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Effects of open and hidden administration of treatment-related information; a multi-experiment study

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ABSTRACT

Background: Two experiments (E1 and E2; $N=44$ and $N=52$, respectively) investigated the effect of positive (PI) and neutral information (NI) about a dental procedure, and if the delivery of the information by the treatment team (open administration) or unbeknownst to the treatment team (hidden administration), affected pain.

Methods: Using a mixed design, patients undergoing drilling in a molar were randomized to the NI or PI groups. Before, during, and after treatment, patients reported their pain and stress levels. In E1 the treatment team delivered the information. In E2, an assistant not engaged in the treatment delivered the information.

Results: In the PI group in E1, pain was reduced by 50 % compared to the NI group, and the effects of stress on pain were mitigated. These effects were abolished in E2. The dentist reported having displayed positive nonverbal behaviours (e.g. smiling and longer eye contact) in the PI group in E1, but not in E2.

Discussion: Positive information reduced pain only when administrated openly. There was no effect of positive information administrated hidden from the treatment team. As information was similar in both experiments, factors other than the information most likely reduced pain in the PI group in E1.

Conclusion: Delivering positive information by the treatment team may generate behavioural cues which generate placebo effects.

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KEYWORDS
Open-hidden administration; dental pain; placebo effects; contextual factors; healthcare providers

Introduction

The present study investigated whether presenting treatment-related information that was more positively framed, could reduce pain during a dental procedure, compared to neutral and standard information. In the first experiment (E1), information was administrated by the dentist and the dental assistant performing the dental procedure (termed open administration of information). The second experiment (E2) investigated whether the results from the first experiment was due to the information, or to factors other than the information. In E2 the information was presented by a dental assistant

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not involved in the treatment, and the treatment team did not know which patients that received which information (hidden administration).

The way information about treatment is framed (Rothman et al., 2006) and communicated to patients (Schneider et al., 2001) can modulate symptom reporting (e.g. Helfer et al., 2022) and response to treatment (e.g. Barnes et al., 2019; Dutt-Gupta et al., 2007; Gallagher & Updegraff, 2012). This effect can occur through modulation of stress and/or enhancement of positive treatment expectations (e.g. Colloca & Miller, 2011; Wilhelm et al., 2018). For example, Wilson et al. (1978) told participants to imagine they had a terminal liver disease and had to consider a risky surgery treatment. When participants were told that they had a 10% chance of survival from a risky surgery treatment, they were more likely to accept the surgery compared to when they were told that they had a 90% chance of dying (Wilson et al., 1987). Gryll and Katahn (1978) showed that dental patients reported lower pain when the dentists gave them positive information about a treatment, as compared to when they were given minimal information about that treatment. However, there are not many studies investigating the role of the method of delivery of positively framed information. This leaves the question open as to whether the improved outcomes attributed to positive framing of the treatment information are solely due to the framing, or if other factors, such as the factors related to the healthcare provider delivering that information can also influence the results.

Healthcare providers are probably the most important contextual component in many therapeutic settings (Levine & De Simone, 1991; Telaak et al., 2023; Verheul et al., 2010), as their suggestions, expectations, characteristics, and their behaviours can affect treatment outcome (Flaten et al., 2003; Howe et al., 2022; Kállai et al., 2004; Kaptchuk et al., 2008; Rosenthal & Jacobson, 1968). For instance, Gracely et al. (1985) showed that the knowledge of the dentists affected dental pain. In this double-blind study, patients were told that they could receive an opioid or a placebo in one group, and an opioid, a placebo or an opioid blocker in another group. The patients were told that the medication could either improve, worsen, or cause no change in pain. However, the dentists were told that there would be no active opioid in group one, and that there was a chance of receiving an opioid in group two. The results showed that patients had lower pain in group two, where the dentists believed an opioid could have been administered. Walach et al. (2001) showed that when the experimenters were made to believe that a placebo caffeine produces physiological responses, the subjects showed higher systolic pressure, compared to subjects who were tested by experimenters that did not believe so. Furthermore, the authors showed that the experimenters' expectations affected physiological responses, whereas the instructions provided to subjects did not. Gracely et al. (1985) argued that the healthcare providers' expectations could transfer to patients through subtle nonverbal behaviours. This notion was further elaborated by Chen et al. (2019) who showed that participants had lower pain reports when their experimenters believed they were administering a pain-relieving treatment, even though the treatment was a placebo agent. They showed that healthcare providers with positive beliefs about the treatment had different facial expressions while interacting with patients.

In single-blinded trials and open administration of treatments, where the healthcare providers are aware of the true intervention/treatment administered to patients

(Kaptchuk, 2001), there is a possibility that the providers, verbally or nonverbally, signal their positive expectations and beliefs about the treatment to patients (Shapiro & Shapiro, 2000). This bias can lead to placebo effects (i.e. reduction in symptoms following a positive expectation that an effective treatment has been administered) and enhancement of treatment outcome (Holroyd et al., 2006). Previous studies have shown that positively framing verbal suggestions about treatment (Dutt-Gupta et al., 2007; Gryll & Katahn, 1978; Helfer et al., 2022) can partially explain this. Other studies also suggest an impact of the expectations and the knowledge of the healthcare providers about treatment (e.g. Gracely et al., 1985). However, it is not clear whether such positively framed information can influence treatment outcome when controlling for the effects of healthcare providers administering the treatment. To our knowledge, the role of the method of delivering positively framed treatment information, open or hidden to the healthcare providers, has not yet been investigated.

Therefore, the present multi-experiment study firstly investigated the effects of positively framed information about a dental treatment procedure, on pain inflicted by that procedure (anesthetizing, drilling, and filling the cavity in a molar); and secondly, if the delivery method of that information, whether delivered by the dental treatment team performing the treatment procedure, or by an assistant not engaged in the treatment, affected the pain report.

Experiment one

The study was performed in a dental clinic. All patients received the same treatment, that is, anaesthesia was applied before drilling and filling of a cavity in a molar. The patients received either neutral information (NI) or extended positive information (PI) about the treatment. The information was provided by the treatment team (open administration). The NI and the PI information were developed following an attribute framing approach (Tversky & Kahneman, 1981). The NI was similar to information that patients would normally receive before undergoing drilling in a molar and it included words such as pain, unpleasantness, sensitive to cold or chewing. The patients in the PI group, on the other hand, received information that was positively framed. This information avoided words associated with pain or unpleasantness, used words like a small damage, easily repaired, improved, gentle, pleasant etc., was more detailed, focused on the positive effects of the anaesthesia, was more assuring, comforting, and gave patients control of when to take breaks. All patients received the same amount of the same anaesthetic before drilling. Subjective reports of pain and stress were recorded before drilling (first timepoint), after drilling (second timepoint), immediately after treatment (third timepoint), and 15 minutes after the end of treatment (fourthtimepoint).

Placebo effects have been found to be larger in male research participants (Daniali et al., 2024; Vambheim & Flaten, 2017) so about an equal number of males ($N=20$) and females ($N=24$) were recruited. It was predicted that (1). Pain increases during drilling (second timepoint) in both groups. (2). Pain increases less during drilling (second timepoint) in the PI group compared to the NI group. (3). Stress increases during drilling (second timepoint). (4). Stress increases less in the PI group during drilling (second timepoint). (5). Stress before drilling (first timepoint) predicts pain during drilling

(second timepoint). (6). High fear of pain predicts stress before (first timepoint) and during drilling (second timepoint). (7). High fear of pain predicts pain during drilling (second timepoint).

Methods

Patients

Participants were 44 patients (24 females, age range 17–68 years, mean age 40 years, *SD* = 11.67) that attended a dental clinic in Stavanger, Norway. None of the patients reported any serious disease. Inclusion criteria: patients that contacted the dental clinic for an appointment, and that received drilling in a molar or premolar. Exclusion criteria: present use of prescribed pain-relieving medications or other medication that could affect the pain ratings.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics in Western Norway (2011/209) and was registered at *ClinicalTrials.gov* (identifier ID: NCT02160028). No treatment was performed solely for research purposes, and all patients provided written informed consent.

Medication

All patients received Xylocain Dental Adrenalin, which is commonly used as a standard anaesthetic in dentistry. To induce less pressure and stress to patients, the WAND STA procedure was implemented to penetrate the needle into the tissue (Milestone Scientific, Livingston, NJ). In this method, the anaesthetic was injected drop by drop, mechanically, through a needle attached to a pen, instead of a large syringe with a long needle that is usually used to anaesthetize the tissue. This method has been shown to be a less painful and less frightening to inject the anaesthesia (Palm et al., 2004).

Questionnaires

Pain intensity and unpleasantness were rated on a numeric rating scale (NRS) as in Price et al. (1983), ranging from 0 to 10. For pain intensity, the patients were instructed to evaluate the strength of the pain in the tooth and report the number from the NRS that best described their pain intensity. The NRS was explained as follows: 'zero' indicates no pain at all, and "one" indicates the point at which you begin to feel 'pain'. Patients were instructed to report a higher number if the pain intensity was greater, choosing the number that best matched their pain intensity. Regarding pain unpleasantness, the patients were told to consider how unpleasant and disturbing the pain was to them. To highlight the difference between pain intensity and unpleasantness, the example made by Price et al. (1983) was used: 'there are two different aspects of pain that we want to measure: the pain's intensity, that is, how strong the pain is, and the pain's unpleasantness, that is, how unpleasant or disturbing the pain feels. The difference between these can be illustrated by thinking of a sound such as from a radio. When the sound of volume increases, I can ask you how loud it sounds or how uncomfortable it feels to hear the sound. The intensity of pain is like the sound level. The unpleasantness of pain depends

not only on the sound level, but also on other factors that can affect you'. The patients were then instructed to judge the aspects of pain unpleasantness and pain intensity independently.

The Norwegian version of Short Adjective Check List (Mackay et al., 1978) was used to assess stress and arousal using two adjective pairs, each rated on a scale from '0' to '10'. Stress levels were assessed by asking subjects to rate how 'relaxed' or 'tense', or how 'calm' or 'nervous' they felt. Arousal was similarly measured on the dimensions of 'sleepy' or 'awake', and 'tired' or 'energetic'. This scale has been employed in various studies exploring the impact of stress and physiological arousal in pain (e.g. Bjørkedal & Flaten, 2011; Lyby et al., 2010; Vambheim et al., 2021).

The Fear of Pain Questionnaire III (FPQ III) (McNeil & Rainwater, 1998) was employed to measure fear of pain. The FPQ III is a 30-item questionnaire that assesses fear of pain in situations involving minor pain, severe, or pain induced by medical procedures. FPQ III yields subscale scores for fear of severe, minor, and medical pain, and a total score reflecting overall fear of pain. The psychometric properties of FPQ III in Norwegian samples have been reported as acceptable (Vambheim et al., 2017).

Blinding

The dentist and the dental assistant were aware of the medication and gave the information to the patients themselves. Therefore, the dentist and the dental assistant performing the treatment knew which patient received the positive information and which patient received the neutral information. The same medication and treatment procedure was used for both groups, and the patients were aware of the treatment. However, the patients were blinded to the real aim of the study, as they were told that the experiment examined pain and stress during dental treatments.

Dentist

One female dentist and one female dental assistant performed the treatment. The dentist was an experienced dental clinician about 40 years old, and the dental assistant was about 30 years old. Both Experiment One (E1) and Experiment Two (E2) were carried out by this same dental team. Since the same dental treatment team performed both experiments, there was no variation in the treatment provided (e.g. drilling skills) to the patients in E1 and E2.

Routine practice

Since the same dentist and her assistant performed both experiments, and as the treatment procedure was part of the routine clinical practice with high familiarity with the intervention, only the experimental aspects of the study, including the randomization, giving out the treatment information, and recording of the subjective measurements of pain and stress were practiced with the dental team.

Randomization

WebCRF, a service for collecting clinical data, was used to randomize patients into the groups. The program plotted a group of random numbers to the targeted sample

size. Then each number was randomly assigned to one of the groups. The numbers were then put in the sealed letters containing information that were ought to be read for the patients. While recruiting the patients, the patients were assigned a number consecutively. Therefore, the first patient was number '1', second patient as number '2' and so forth. An equal number of patients were randomized to the groups (22 patients in the NI and 22 patients in the PI).

Procedure

The patients were informed about the research project when they contacted the clinic, and were told that the experiment examined pain and stress during a dental treatment. Those who expressed an interest in taking part, received the consent form *via* ordinary mail. The patients who agreed to take part in the experiment returned the signed consent form when they arrived at the clinic. After arrival at the dental clinic, all patients filled out the FPQ III, that was collected by the dental assistant. The first ratings of pain and stress were recorded before the information was provided to the patients.

Before the treatment started, the dental assistant drew an envelope that provided information to each patient according to whether the patient was randomly allocated to the NI group or the PI group. Before providing the information, the patient reported his/her ratings of pain, stress and arousal, and the dental assistant recorded them.

The NI group received the following information prior to receiving the anaesthetic: 'The treatment you will receive consists of a standard filling therapy where we use plastic as a filler. You will receive anaesthesia. It is common to have a little pain or unpleasantness when the anaesthesia wears off. The tooth can be very sensitive to cold and/or chewing for a shorter or longer period. If you have much unpleasantness, you may contact us for a check. The treatment will take about 30 min'.

The PI group received the following information prior to receiving the anaesthetic: 'Today we will be putting a plastic filling in a molar. This is a small damage that easily can be repaired with a filling. We will use a method of anaesthesia where only that tooth that needs medical care will be anaesthetized. This is an improved and gentle method, where the mucosa is first anaesthesized with a cream. We are using this method so you shall have a pleasant and positive experience. The anaesthetic cream tastes like cherry. Many people think the sound of the drill and the suction apparatus are strong. I will start the drill and the suction afterwards, so you can hear the sound before we start. During the treatment, we will stop with short intervals so you can have a break. If you need more breaks, just lift your hand and we will stop immediately. You decide the tempo. The treatment will take about 30 min. Do you have any questions before we start?'.

The dentist performing the procedures inspected and anaesthetized the molar with the Wand STA, and then after ten minutes waiting for the anaesthesia to take effect, the dentist started drilling the molar. The drilling took an average of about 10 min.

Present and remembered reports of pain and negative emotions. For the second timepoint, half of the patients ($N = 22$; 10 in the NI and 12 patients in the PI

group) were asked to report their pain and stress at the end of the drilling (present pain), and the other half were asked to report what pain intensity, unpleasantness, stress and arousal they remembered from during the drilling (remembered pain). The difference in time between these reports was less than 10 min.

The treatment was concluded following the filling of the molar/premolar cavity with the plastic filling. Immediately after the treatment was over, the patients were asked to report their ratings of pain, stress and arousal (third timepoint) and then were guided to the waiting room. After 15 min, the patients were again asked to report their ratings of pain, stress, and arousal (fourth or last timepoint). The last registration was made at the waiting room, either by the dentist or by the dental assistant who was engaged in the treatment (see Figure 1).

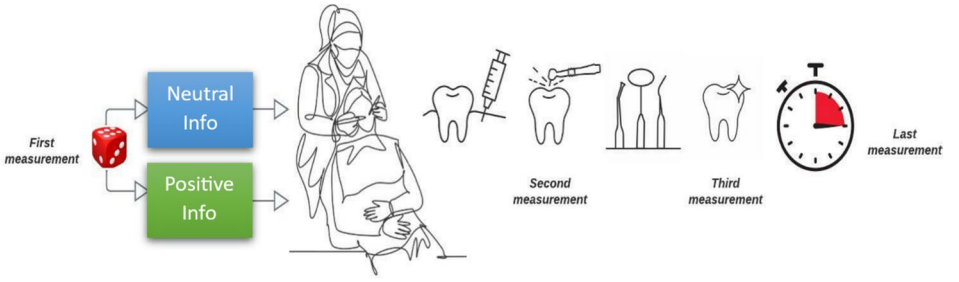

Figure 1. Overview of treatment procedure. The first timepoint measurement of pain, stress and arousal were recorded before patients were randomized to the groups. After being randomized to either the Neutral (NI) or Positive information (PI) groups, all patients underwent the same dental treatment procedure. The second timepoint measurement of pain, stress and arousal were recorded immediately after the drilling, for half of the participants asking for their concurrent pain (present pain), and for the other half asking the pain levels they remembered from during the drilling (i.e. remembered pain). The third timepoint measurement was recorded right after the treatment was finished. The last measurement was administered 15 min after the conclusion of the treatment, while the patients were waiting in the reception room.

Statistical power

No priori sample size calculations were performed before data recruitment, and the sample size was determined based on the practical restraints of the study rather than statistical considerations. However, a post hoc power analysis was performed to estimate the achieved power. The post hoc analysis was based on the partial eta square (n_p^2) of .07, a medium to moderately large effect size, which was observed within the PI group at the second timepoint measurement of pain unpleasantness (see Results section, Pain unpleasantness). To facilitate the post hoc power analysis, the n_p^2 of .07 was converted to an *f* effect size using the formula $\left(f = \sqrt{\frac{n_p^2}{1-n_p^2}}\right)$ (Faul et al., 2007), resulting in an *f* effect size of .276. Using G*Power software (Faul et al., 2007), the post hoc analysis for an ANOVA test with repeated measures and between factors with the sample size of $N = 44$, and a significance level (α) of .05 with 4 groups showed that the achieved power ($1 - \beta$) for detecting

the true effect of the information manipulation in this experiment was .43 (Cohen, 2013).

Design and statistics

The statistics for both experiments were performed using STATISTICA V7 and SPSS V22. The design was a 2 Information (NI Group, PI Group) × 4 Timepoint × 2 RememberedPresent (present or remembered pain for the second Timepoint) mixed-design, with the Information and RememberedPresent treated as between-group factors, and Timepoint as the within-subjects factor. The second pain, stress and arousal measurements were rated either present or as remembered, and this was entered as a between-subjects factor termed as RememberedPresent. The data were analysed by repeated-measures analysis of variance. The Greenhouse-Geisser correction (Schwertman, 1978) was used to correct for inflated degrees of freedom. Separate linear regression analyses were used to analyse the effect of continuous predictors (stress, arousal, fear of pain) on pain. The mean of the four timepoint measurements of pain unpleasantness was used as the dependent variable for the regressions on pain reports. Moreover, stress was regressed on fear of pain. To do so, the mean of the stress reported at the four timepoint measurements was used as the dependent variable. The predictions were tested by a priori contrast analyses, and other follow-up tests were conducted by Tukey's HSD. The overall pain and stress reports across all Timepoints was normally distributed and other assumptions to conduct regression analyses were met.

Results

The mean and standard deviation of pain intensity, unpleasantness, stress and arousal of groups across timepoint measurements are reported in Table 1.

Pain unpleasantness

Pain intensity and pain unpleasantness data correlated within each timepoint (*r*s between 0.48 and 0.75, *p*s < .01), thus only the pain unpleasantness data are reported.

Table 1. Pain Intensity, unpleasantness, stress, and arousal data across groups and timepoints.

Group	Timepoint	Pain intensity	Pain unpleasantness	Stress	Arousal
Positive Info (*M*; *SD*)	TM1	0.18; 0.66	0.31; 0.89	3.70; 2.75	7.00; 2.04
N = 22	TM2P	1.00; 1.88	1.30; 2.26	2.85; 2.31	7.55; 1.65
	TM2R	0.87; 0.90	2.45; 2.16	4.14; 2.40	6.66; 2.00
	TM3	1.34; 2.13	1.90; 2.38	2.73; 2.63	7.15; 1.74
	TM4	0.36; 1.49	0.63; 1.70	1.04; 1.19	7.60; 1.29
Neutral Info (*M*; *SD*)	TM1	0.20; 0.45	0.72; 1.24	4.56; 2.39	6.68; 2.11
N = 22	TM2P	0.80; 1.36	1.45; 1.46	3.20; 2.72	6.95; 1.99
	TM2R	2.08; 2.26	5.08; 2.20	5.56; 2.20	7.20; 2.58
	TM3	0.86; 1.12	1.65; 1.65	2.84; 2.04	6.86; 2.24
	TM4	0.27; 0.55	0.90; 1.23	1.02; 1.58	6.89; 2.13

Abbreviations: *M*: mean; *SD*: standard deviation; TM: timepoint measurements. TM2P: present pain report at the 2nd timepoint measurement (present pain); TM2R: remembered pain report at the 2nd timepoint measurement (remembered pain).

There was no effect of the sex of the patients on any dependent variable, and this variable is not discussed further.

The main effect of Timepoint was significant ($F(2.44, 97.75) = 23.96$, $p = .000001$, $n_p^2 = .52$), as were the interactions of Information by Timepoint ($F(2.44, 97.75) = 3.24$, $p = .03$, $n_p^2 = .20$), and RememberedPresent by Timepoint ($F(2.44, 97.75) = 12.26$, $p = .000004$, $n_p^2 = .23$). These interactions were qualified by the interaction of Information by RememberedPresent by Timepoint ($F(2.44, 97.75) = 2.90$, $p = .049$, $n_p^2 = .07$). A contrast analysis showed that pain unpleasantness was significantly lower during the drilling (Timepoint 2) in the PI group compared to the NI group, but only in the remembered-pain from during the drilling ($F(1, 40) = 9.70$, $p = .004$, 95% CI [.92 – 4.32]) (Figure 2, left panel). There was no effect of Information in the patients that reported present pain ($F(1, 39) = 0.02$, $p = .71$). The quadratic trend across Timepoint ($F(1,40) = 41.44$, $p = .000001$) was due to the increase in pain during drilling, that rapidly waned off after drilling.

Stress and arousal

Stress: The main effect of Timepoint was significant ($F(2.64, 100,80) = 40.78$, $p = .000001$, $n_p^2 = .69$). Tukey's HSD showed that stress levels were similar in the first two Timepoints ($p = .97$), and then decreased immediately after drilling (Timepoint 2 vs. Timepoint 3, $p = .001$), with a further decrease at 15 minutes after drilling (Timepoint 3 vs. Timepoint 4, $p = .0002$).

The stress levels were the same in both groups, and there was no main effect of Information or interaction of Information by Timepoint ($p = .10$) (Figure 2, right panel). No other main effects or interactions were significant for stress.

There were no significant main effects or interactions in the arousal data.

Effect of stress on pain

Linear regression further showed that stress at the first timepoint (before the treatment started), predicted mean pain report in the four timepoints ($F(1, 42) = 8.24$, $\beta = .40$, $t = 2.87$, $p = .006$, 95% CI [.06–.38]). A separate analysis with pain report at the second timepoint during drilling as dependent variable confirmed that higher stress at the first timepoint predicted higher pain unpleasantness at the second timepoint ($F(1,42) = 9.49$, $\beta = .43$, $t = 3.08$, $p = .004$, 95% CI [.15–.72]). A follow-up analysis

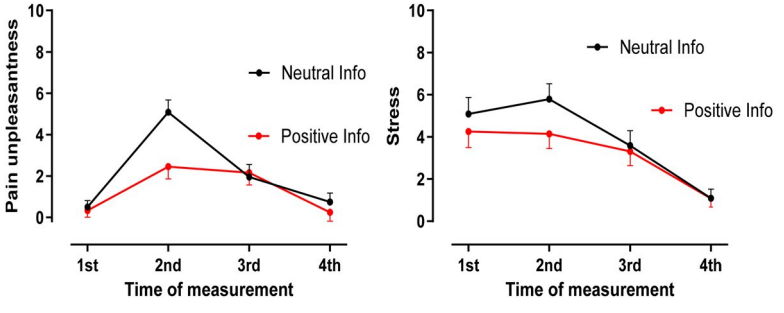

Figure 2. Remembered pain unpleasantness (left panel) was lower at the second timepoint measurement in the Positive information (PI, red line) group compared to the Neutral information (NI, black line) group. Stress (right panel) was not significantly different between the groups.

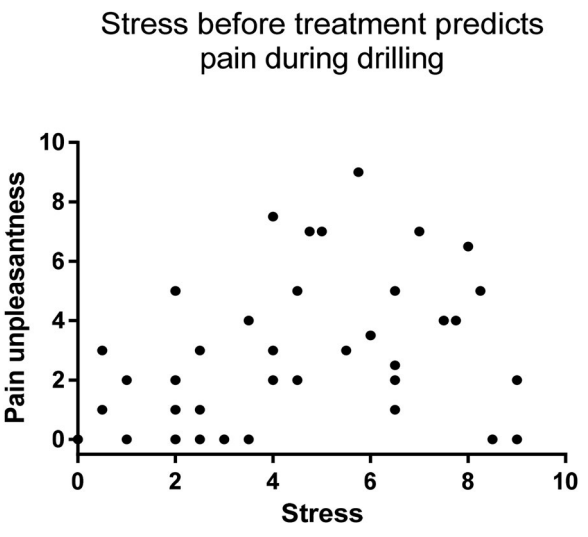

Figure 3. In the Neutral information group, higher stress at the 1st timepoint measurement predicted higher pain unpleasantness at the second timepoint measurement.

showed that this was true only for the NI group ($F(1,20) = 4.63$, $\beta = .43$, $t = 2.15$, $p = .044$, 95% CI [.15–.93]). Stress at the first timepoint did not predict pain during drilling in the PI group ($F(1, 20) = .29$, $p = .29$) (Figure 3).

Fear of pain

Fear of medical pain predicted stress levels across timepoints ($F(1, 41) = 4.88$, $\beta = .32$, $t = 2.21$, $p = .03$, 95% CI [.08 – 1.84]), and the interaction of fear of medical pain by Timepoint was also significant ($F(2.73, 103.89) = 4.53$, $p = .006$). Follow-up tests showed that fear of medical pain predicted stress levels at the first ($F(1,39) = 10.26$, $p = .03$) and second timepoint ($F(1, 39) = 4.52$, $p = .040$), but not in timepoint three and four ($Fs < 1$, n.s.). Fear of severe and minor pain did not predict stress levels ($F(1, 39) < 3.64$, $p > .063$). There were no main effects or interactions in the arousal data.

Fear of pain did not predict arousal levels in any timepoints ($F(1, 35) = 2.18$, $p = .14$).

Separate linear regression analyses showed that neither fear of severe, minor nor medical pain predicted pain across the four timepoints ($Fs(1, 39) < 3.19$, $p > .082$). A linear regression analysis with pain levels at the second timepoint as the dependent variable, showed that no dimension of fear of pain predicted pain levels ($Fs(1, 35) < 2.27$, $ps > .13$).

Discussion

The main findings were first that the pain ratings in the PI group were about 50% lower than pain ratings in the NI group at the second timepoint, when pain was most intense. Second, stress levels before treatment predicted pain at the second timepoint only in the NI group. Lastly, fear of medical pain predicted stress levels.

Confirmation of Hypothesis '1', that pain increased during drilling, was a prerequisite for the testing of Hypothesis '2' that the PI group should display lower pain than the NI group during drilling. The lower pain in the PI group during drilling confirmed hypothesis '2'. The reduced pain could be due to one or several dimensions in the information provided to the PI group. This group received information that was more positive (small damage, easily repaired, improved, gentle, pleasant etc.), more detailed, more assuring, more comforting, and gave patients the control of when to take breaks. Importantly, the dentist and the dental assistant performing the treatment gave the positive information to the patients in the PI group. The reduction in pain at the second timepoint in the PI group was not seen in the present pain reported immediately after the drilling, which was most likely due to very low reports of pain after drilling. The retrospective (remembered) report of pain was about the pain that was remembered from during the drilling, which was reported less than about 10 minutes after the time the pain was inflicted by drilling, therefore, there is a possibility that the retrospective reports were distorted due to memory (Corli et al., 1986; Rainville et al., 2004). When patients are asked to remember how painful a medical procedure was, they usually recall based on the most painful moments of that procedure. For instance, Redelmeier and Kahneman (1996) showed that when patients were asked to remember how painful a colonoscopy and a lithotripsy were an hour after the conclusion of the procedures, the retrospective pain reports from the procedure was highly correlated with the peak pain reports during the procedures. Thus, it is possible in our experiment that when patients were asked to remember the pain during the drilling, they recalled the most painful moments of the procedure. It is also shown that retrospective reports of pain can be higher than real time reports, mostly based on how long the time window between the real time pain and the retrieval is, with longer time windows associated with higher retrospective reports (e.g. Broderick et al., 2008). As the time interval between the present pain reports and the remembered pain usually was less than 10 minutes, it is therefore less likely that the remembered reports were much higher than the experienced pain during drilling.

Stress levels before drilling were the same as during drilling, disconfirming Hypothesis '3' that stress should increase during drilling. Thus, anticipatory stress was at the same levels as stress experienced during drilling, which is in contrast with former studies. For instance, Logan et al. (1996) reported that the anticipatory stress before a molar extraction procedure was higher than the stress experienced during the procedure, and this difference was larger for patients with chronic pain. Hypothesis '4' was also disconfirmed, as stress levels were the same in the PI and NI groups, showing that the positively enhanced information about the treatment failed to lower the experienced stress during the procedure. Prior studies have shown that positive information about treatment reduces symptoms and negative emotions (e.g. Aslaksen & Flaten, 2008). However, these studies have usually tested the effects of suggestive information against 'no information' or 'negative information' (e.g. Bingel et al., 2011), whereas in this experiment, the positive information was tested against neutral and standard information, that even though less positive, still informed about the effectiveness of the treatment. Therefore, the neutral information may also have reduced stress.

Hypothesis '5', that stress levels at the first timepoint predicted pain levels across the four timepoints, was confirmed. This is in line with previous research showing

that negative emotions are associated with negative treatment outcomes (e.g. Aslaksen et al., 2011; Rhudy et al., 2018). Aslaksen and Flaten (2008) reported that reduced stress predicted reduced pain after administration of a placebo with suggestive verbal information. Interestingly, our data showed that higher stress at the first timepoint predicted increased pain during drilling (second timepoint) only in the NI group. Stress at the first timepoint (anticipatory stress) did not predict pain during drilling (second timepoint) in the PI group. Aslaksen et al. (2011) showed that lower anticipatory stress before experimentally induced pain was related to reduced pain following the administration of a placebo with positive verbal suggestions. Thus, beside confirming the role of stress in treatment outcome, our data shows that although positive information administered in the PI group did not reduce stress, it weakened the effects of stress on pain.

Higher fear of medical pain predicted stress levels, which has been reported before (e.g. Lyby et al., 2010), and confirmed Hypothesis '6'. Hypothesis '7' was disconfirmed, as fear of medical pain did not predict pain. This is contrary to earlier reports showing that higher fear of pain increased pain reports, and reduced placebo analgesia (Lyby et al., 2010). Aslaksen and Lyby (2015) in a laboratory experiment on healthy participants showed that higher levels of fear of medical pain predicted stress levels, and the stress levels in turn predicted the increased pain due to administration of medically inactive agent with negative verbal information (i.e. that it will increase pain). One possibility that the medical fear did not predict pain in our experiment is that out of the 10 items that index medical fear in the FPQ III, only two describe dental procedures. Thus, a questionnaire construed to index dental fear might have been more appropriate.

Pain unpleasantness and pain intensity were consistently correlated within each timepoint. However, mean pain unpleasantness was consistently higher than mean pain intensity at all timepoints. Furthermore, the effect of information was stronger in the pain unpleasantness data. Pain intensity is hypothesized to index the sensory aspects of pain, whereas pain unpleasantness indexes the emotional aspects (Price et al., 1983). That stronger effects were seen in pain unpleasantness can probably be explained by the fact that the study was run in a dental clinic and stress levels were quite high before and during drilling.

The placebo effect is usually defined as the psychological and/or physiological response to a placebo that is administrated with information that the substance or procedure will have an effect in the individual (Flaten & Al'absi, 2020). Although effective treatment and not a placebo was administrated in the present experiment, the reduction of pain in the PI group can be defined as a placebo effect as the reduced pain may have been due to the positive information about treatment (e.g. Barnes et al., 2023; De Pascalis et al., 2002). A number of studies using an open—hidden procedure, where active medication has been administrated to participants, but without information about the time of administration, have displayed robust placebo effects (e.g. Benedetti et al., 2006; Levine & Gordon, 1984). Open administration of treatment, where both the doctor and the patient know an active treatment has been administrated, has been shown to enhance treatment outcome compared to hidden administrations, where the patient does not know that the active treatment has been administrated (e.g. Amanzio et al., 2001; Colloca et al., 2004). Thus, even

when active treatment is administered, placebo effects can enhance the effect of the treatment.

Other studies have shown that more positive and more comforting verbal instructions can enhance placebo effects and treatment outcome, compared to when negative words are used. For instance, Dutt-Gupta et al. (2007) showed that when gentler and more comforting verbal instructions were used for patients undergoing an IV cannulation before elective surgery, patients had lower spontaneous pain vocalizations at the time of IV insertion, compared to when 'harsh' verbal instructions (i.e. using words such as sting or pain) were used. In present study, a placebo effect was observed in pain unpleasantness and not in pain intensity, probably because the positive information reduced the correlation between the negative emotion of stress and pain unpleasantness. In the NI group, on the other hand, increased stress predicted increased pain unpleasantness.

An alternative explanation of the placebo effect in the PI group is that the treatment team may have behaved differently to the patients in that group, compared to the NI group. Since the positive information given to the patients in E1 was provided by the dental treatment team, it could not be ruled out that the dentist behaved differently to the two groups. This was investigated in Experiment Two.

Experiment two

The dentist and the dental assistant in Experiment One (E1) provided the treatment information to the patients. In Experiment Two (E2) the delivery of information was performed by another dental assistant (hereafter 'second dental assistant') who was not involved in the treatment procedure, termed hidden administration, meaning that the dentist and the dental assistant performing the dental procedure were blinded to which patients received the neutral (NI) or positive information (PI). Moreover, in E2 the expected and rated efficacy of the anaesthetic were recorded. Furthermore, the five item Modified Dental Anxiety Scale (MDAS; Humphris et al., 1995) was included, as it was hypothesized to be more appropriate for the patient population than the FPQ III. Lastly, as the same dentist performed both experiments, an interview was carried out with the dentist (second author) after the results of both experiments were disclosed to her.

The same design as in E1 was used in E2. Pain and stress were reported before drilling (firsttimepoint), after drilling (second timepoint), immediately after treatment (third timepoint), and 15 minutes after the end of treatment (fourth or last timepoint). Before administration of the anaesthetic at the first timepoint, the patients were asked to rate their expected efficacy of the anaesthetic, and after the treatment was over (third timepoint), they were asked to rate how effective they thought the anaesthetic was (rated efficacy) in reducing pain. In E2 a more elaborated positive information was administrated to the PI group. Moreover, in E2 only the remembered pain was measured at the second timepoint, as pain levels were too low in patients reporting pain after the drilling in E1. Beside testing the hypotheses in E1 (Hypotheses 1–7, see E1), the following hypotheses were investigated in E2: 8). If the placebo effect seen in E1 was due to the information provided about the treatment, then pain should be lower in the PI group of E2 as well. However, if the placebo effect was due to other aspects, then there should be no

differences between the two groups. Furthermore, 9). Patients in the PI group will have higher expected efficacy of anaesthetic than patients in the NI group, and 10). Patients in the PI group will rate the efficacy of the anaesthetic higher than patients in the NI group. 11). Lastly, higher dental anxiety assessed by the MDAS predicts higher stress and pain levels.

Methods

Patients

Participants were 52 (age range 23-73 years, mean age 46.57 years, 28 females, $SD = 13.07$) patients that attended a dental clinic in Stavanger, Norway. None of the patients reported any serious disease. Five patients did not fill out the FPQ III and MDAS, so the analyses for FPQ and MDAS were performed on 47 patients. Nine patients did not rate the expected and rated efficacy of the anaesthesia, so the analyses for these two scales were performed on 43 patients (24 patients in the NI and 19 patients in the PI group). The recruitment procedure, and the inclusion and exclusion criteria were the same as in E1.

Ethics

E2 was ethically approved through the same permission for E1.

Questionnaires

The questionnaires were the same as in E1, as were the recording of pain, stress, and arousal, which followed the instructions used in E1 to describe to patients how to report pain intensity and unpleasantness. In addition, the *Modified Dental Anxiety Scale* was administered (MDAS; Humphris et al., 1995). MDAS is a self-rating scale with five items using a five-point Likert scale (1-5) with higher scores representing higher dental anxiety. The items ask about anxiety a day before the dental treatment (item 1), anxiety while sitting in the waiting room to receive treatment (item 2), anxiety about getting a tooth drilled (item 3), and scaled (item 3), and lastly, anxiety about receiving an anaesthetic (item5). The total score, calculated by summing all scores is used as the dental anxiety score (Humphris et al., 2000).

Expected and rated efficacy. The patients were also asked to rate on a scale from '0' to '10' how much they expected the anaesthetic to reduce pain, and how much the anaesthetic reduced pain, after administration of the anaesthetic (i.e. rated efficacy).

Medication

Medication was the same as in E1.

Blinding

The dental treatment and the procedure were the same in both groups and the dental team and the patients were aware of the treatment administered. The study was introduced the same way as in E1, so the patients were blinded to the true aim

of the study. Contrary to E1, the dental treatment team was not aware which information the patients received. Therefore, the dental team was blinded to the grouping of the patients, i.e. which information was delivered to which patients. This was done by having a second dental assistant not engaged in the treatment, who performed the randomization and provided the information to the patients according to their assigned groups. The study did not test the effectiveness of the blinding on dental team.

Dentist

The same dentist and the dental assistant as in E1 performed the treatment in E2. However, to blind the dental treatment team about grouping of patients, a second dental assistant, a female about the age of 30, who was not engaged in the treatment procedure delivered the information to the patients in both groups.

Routine practice

Similar to E1, the experimental aspects of the study, including randomization, giving out the treatment information (for the second dental assistant), and recording of the subjective measurements of pain and stress were practiced with the dental team.

Randomization

The same method of randomization as in E1 was used to randomize patients to the groups in E2. Following the randomization, 27 participants (12 females) were assigned to the NI group, and 25 (12 females) to the PI group.

Procedure

The procedure for E2 was generally the same as E1, with the difference that the grouping of the patients and the delivery of the information were performed by a second dental assistant who was not engaged in the treatment procedure. After arrival at the dental clinic, the second dental assistant who was not involved in the treatment guided the patients. Before the treatment information was provided to patients, the second assistant asked the patients to fill out the FPQ III and MDAS, and explained how to report ratings of pain, stress, and arousal similarly to E1. At the time of randomization, the second dental assistant performed the randomization and provided the information to the patients. Then, the second dental assistant went out of the room and the dentist and her dental assistant performing the treatment came back to the room and started the treatment procedure (see Figure 1 for treatment procedure). The dentist inspected the molar and asked patients to rate how much they expected the anaesthesia would be effective in reducing pain. After rating the expected efficacy of the anaesthetic, the dentist anaesthetized the molar with the Wand STA as in E1, and then after ten minutes waiting for the anaesthesia to take effect, the dentist started drilling the molar. For the second timepoint all patients were asked to report what pain intensity, unpleasantness, stress and arousal they remembered from during the drilling (remembered pain). The treatment was concluded following the filling of the molar/premolar cavity with the plastic filling. Immediately after the treatment was over, the patients were asked to report their ratings

of pain, stress, arousal and rated efficacy of the anaesthesia in reducing pain (third time-point). Then the patients were guided to the waiting room. After 15 min, the patients were again asked to report their ratings of pain, stress, and arousal (fourth or last time-point) (See Figure 1).

The NI group received the following information: 'The treatment you will receive is a standard filling therapy where plastic is used as the filler. The duration of the procedure will be around 45 minutes. We will use the most common anaesthesia that is called Xylocain/adrenalin. The mucuosa on the area where the injection will be made will first be anaesthesized with a cream containing anaesthesia. The injection with the anaesthetic will be made with a pen. It is common to have some pain or unpleasantness when the anaesthesia wears off. The tooth can be very sensitive to cold and/or chewing for a shorter or longer period. If the unpleasantness is very strong you may contact us for a check'.

The PI group received the following information: 'The treatment you will receive is a standard filling therapy where a plastic or composite filler is used. The composite consists of light hardening resin, about 20%, and the rest is filler particles that are already hardened. Composite is the most used material in small and medium fillings, and is of medium strength. We will use the most common type of anaesthesia that is called Xylocain/adrenalin Dental. It contains lidocaine, which blocks the nerve signals, and adrenaline which contracts the blood vessels so that the anesthetic stays in the gums. The anesthesia works quickly and lasts up to 60 min. The purpose with the anaesthesia is that you should not feel any pain during the treatment. You can still feel pressure in the area, but the sensation of pain is abolished. Tell me if you still feel unpleasantness, and you will get more anaesthesia. It is usual with a little unpleasantness when the anaesthesia wears off. This is temporary, but can be experienced as gross and maybe even painful. The tooth can be very sensitive to cold and/or chewing for a shorter period of some days, or for a longer period of some months. The reason for this is the filler we use might shrink a little after hardening. This leads to some tension in the tooth, and the nerves in the tooth will register this. After a while this will balance out and the tooth calms down. This is a very common complication and is completely harmless. This will give the tooth the calmness to find the balance again. The filling can be too high, so the pressure will get too high during biting. In this situation it will be necessary to adjust the filling to normalize biting. On rare occasions the nerve in the tooth will die as a result of attack by caries or by the following treatment. In this situation the tooth may need to have root canal treatment. In all cases, you should contact us should you have any discomfort that persists. If you have questions about the treatment that has been done or other things you want to talk to the dentist about, you are welcome to contact us. The treatment will last for about 45 min'. The PI group also were shown an X-ray of the tooth and were told what a healthy tooth is and what a sick tooth is, and where on the tooth the filling will be put. The X-ray was also used to explain the technique of anaesthesia, where it is administrated and how the drug is transported to the tooth'.

During treatment the patients in the PI group received the following information: 'Let me know when you are ready to start treatment. You can stop the treatment if you feel that you need a break, either by lifting a hand or by giving a sign another way. I will stop treatment underway to make sure that you are OK. You

should then tell me how you feel about the treatment. You can stop the treatment at any time. Then we will put in a temporary filling and finish the treatment another day'.

Statistical power

A partial eta square of .07, equivalent to a *f* effect size of .276, was observed in E1 within the PI group at the second timepoint measurement of pain unpleasantness. This effect size was used to calculate the sample size for E2. Using G*Power software (Faul et al., 2007), a priori power analysis for an ANOVA test with repeated measures, and between factors, assuming an *f* effect size of .276, α = .05, and a power of .80 for an experiment with 2 groups suggested a minimum total sample size of 70. However, a sample size of 52 was chosen based on the practical restraints of the study, and the observation in E1 of a medium effect (n_p^2 = .07) for the manipulation of the information was observed even though the study was underpowered.

Design and statistics

The design was a 2 Information × 4 Timepoint mixed design, with Information as between-group factor, and Timepoint as the within-subjects factor. The data were analysed by repeated measures analysis of variance. The Greenhouse- Geisser correction (Schwertman, 1978) was used to correct for inflated degrees of freedom. The predictions were tested by a priori contrast analysis, and other follow-up tests were done by Tukey's HSD. Separate linear regression analyses were used to analyse the effect of stress, arousal, and fear of pain, expected and rated efficacy on pain unpleasantness. The mean of the four Timepoint measurements of pain unpleasantness was used as the dependent variable for the regressions. Since the MDAS predicted pain unpleasantness at the second timepoint, a mediation analysis (Hayes, 2017) was performed using Process Macro (applying model 4 with 5000 bootstrap samples) (Hayes, 2017), with MDAS as independent variable, stress and arousal as mediators, and pain unpleasantness at the second timepoint as the dependent variable. Moreover, Stress was regressed on fear of pain and dental anxiety. The mean of the four Timepoint measurements of stress was used as the dependent variable for the regressions. The overall pain and stress report across all Timepoints was normally distributed and other assumptions to conduct regression analyses were met.

Results

The pain intensity and pain unpleasantness data correlated within each Timepoint (*r*s between 0.59 and 0.92, *p*s < 0.001) and thus only the pain unpleasantness data are reported. The mean and standard deviation of pain intensity, unpleasantness, stress, arousal, expected and rated efficacy of anaesthesia of groups across timepoints are reported in Table 2.

Pain unpleasantness

The main effect of Timepoint ($F(2.41, 120.54) = 24.24$, $p = .00001$, $n_p^2 = .49$) was due to increased pain at the second and third Timepoints compared to first and last

Table 2. Pain intensity, unpleasantness, stress, and arousal data across groups and phases.

Group	Timepoint	Pain intensity	Pain unpleasantness	Stress	Arousal	Expected efficacy	Rated efficacy
Positive Info	TM1	0.08; 0.40	0.14; 0.72	2.99; 2.67	6.90; 1.58	8.53; 1.89	–
(*M*; *SD*)	TM2	0.98; 1.56	1.98; 2.25	4.30; 2.75	7.35; 1.52	–	–
N = 25	TM3	1.00; 1.54	1.74; 1.99	3.30; 2.52	7.30; 1.58	–	9.32; 0.46
	TM4	0.26; 1.20	0.42; 180	1.19; 170	7.09; 1.99	–	–
Neutral Info	TM1	0; 0	0.15; 0.43	3.21; 2.72	6.83; 1.68	8.92; 1.84	–
(*M*; *SD*)	TM2	0.49; 0.74	2.04; 2.46	5.07; 7.79	6.95; 1.82	–	–
N = 27	TM3	0.75; 1.24	1.97; 2.10	3.17; 2.54	7.24; 1.89	–	9.54; 0.32
	TM4	0.15; 0.45	0.52; 0.84	0.86; 1.30	6.63; 2.24	–	–

Abbreviations: *M*: mean; *SD*: standard deviation; TM: timepoint measurements.

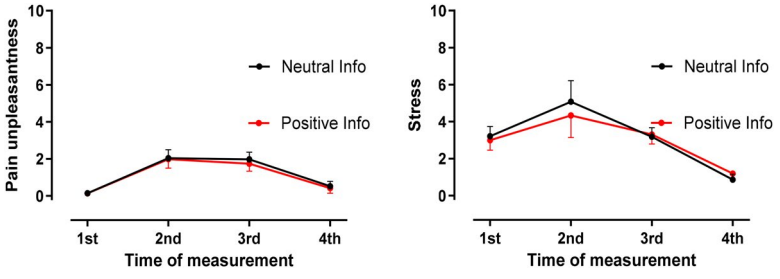

Figure 4. Pain unpleasantness (left panel) and stress (right panel) did not differ between the PI (red line) and NI (black line) groups at any timepoint measurement.

Timepoints (p = .00009). There was no effect of Information and no interaction of Information by Timepoint (Fs < 1, n.s.) (Figure 4, left panel).

Stress and arousal

Stress: the main effect of Timepoint was significant (F(1.47, 73,58) = 12.71, p = .0001, n_p^2 = .56). Tukey's HSD showed that stress increased from the first to the second Timepoint (p = .037), and then decreased from the second to the fourth Timepoint (p = .000008). No other main effects or interactions were significant (ps > .43) (Figure 4, right panel).

There were no main effects or interactions in the arousal data.

Effects of stress and arousal on pain

The linear regression showed that stress at the firstTimepoint before the treatment started, did not predict mean pain report across the four Timepoints (F(1, 49) = 2.23, p = .15). Arousal at the first Timepoint, on the other hand, predicted pain report across the four Timepoints (F(1,50) = 6.15, β = −0.33, t = −2.48 p = .018, 95% CI [-0.45—−0.04]). Arousal at the first Timepoint did not predict pain during drilling at the second Timepoint (F(1, 49) = 1.50, p = .23).

Fear of pain

Separate linear regression analyses showed that fear of medical pain did not predict pain unpleasantness across the four Timepoints (F(1, 45) = 3.84, p = .056). Fear of severe pain and fear of minor pain did not predict pain (Fs < 1.6, ps > .20) neither. However, fear of medical pain predicted stress across all Timepoints (F(1, 45) = 20.59,

β = .36, t = 4.53, p = .00004, 95% CI [.92 – 2.39]). Fear of severe and minor pain did not predict stress levels ($F(1, 40) < 2.20$, $ps > .16$). Fear of minor pain predicted arousal levels across Timepoints ($F(1, 44) = 5.47$, β = .33, t = 2.33, p = .02, 95% CI [.13–1.82]). Fear of severe and fear of medical pain did not predict arousal levels ($Fs < 2.20$, $ps > .16$).

Dental anxiety

Dental anxiety predicted stress before ($F(1, 45) = 165.47$, β = .88, t = 12.86, p = .001, 95% CI [.44–.60]) and during drilling (second Timepoint; $F(1, 45) = 9.41$, β = .41, t = 3.06, p = .004, 95% CI [.20–.97]). Dental anxiety predicted arousal before ($F(1,45) = 11.41$, β = −0.45, t = −3.37, p = .002, 95% CI [−0.26 to −0.06]) and during drilling (at the 2nd Timepoint; $F(1,45) = 4.93$, β = −0.31, t = −2.22, p = .032, 95% CI [−0.23 to −0.01]). Dental anxiety also predicted pain unpleasantness during the drilling, at the second Timepoint ($F(1, 45) = 8.66$, β = .40, t = 2.94, p = .005, 95% CI [.07–.37]).

Since dental anxiety predicted stress, arousal and pain, two mediation analyses investigated whether the effect of dental anxiety on pain at the second timepoint was mediated by stress and/or arousal before and during the drilling. When stress and dental anxiety were entered into the linear regression, none of them predicted pain at the second Timepoint ($Fs < .20$, $ps > 0.58$). However, when arousal and dental anxiety were entered into the linear regression, dental anxiety was still significant ($F(1, 45) = 6.39$, B = 1.11, p = .015), whereas arousal was not ($F < 1$, ns.).

Expectations of effects of anaesthesia

There was no main effect of Information on expected efficacy of the effect of the anaesthetic ($F(1, 50) = .61$, p = .42), nor was there any difference between the groups in how much they rated that the anaesthesia had reduced pain ($F(1, 50) = .64$, p = .42). However, the rated efficacy of the anaesthesia correlated with the pain levels in the PI group ($r(25)$ = second Timepoint = −0.47, p = .031; thirdTimepoint = −0.49, p = .023), and not for the NI group ($r(27)$ = second Timepoint = −0.21, p = .21; thirdTimepoint = −0.29, p = .13).

Interview with the dentist

The same dental treatment team (including a dentist and a dental assistant) performed both experiments. Therefore, to further investigate the possible reasons for the reduced pain in E1 and the lack of a reduction in pain in E2, a short interview was made with the main dentist (the second author; PH) who carried out both experiments [the statements in italics are quotes from the dentist].

After the results were disclosed to the dentist, the dentist was asked about what she thought about the reasons for the lower pain report in E1, and the lack of a reduction in pain in E2. The dentist stated that in E1, she felt more *comfortable and relaxed* during the treatment when they provided the positive information themselves, and they felt like the patient and the treatment team were in the same team: '*I* [the dentist] *felt like that the patients knew that we were on their side, cared about them*'. The dentist mentioned that for her it felt '*more like an experiment when we* [the dental treatment team] *were instructed to provide the neutral information to the patients*, as *it*

was not the same way we [the dental treatment team] *usually provide the information to our* [the dental treatment team] *patients*'. The dentist said that in E2, she felt as it *was* '*more serious, and I was not allowed to have the connection with my patient. I felt a little more stressed, as it was not like the way I usually perform the treatment. I remember I smiled less and had less eye contact with the patients. In experiment One I felt more relaxed when we gave the extended* [positive] *information about the treatment ourselves*'.

Discussion

The main finding in E2 was that pain and stress levels were similar between the group that received neutral information and the group that received positive information about dental treatment. Second, higher arousal levels before treatment predicted the pain across four timepoints. Third, a mediation analysis showed that dental anxiety explained the effect of arousal on pain. Fourth, fear of medical pain predicted stress levels, and fear of minor pain predicted arousal levels. Fifth, dental anxiety predicted stress and arousal levels before and during drilling, and pain levels at the second timepoint.

The pain report increased during drilling (second timepoint) confirming Hypothesis '1', which was a prerequisite to test Hypothesis '2'. The pain reports during drilling (second timepoint) did not differ between the groups, disconfirming hypothesis '2', showing that the positive information provided to the PI group failed to generate a placebo effect as it did in E1. Both pain intensity and unpleasantness reports were low at the second and third timepoint and this floor effect partly explains the lack of an effect of the positive information in the PI group.

Previous studies have shown that open administration of treatment have beneficial effects on treatment outcome (Amanzio et al., 2001; Benedetti et al., 2003; e.g. Coleshill et al., 2018). In the present study, both groups knew that an effective medication was administered to block the pain from drilling, and the positive information did not enhance the effect of the treatment.

Administration of treatment with positive information yields a better treatment outcome than when the treatment is administered without positive information or with harsh verbal instructions (Aslaksen & Lyby, 2015; Dutt-Gupta et al., 2007; Helfer et al., 2022; Wang et al., 2008). Varelmann et al. (2010) for example showed that when 'gentler' and 'more comforting' words were used before administration of a local anaesthesia, women at term gestation undergoing a neuraxial analgesia reported lower pain compared to when the anaesthesia was administered with negative verbal instructions including words about 'pain' and 'burning'. However, this was not seen in this experiment. Different from former studies, in this experiment the positive information was delivered by a second dental assistant who was not engaged in treatment, and the dentist and the dental assistant performing the treatment were blinded to which information patients received. This method of delivery of information may have blocked the effects of positive information in generation of a placebo effect. Thus, our results suggest that the effectiveness of positive information in enhancement of treatment and placebo effects depend on the method of delivery of that information.

As shown by the power analysis, this study was moderately underpowered, and instead of the planned 70 patients, 52 patients were tested due to practical restraints.

This may have increased the chance of a Type II error, resulting in a failure to observe a true effect, and therefore, the results should be interpreted with caution. However, an effect of the positive information was observed in E1 even though the achieved power of that study was lower than E2. This makes the lack of an effect in the E2 less likely to be due to low power, but due to a different method of delivery of positive information.

Stress increased during drilling (at the second timepoint) in both groups, confirming hypotheses '3'. The positive information delivered to the PI group did not reduce stress, which disconfirmed hypothesis '4' and is discussed in E1. Stress levels before drilling (at the first timepoint) did not predict pain levels during drilling (at the second timepoint). Even though the stress levels were moderate, the pain levels during drilling were low and this may explain the lack of association between stress and pain in this experiment. However, arousal at the first timepoint predicted pain levels across all timepoints. The more aroused the patients were, the less pain they felt. A review on the effect of situationally induced arousal on pain (Rhudy & Meagher, 2001) concluded that negative emotions lead to inhibition of pain when the emotions are highly arousing. Arousal levels were about seven on a 10-point scale in E2, so arousal was high. Thus, the relation of high arousal and reduced pain was in line with previous studies. There are also studies on the effect of caffeine-induced arousal on pain. Caffeine is an adenosine antagonist that increases physiological and subjective arousal (Ribeiro & Sebastião, 2010). Caffeine has a slight analgesic effect (Bjørkedal & Flaten, 2011), and several pain-relieving medications are sold with caffeine as adjuvant. This combination has a larger analgesic effect than the pain-relievers alone. However, as caffeine has effects other than increasing arousal, it cannot be stated that it is the arousal that reduces pain. The present findings, however, indicate that increased arousal reduces pain, although the effect is slight.

Stress before drilling did not predict pain during drilling, disconfirming hypothesis '5', showing that anticipatory stress did not affect pain levels. Negative emotions have been shown to be linked with higher pain reports (e.g. Aslaksen et al., 2011; Rhudy et al., 2018), however, negative emotions can also have pain inhibitory effects when they are highly arousing (e.g. Rhudy & Meagher, 2001). As indicated by the mediation analysis, dental anxiety predicted pain levels independently from stress and arousal. Therefore, one explanation for the lack of an association between stress and pain in this experiment is high levels of arousal which may have masked the effects of stress on pain.

Fear of medical pain predicted stress levels and fear of minor pain predicted arousal across timepoints, and this partly confirmed hypothesis '6'. Moreover, fear of pain did not predict pain levels at the second timepoint, and this disconfirmed hypothesis '7' and is discussed in E1.

The expected and rated efficacy of anaesthesia were the same in the PI group and the NI group, rejecting hypotheses '9' and '10', so the positive information about the anaesthetic failed to enhance expectations about the treatment. This is in line with the lack of a placebo analgesic effect in patients in the PI group. The pain at the second and third timepoints were negatively correlated with the rated efficacy of the anaesthetics in the PI group, meaning that the less pain the patients experienced, the higher they rated the efficacy of the anaesthetics.

Dental anxiety predicted stress, arousal, and pain levels during drilling, therefore hypothesis '11' was confirmed. These results confirmed former studies suggesting that higher dental anxiety is linked to higher report of dental pain, and also confirmed our hypothesis that a scale more specific to dental pain would be more appropriate for dental patients (Humphris et al., 2009).

General discussion

In two experiments on dental patients, it was observed that the positive information about a dental treatment elicited a placebo effect when it was delivered to patients by the dentist and the assistant who performed the treatment in E1 (open administration). In E2, however, when similar information was delivered by a dental assistant who was not engaged in the treatment (hidden administration), the positive information did not reduce pain. Thus, the hypothesis that the positively framed information was the cause of the placebo effect in the PI group in E1 was rejected, suggesting that factors other than the positive information elicited the placebo effect in E1. One possibility is that the behaviour of the treatment team, unbeknownst to the team, was different in the PI and NI groups in E1. In E2, where the treatment team was blinded about which information was delivered to which patients, the behaviour of the treatment team was the same in both groups. Kaptchuk et al. (2008) studied the effect of the patient-practitioner relationship on placebo acupuncture of irritable bowel syndrome. Patients were randomized to a waiting list control group, to placebo acupuncture, or to a placebo acupuncture group where the patient-practitioner relationship was 'augmented' by warmth, attention, and confidence. The practitioners in the placebo acupuncture did not communicate with the patients. The results showed that all measures of symptom severity and quality of life improved in the group that received the augmented patient-practitioner interaction. Thus, the augmented patient-practitioner relationship had a significant effect on pain. Similar processes could have played a role in the present study. This hypothesis is further supported by the finding that positive information in E1 weakened the relationship between stress and pain, which was not seen in E2.

The interview with the dentist revealed that the dentists had more positive behaviours such as more smiling and eye contact with the PI group in E1, which the dentist did not have in E2. As information was about the same in both experiments, information about the treatment most likely was not the reason for the reduced pain in E1. Rather, the behaviour of the dentist, such as smiling and having enhanced eye contact, could have reduced pain in E1, which also weakened the effects of stress on pain. This is in line with Levine and Gordon (1984) that showed that even when placebo was given intravenously by a person in another room, out of sight and knowledge of the research participant, a placebo response was elicited, suggesting that subtle cues were responsible for the reduction in pain. Such subtle cues have been shown to include the behaviours of the person administering the treatment. Chen et al. (2019) tested two groups of participants who played either the role of a doctor or a patient. Both groups were told that the doctors would apply either a pain-relieving or an inert cream to the patient's hand, followed by painful stimulation. However, both creams were inactive. Before the patients received the cream, the

doctors were made to believe that one of the creams (the so-called pain-relieving cream) lowered pain through a classical conditioning procedure. Then, the doctors applied the creams, that they thought were active or inactive, but without telling patients which cream was the pain-relieving cream. The results showed that patients had lower pain reports and stress when doctors applied the so-called active cream. Videos of the experimenters and participants faces showed that experimenters who believed the creams were real had different facial expressions (e.g. more positive behaviours, and expressing less facial pain expressions) than the experimenters who believed that only half of the creams were real. This indicates that the doctors somehow transmitted their "knowledge" of the content of the cream to the participants through the subtle cues of facial expressions. A review by Daniali and Flaten (2019) found that positive non-verbal behaviours of healthcare providers can enhance placebo effects. Although the nonverbal behaviours were not investigated in the present study, the reported pain during the drilling was shown to be lower when the positive information was accompanied by positive nonverbal behaviours of the dentist, suggesting the role of the nonverbal behaviours of the providers in the effectiveness of positive information. The role of nonverbal behaviours of healthcare providers have been reported in previous studies (e.g. Chen et al., 2019; Ruben et al., 2017), however, the underlying mechanisms are not clear. A more recent study reported no significant differences between the effects of facial expressions, body gestures, and tone of voice of experimenters on pain reports, suggesting that the separate nonverbal behaviours of healthcare providers may not have an effect (Daniali et al., 2024). Instead, the impact may arise from the combination of nonverbal behaviours that convey a psychosocial meaning (Daniali et al., 2023). What the present results add is that the effectiveness of positive information in generation of placebo effects can depend on the method of delivery of that information, which may be more successful when is performed by a healthcare provider administering the treatment with more positive nonverbal behaviours. This notion needs to be investigated in future studies.

The placebo effect was observed in pain remembered from the drilling. The amplitude of placebo effects can be larger in retrospective reports of pain (e.g. De Pascalis et al., 2002; Price et al., 1999), and remembered pain can be of higher amplitude compared to reports of that pain at the time of painful stimulation (e.g. Broderick et al., 2008; Kaptchuk et al., 2009; Rainville et al., 2004). However, the time from the painful drilling to the report of pain was usually less than 10 minutes, making it unlikely for the retrospective reports to be severely affected by memory.

In E1, the positive information delivered by the treatment team weakened the effects of stress on pain. Vambheim et al. (2021) showed that the placebo effect on pain and stress might have different underlying mechanisms. In that study authors tested the effects of a placebo cream on experimentally induced pain and reported that the cream plus positive information and conditioning was successful in eliciting a placebo response in stress levels, but not on pain reports.

Conclusion

The placebo effect was dependent on the method of delivery of information, and the positive information alone was not sufficient to elicit a placebo effect. This is

probably through the effects the method of delivery of information has on weakening the effects of negative emotions on pain. Moreover, this could also indicate that the behaviour of healthcare provider can be more important in elicitation of placebo effects than what has been acknowledged before.

Limitation

This multi-experiment study bears several limitations. Firstly, both studies had low power due to small sample sizes, primarily because no patients were tested solely for the purpose of the study, and the research was conducted alongside the routine practice of the clinic. A low sample size typically increases the risk of Type II error, or failure to find a true effect. However, experiment one showed that positive information delivered by the dentist administering the treatment led to a lower pain report during drilling, with a moderate effect size. This effect was not observed in experiment two, despite a larger sample size than in experiment one. As discussed earlier, the lack of an effect in experiment two is more likely related to the method of information delivery rather than the low sample size, as the positive effect observed in experiment one was derived from a smaller sample than in experiment two, and both experiments were fairly similar and carried out by the same dental treatment team. Therefore, although both experiments had low sample sizes, it is less likely that the results were influenced by this limitation. Secondly, caution is required in the interpretation and generalization of the findings, as another risk of low sample sizes and weak statistical power is yielding unreliable results that are hard to reproduce (Button et al., 2013). Despite these limitations, the findings of this study are consistent with several earlier studies investigating the effect of nonverbal behaviours of healthcare providers and experimenters on pain and placebo effects (e.g. Daniali & Flaten, 2019; He et al., 2018; Howe et al., 2017; Kaptchuk et al., 2008; Verheul et al., 2010), supporting the reliability of findings. Thirdly, the effectiveness of the blinding of the grouping in E2 was not tested. However, it is unlikely that the treatment team identified the grouping of patients, as there were no between-group differences in pain and stress reports, suggesting that the blinding procedure was effective. Fourthly, the doctor-patient relationship and the factors illustrating this relationship such as how friendly, empathic, or caring the patients found the doctors and the treatment team were not recorded. Fifthly, all data were collected from subjective aspects of pain and no objective index, for example, physiological measurements relevant to stress such as cardiac activity (e.g. Daniali & Flaten, 2020) were recorded. Furthermore, the treatment team were all females, and this limits generalization of findings. Lastly, the interview was anecdotal and subject to error, therefore no robust data was provided on the role of healthcare providers' behaviours on elicitation of placebo effects. Future investigations are called to research the role of healthcare providers and their nonverbal behaviours on effectiveness of suggestive information in reducing symptom reporting.

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Ethics statement

The study was approved by the Regional Committee for Medical Research Ethics Norway (2011/209) and was pre-registered at ClinicalTrials.gov (identifier ID: NCT02160028).

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

Data can be made available upon request from the first author (HD).

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