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A Randomized Trial

The Role of Placebo and Nocebo Effects of Perioperative Administration of Sedatives and Opioids in Interventional Pain Management

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Background: The role of nonspecific treatment effects in the outcomes of patients receiving interventions for pain has been the subject of controversy and interest. While the administration of placebo and its effects have been widely studied, the role of placebo and nocebo effects of active agents administered prior to or during interventional techniques has not been explored.

Objectives: The evaluation of placebo and nocebo effects of sodium chloride solution and active agents (midazolam and fentanyl) administered during interventional techniques.

Study Design: Randomized, placebo-controlled, evaluation.

Methods : A total of 360 patients were divided into three groups, with Group I receiving placebo, Group II receiving midazolam, and Group III receiving fentanyl.

At 3 months, information was obtained with regards to their impressions or the experience of the study, compared to their previous experiences with the treatment and sedation. They were asked to rate their experience as better, worse, or no change compared to their previous experience.

Results: Between 13% to 30% of patients across all three groups of the study, rated their pain relief following injection as better than their previous experience. A smaller proportion, 3% to 8%, of patients in all three groups rated their experience following injection as worse than their previous experience. The majority of patients, 67% to 79%, regardless of group, described no significant differences as compared to their previous experiences with sedation and treatment for cervical or lumbar facet joint pain.

Conclusion : In patients undergoing interventional procedures, sodium chloride solution, midazolam, and fentanyl produced placebo effects in 13% to 15%, 15% to 20%, and 18% to 30% of the patients respectively. Similarly, a nocebo effect was seen in 5% to 8% of the patients in the sodium chloride group, 8% of the patients in the midazolam group, and 3% to 8% of the patients in the fentanyl group. It is concluded that positive and negative effects may be seen either with placebo or active agents in 13% to 30% of the patients.

Keywords: Placebo, nocebo, randomized, double-blind, sedation, cervical facet joint pain, lumbar facet joint pain, midazolam, fentanyl, sodium chloride.

Among patients receiving interventions for pain, the role of nonspecific treatment effects on their outcomes has been the subject of much interest and controversy. Placebo and nocebo effects are widely seen in medicine and biology; however, their underlying psychological and neurobiological mechanisms are only beginning to be more fully understood.

Placebo analgesia occurs when a non-analgesic substance (or action) evokes a reduction in pain sensation, perception and/or cognitive response(s). By contrast, nocebo hyperalgesia represents a phenomenon opposite that of placebo analgesia, characteristically considered to be a worsening or consistent lack of change of symptoms after the administration of some agent known to be effective. However, nocebo effects in interventional pain management need to be carefully distinguished from drug-induced hyperalgesia, tachyphylaxis, tolerance, and/or progression of the underlying organic pathology causing increased pain and diminished sensitivity to particular pharmacologic agents. Drug-induced hyperalgesia may be due to pharmacological mechanisms, such as in opioid hyperalgesia and diminished sensitivity to pharmacologic agents may be due to the down-regulation of opioid sites secondary to neuropathic central sensitization.

Placebo analgesia has been shown to be one of the most successful models in the study of placebo effect (1-8). From both neuropharmacological and neuroanatomical viewpoints, placebo effects have been widely studied. It is believed to be secondary to the release of endogenous opioids. However, the involvement of ascending monoaminergic and non-opioid peptidergic (e.g., oxytocin, vasopressin) systems have been described in placebo and non-specific analgesia. The mechanisms leading to the release of endogenous opioids are believed to involve both conditioning and cognitive factors (6,9-11). It has also been shown that if humans or animals are exposed to a biologically active medication, the efficacy of a subsequently administered placebo that physically resembles the initial active drug will be enhanced (4-6,12-15). This observation suggests that classical conditioning of contextual cues associated with drug action can contribute to the placebo response. A commonly-observed phe-

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nomenon is the administration of placebo treatment as an active medication without a patient's knowledge; in such cases, often patients believe that the treatment has been effective, and their expectations of analgesia actually results in a significant placebo analgesic effect (5,6,18,19). However, no such explanations have been provided for negative effects reported after the administration of not only placebo, but also pharmacologically active agents. Some (9,20,21) have postulated that patient fearfulness is a prerequisite for the nocebo response.

The treatment expectations of both patient and healthcare provider are believed to be particularly important in the production of placebo and nocebo effects (22,23). Studies have demonstrated that patient expectations concerning their medication significantly affected their response to that medication (22,24-26). Psychotherapy studies also have shown that when a client expects a positive treatment outcome, they tend to report improvement (27). Further, the provider's expectations related to study medications were also found to have an association to patient responses to treatment (28,29). In one study, physician (not patient) expectations as to the amount of pain amelioration immediately following a pain-relieving procedure were significantly associated with patients' actual pain relief (30). A study of acupuncture or massage therapy found that patients with high pretreatment expectations were more likely to have improved function after treatment (31). However, it was shown that research nurse/physician expectations did not predict patient pain relief (22).

In normal volunteers, spinal facet joints have been shown to be a source of pain in the neck and of referred pain in the head and upper extremities (32-36); upper back, mid back and referred pain in chest wall (37); and low back and referred pain in the lower extremities (38-43). Further, based on controlled diagnostic blocks of facet joints in accordance with criteria established by the International Association for the Study of Pain (IASP) (44), facet joints have been implicated as responsible for spinal pain in 15% to 45% of patients with low back pain (45-54), 54% to 67% of patient with neck pain (52,54-57), and 42% to 48% of the patients with thoracic pain (52,58). The confirmatory diagnosis of facet joint pain is best made by means of controlled diagnostic blocks either with two local anesthetics or with placebo controlled blocks.

The construct validity of facet joint blocks is established by controlled diagnostic blocks and this is important in order to eliminate placebo effect as the source of confounding results and to secure true positive results (59,60). The hypothesis that testing a patient first with lidocaine and subsequently with bupivacaine can provide some means of identifying the placebo response has been tested and proven (59,61). False positive rates ranging from 22% to 63% were reported in multiple investigations (45-58,62,63). However, in a manner similar to false-positive rates, false-negative rates are also present in a significant proportion of patients. Diagnostic tests are typically based on objective physical data such as blood tests, biopsies, or radiographs in various fields of medicine. However, in interventional pain management, the diagnosis differs in that it relies on the subjective response of the patient.

Thus far, the effect of placebo and active agents on patients' pain perceptions have not been evaluated in interventional pain management settings. Two recent studies (64,65) evaluated the effect of sodium chloride solution, midazolam, and fentanyl on the validity of diagnosis of cervical and lumbar facet joint pain in patients with chronic neck and low back pain. The present study was conducted to evaluate patients' overall experience, and to compare that experience to their previous treatment(s) prior to the study.

Methods

The protocol for the study was approved by the Institutional Review Board. The design consisted of Group 1 (a control group) receiving sodium chloride solution, Group II receiving midazolam, and Group III receiving fentanyl for sedation prior to treatment with facet joint nerve blocks for cervical or lumbar facet joint pain.

The study was undertaken in an interventional pain management practice (a specialty referral center) in a private practice setting.

Informed Consent

All patients were provided with the approved protocol and informed consent documentation approved for this study by the Institutional Review Board. Details of the trial were described in the informed consent documents. The informed consent document described inclusion and exclusion criteria, randomization, and details of the administration of the solutions with 1 in 3 patients receiving sodium chloride solution.

Inclusion and Exclusion Criteria

Patients for the study were identified and recruited from the existing patients of the interventional pain management practice. All the patients had a proven diagnosis of either cervical or lumbar facet joint pain as verified by controlled comparative local anesthetic blocks of medial branches and L5 dorsal rami, and had experienced good response to therapeutic cervical or lumbar facet joint nerve blocks previously. All the patients presented with a history of chronic function-limiting neck or low back pain of at least 1-2 year's duration. Patients also had been treated in the past with cervical or lumbar facet joint nerve blocks with sedation utilizing midazolam and fentanyl; they were presenting for repeat treatment after a significant period of symptom relief.

Evaluation

Evaluation of all the patients included in the study consisted of the following:

1. Demographic data
2. Pain assessment by numeric pain scale
3. Identification of painful movements
4. Evaluation of the patient's overall experience after 3 months and comparison to their experience with treatment prior to the study

Study Design and Preparation

Patients in all three groups were provided an identical explanation in the context of pain assessment and painful movements, preparation, and the planned administration of identical volumes of drugs in unlabeled syringes. The assessment was performed in the holding area of the ambulatory surgery center by registered nurses experienced with evaluation, administration, and monitoring of sedatives and opioids prior to taking the patients to the procedure room for facet joint nerve blocks. Based on randomization, each patient received one of the following three solutions in incremental doses of 1 mL to a maximum of 5 mL: Group I received sodium chloride

(0.9%); Group II received 1 mg of midazolam per 1 mL (5 mg per 5 mL); and Group III received 50 mcg of fentanyl per mL (250 mcg per 5 mL).

The solutions were administered slowly based on patient's response with relaxation and/or feeling of drowsiness or until the entire syringe of 5 mL was administered. Once the patients expressed either drowsiness or relaxation or the maximum dose was administered, assessment of pain on a numeric pain scale and ability to perform painful movements were reassessed. All the results were documented.

Patients and investigators were blinded to the randomized allocation as well as the solution administered in each and every case. After the completion of the evaluation, unblinding was carried out and the amount of solution administered was noted on the record.

Outcomes Assessment

Patients underwent the facet joint nerve blocks as planned after assessment of the responses to the intravenous injections. When they returned for the follow-up visits after approximately 3 months, their impressions, compared to their previous experiences with treatment and sedation were recorded. They were asked to rate their experience as better, worse, or no different compared to their previous experience.

Statistical Methods

Results were considered in each group and were compared with each other. Differences in proportions were evaluated using the Chi-squared test. One-Way Analysis of variance was used for comparison of mean values (proportional values). After significance was found, the least significant difference (LSD) pair-wise multiple comparison test was used to test the difference between means. Results were considered statistically significant if the *P* value was less than 0.05. Confidence intervals (95% CI) and levels (95% CL) were calculated for proportions and means.

Results

The study was performed from February 2004 through December 2004. A total of 360 patients were part of the study and were divided into two categories – 180 with cervical facet joint pain, and 180 with lumbar facet joint pain. There were 60 patients in each category for all three groups. The patient flow is depicted in Figure 1.

Demographic Characteristics

Table 1 illustrates the demographic characteristics of patients included in the study. No significant differences were noted with regards to gender, age, height, weight, and history of previous surgery within the three groups or between the study categories of those with cervical facet joint pain as compared to those with lumbar facet joint pain. .

Study Characteristics

Table 2 illustrates details with regards to time required for relaxation, amount of solution or drug in dosage, and relaxation status. There were no significant differences noted in the time required for relaxation. However, the amount of solution or drug dosage was significantly less in Group III as compared to Group I, both

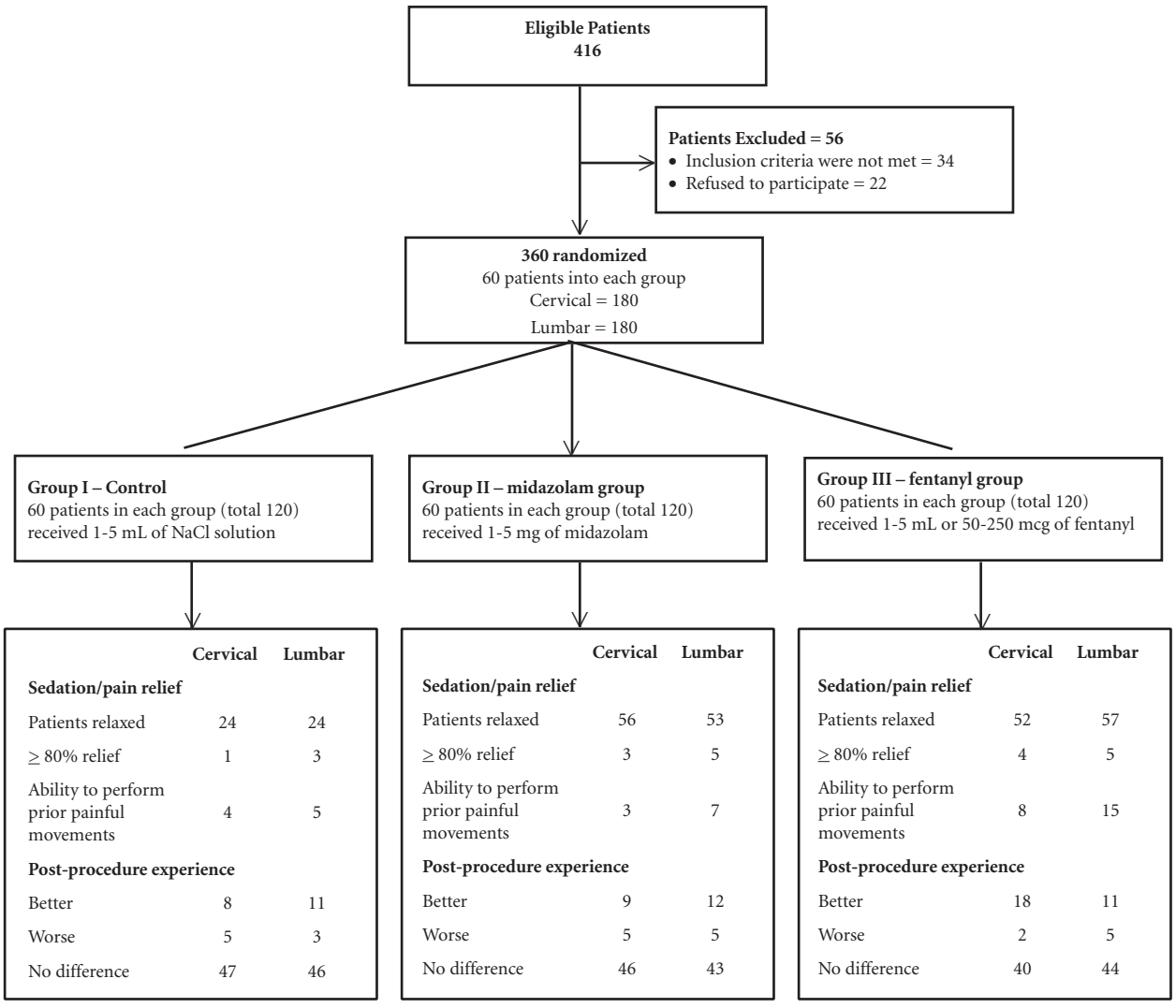
Table 1. *Demographic characteristics*

		Group I Sodium chloride		Group II Midazolam		Group III Fentanyl	
		Cervical	Lumbar	Cervical	Lumbar	Cervical	Lumbar
Gender	Male	40% (24)	35% (21)	30% (18)	37% (22)	35% (21)	37% (22)
	Female	60% (36)	65% (39)	70% (42)	63% (38)	65% (39)	63% (38)
Age (yrs)	Range	28 – 83	25 – 77	25 – 79	25 – 77	21 – 72	22 – 83
	Mean ± SD	48 ± 11.1	48 ± 11.9	49 ± 11.5	48 ± 11.7	48 ± 11.9	48 ± 14.5
Height (inches)	Mean ± SD	67 ± 4.4	66 ± 4.1	66 ± 4.2	66 ± 3.8	67 ± 4.3	66 ± 3.8
Weight (lbs)	Mean ± SD	190 ± 52.1	181 ± 54.2	176 ± 45.7	181 ± 50.2	177 ± 47.0	184 ± 43.4
Post Surgery		15% (9)	25% (15)	20% (12)	18% (11)	12% (7)	27% (16)

Table 2. *Characteristics of administration of drugs and their effect*

		Group I Sodium chloride		Group II Midazolam		Group III Fentanyl		P Value	
		Cervical	Lumbar	Cervical	Lumbar	Cervical	Lumbar	Cervical	Lumbar
Time required for relaxation (in minutes)	Mean ± SD	9.6 ± 3.2	8.7 ± 2.9	8.9 ± 2.8	8.6 ± 2.9	8.3* ± 2.7	8.8 ± 3.0	0.043	0.942
	Range	5 – 20	4 – 20	3 – 13	4 – 15	4 – 13	3 – 16		
Amountof solution or drug dosage (in ml)	1 ml	1% (1)	1% (1)	2% (1)	-	0%	1% (1)	0.000	0.000
	2 ml	7% (4)	12% (7)	28% (17)	30% (18)	28% (17)	25% (15)		
	3 ml	7% (4)	12% (7)	23% (14)	28% (17)	44% (26)	42% (25)		
	4 ml	13% (8)	10% (6)	17% (10)	19% (11)	13% (8)	13% (8)		
	5 ml	72% (43)	65% (39)	30% (18)	23% (14)	15% (9)	19% (11)		
	Mean ± SD	4.5 ± 1.0	4.3 ± 1.2	3.5 ± 1.2	3.4 ± 1.2	3.2 ± 1.0	3.2* ± 1.1	0.062	0.000
Relaxed Status		40% (24)	40% (24)	88%* (53)	93%* (56)	95%* (57)	87%* (52)	0.000	0.000
95% Confidence Interval		28% - 53%	28% - 52%	80% - 96%	87% - 99%	89% - 100%	79% - 96%		

() Number of patients * Indicates significant difference with Group I



	Cervical	Lumbar
Sedation/pain relief		
Patients relaxed	24	24
≥ 80% relief	1	3
Ability to perform prior painful movements	4	5
Post-procedure experience		
Better	8	11
Worse	5	3
No difference	47	46

	Cervical	Lumbar
Sedation/pain relief		
Patients relaxed	56	53
≥ 80% relief	3	5
Ability to perform prior painful movements	3	7
Post-procedure experience		
Better	9	12
Worse	5	5
No difference	46	43

	Cervical	Lumbar
Sedation/pain relief		
Patients relaxed	52	57
≥ 80% relief	4	5
Ability to perform prior painful movements	8	15
Post-procedure experience		
Better	18	11
Worse	2	5
No difference	40	44

Fig 1. *Schematic description of patient flow during the trial*

in cervical and lumbar studies.

Relaxation status varied in all three groups. Group II which received midazolam, had the greatest proportion of relaxed patients at 93%, whereas the lumbar facet joint patients in Group III reported 87% relaxation. However, among those patients with cervical facet joint pain, Group II recorded 88% of patients relaxed, while Group III had relaxation reports at 95%. Both Groups II and III differed from Group I (placebo group) in which only 40% of the patients in both the cervical and lumbar facet joint pain categories reported relaxation. There were no differences reported in relaxation rates between cervical and lumbar categories.

Pain Relief and Ability to Perform Prior Painful Movements

Figure 2 shows pain measurements prior to, and after, the administration of appropriate drugs or sodium chloride solution and the ability to perform previously painful movements with significant pain relief of ≥80%. There were no differences noted, either in the proportion of relief or the ability to perform previously painful movements with the intravenous injections.

Patient Perceptions and Experiences

Table 3 illustrates patient experiences and perceptions in all three groups, comparing their experience in the study to their previous experience. Patients in both cervical and lumbar categories received additional sedation if requested. Thirteen percent to 30% of the patients referred to their experience in the study as better than their previous experience.

A significant difference was noted among the patients feeling better in Group III in the cervical facet joint pain category, with 30% of the patients receiving fentanyl noting improvement compared to the placebo group (Group I) and the midazolam group (Group II); in the cervical category, 8 patients (13%) in Group I reported feeling better, and 9 (15%) in Group II reported improvement, as compared to 18 (30%) in Group III. In the lumbar category, similar numbers of patients reported feeling better: 11 patients (18%) in Group

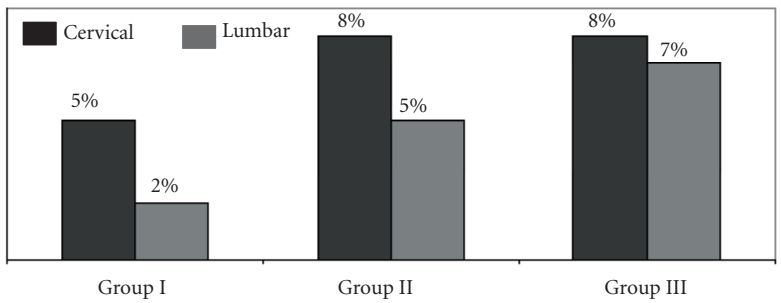


Fig. 2. *Illustration of significant pain relief (≥80%) with ability to perform prior painful movement in each study group in cervical and lumbar regions, after intravenous injections, but before facet joint nerve blocks.*

Table 3. *Results of patient experiences in the study group, compared to sedation and analgesia of previous treatment(s)*

	Group I Sodium chloride		Group II Midazolam		Group III Fentanyl	
	Cervical	Lumbar	Cervical	Lumbar	Cervical	Lumbar
Better	13% (8)	18% (11)	15% (9)	20% (12)	30%* (18)	18% (11)
Worse	8% (5)	5% (3)	8% (5)	8% (5)	3% (2)	8% (5)
No difference	79% (47)	77% (46)	77% (46)	74% (43)	67% (39)	72% (43)
Lost to follow-up	0	0	0	0	1	1

( ) Number of patients
* indicates significant difference between Group III vs. Group I, (30% vs. 13%) Group III vs. Group II (30% vs. 15%)

I, 12 patients (20%) in Group II, and 11 patients (18%) in Group III reporting reduced pain.

Reports of "worse" pain ranged from two patients (3%) to five patients (8%) in both categories of all three groups. There were no significant differences noted between the categories of cervical and lumbar facet joint pain.

The majority of patients, between 67% to 79% in all three groups of both categories reported no difference compared to their previous experience.

Discussion

This randomized placebo-controlled evaluation demonstrated that 13% to 30% of patients in all three groups and both categories rated their experience as better as compared to their previous experiences. A greater proportion of patients receiving fentanyl (Group III) felt better. A small proportion (3% to 8%) of patients in the placebo group as well as in the midazolam and fentanyl groups also felt worse, with no significant differences noted among the two categories. The majority of the patients in the study (67% to 79%) described no significant change from their previous experience. There were no differences with any of the patients as to the amount of sedation they received or the modality of treatment.

Based on the results, it appears that patients who felt better after sodium chloride administration may be considered to have had a placebo response and those who felt worse after sodium chloride solution, midazolam, or fentanyl may be considered to have had a nocebo response. It is possible that better responses in the cervical fentanyl group may be due to higher amounts of drug administered (i.e., a true analgesic effect). The potential for a nocebo response due to change in underlying pathology or increased pain sensitivity with refractoriness to peripheral nerve injection was ruled out. Appropriate precautions were taken as these patients were responding with a similar duration of relief without variation in the procedure itself. Placebo responses have been subject to different interpretations based upon specific clinical orientations; as well, this effect may reflect different meanings to individual patients.

A controlled trial (60) evaluated the utility of comparative local anesthetic blocks versus placebo controlled blocks for the diagnosis of cervical zygapophysial joint pain. In that randomized, double-blind, placebo-controlled study, patients underwent three blocks, administered on separate occasions, each with different agents – lidocaine, bupivacaine, and normal saline. Diagnostic decisions based on comparative blocks alone were compared with those based on placebo-controlled blocks. Comparative blocks were found to have a specificity of 88%, but only a marginal sensitivity of 54%. The authors of that study concluded that even though comparative blocks resulted in a few false-positive diagnoses, they also resulted in a high proportion of false-negative diagnoses. They also described that expanding the comparative block's diagnostic criteria to include all patients with reproducible relief irrespective of duration, increased the sensitivity to 100%, but lowered the specificity to 65%.

Questions raised include: Can placebo be incorporated into clinical practice as a sedative and "analgesic" to improve patient safety, or is placebo ethically problematic (66)? Functional magnetic resonance imaging studies demonstrated that placebo alters the perception of pain along with expectations as to pain relief (67). Analgesia induced by placebo is related to decreased activity in pain-sensitive brain regions such as the thalamus, insula, and anterior cingulate cortex (ACC) (67). Placebo and opioid analgesia share similar neuromechanisms, specifically affecting the ACC and brain stem as verified by PET scanning (68). Despite neurological complexities, placebo analgesia is considered similar to opioid analgesia. Placebo effect can be easily induced simply by a patient's expectations that a procedure will alleviate their pain. Perhaps, placebo is not ethically problematic after all, and could affect outcomes in interventional pain management settings. It is essential to consider the placebo effect in design and interpretation of studies in interventional pain management.

In two controlled, randomized, double-blind, placebo-controlled trials (64, 65) it was shown that placebo administration of sodium chloride solution provided greater than 80% pain relief plus the ability to perform prior painful movements in 5% and 2% of studied patients with cervical and lumbar facet

joint pain. These results were similar to those receiving midazolam and fentanyl. It was concluded that an intravenous preoperative sedative dose of an opioid such as fentanyl, or an anxiolytic such as midazolam, is no more likely than a sodium chloride placebo to cause a small proportion of patients to report false-positive pain relief with active motion testing. Results of these two studies demonstrate that prudent use of short-acting sedatives and analgesics, along with careful monitoring, seems appropriate.

The mechanisms of the placebo response and its impact on clinical trials and clinical practice are not well understood (18,68,69). The placebo response is bidirectional (i.e., analgesic and algesic) but in most studies the algesic response is disregarded and subjects reporting increased pain after placebo are labeled as nonresponders (70). The response to fentanyl was superior to placebo, and likely can be attributed to its analgesic effect. To distinguish the pleasing and salubrious effects of placebo from unpleasant and noxious effects, the term nocebo was introduced (71). This aspect of the placebo response should be considered when evaluating the response to treatment in clinical trials.

Conclusion

Based on the results of this randomized, placebo-controlled evaluation, 13% to 30% of all the patients receiving either sodium chloride solution, midazolam, or fentanyl, reported a placebo response. A small proportion (3% to 8%) of patients also reported a nocebo response, where they felt worse. The majority of the patients (67% to 79%) described no significant change from their previous experience. It is concluded that sodium chloride, midazolam, and fentanyl are capable of producing placebo, as well as nocebo responses in patients undergoing interventional procedures. In designing research and interpreting outcomes, placebo and nocebo effects must be taken into consideration.

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