of hospital routine, pain protocol and medical content.

LV and SI (as of August 2016 also supported by MK, while SI left the project in 2017) lead on the daily management of the trial, supported by MG, BT, GvD, SvD and JB

All authors have read, contributed and approved the final manuscript.

Acknowledgements

We thank Peter Spreeuwenberg for his help with the data analysis plan and power calculation. We thank the clinicians working at the daycare ward, the operation theater, the PACU and at the ENT and Anesthesia department for their help in facilitating the study logistics. We especially thank the daycare ward nurses for delivering the intervention.

Funding

The study is funded by the Spinoza Prize from the Dutch Research Council awarded to Prof. dr. Jozien M. Bensing.

LV is partly funded by a grant from the Foundation for the Science of the Therapeutic Encounter (F-STE).

The funder had no role in the study design and decision to submit the report for publication. The funder will have no role in the collection, management, analysis and interpretation of data or writing and publication of future publications.

Competing interest

None declared

Legends

Figure 1. Study design.

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Figure 1. Study design.

		Expectancy	
		enhanced	standard
Empathy	enhanced	Group 1	Group 2
	standard	Group 3	Group 4

209x296mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_NA-registered at the Dutch Trial Register _
Protocol version	3	Date and version identifier	_ NA, Not in article, __
Funding	4	Sources and types of financial, material, and other support	__24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1-2_____
	5b	Name and contact information for the trial sponsor	___24_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__24_____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____NA, a collaboration agreement between the hospital (OLVG) and NIVEL has been created_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__4-6_____
	6b	Explanation for choice of comparators	__4-6_____
Objectives	7	Specific objectives or hypotheses	__5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-12_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_12,7_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_9-12 19,20____

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__20,21, 6,_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_12-20_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_8,9,11,12-19___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___7-8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__8-9_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8-9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____8-9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__11-12, 9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__12_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_12-20_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__21,7_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_21_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_19_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_20_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_19_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_NA, no DMC has been set up_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__NA, no interim analyses are performed_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___21_____

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__NA_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___21_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__21_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___8,12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__21_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__24-25_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___21_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___12_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__22_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__NA – ICMJE criteria will be used___

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not provided in article____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.