

A RANDOMIZED EVALUATION

EVALUATION OF THE EFFECT OF SEDATION AS A CONFOUNDING FACTOR IN THE DIAGNOSTIC VALIDITY OF LUMBAR FACET JOINT PAIN: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION

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Background: Lumbar facet (zygapophysial) joints have been implicated as the source of chronic pain in 15% to 45% of patients with chronic low back pain. Diagnosis may be confounded by false-positive results with a single diagnostic block and administration of anxiolytics and narcotics prior to or during the diagnostic facet joint blocks.

Objective: To evaluate the effect of midazolam and fentanyl on the diagnostic validity of lumbar facet joint pain.

Study Design: Randomized, prospective, double-blind, placebo-controlled evaluation.

Methods: The design consisted of a placebo group receiving sodium chloride solution and two experimental groups receiving either midazolam or fentanyl. The patients included in the study were diagnosed with facet joint pain with controlled comparative

local anesthetic blocks of medial branches or L5 dorsal rami. They had been treated with lumbar facet joint nerve blocks with good pain relief, and were presenting for repeat treatment after a period of symptom relief.

The study was undertaken in an interventional pain management practice.

Outcome Measures: Outcomes were assessed at baseline and after the administration of 1 of the 3 solutions (Group I, sodium chloride solution; Group II, midazolam; or Group III, fentanyl).

Outcome measures included numeric pain scale, proportion of pain relief, and ability to perform prior painful movements.

Results: Pain relief of $\geq 80\%$ was noted in 2% of the patients in Group I, 5% of the patients in Group II, and 7% in Group III. Pain relief of $\geq 50\%$ was noted in 7% of the patients in Group I, 5% of the patients in

Group II, and 13% of the patients in Group III. There were no significant differences among the groups.

Conclusion: The administration of sedation with midazolam or fentanyl is a confounding factor in the diagnosis of lumbar facet joint pain in patients with chronic low back pain. However, this study suggests that if strict criteria including pain relief and ability to perform prior painful movements is used as the standard for evaluating the effect of controlled local anesthetic blocks, the diagnostic validity of lumbar facet joint nerve blocks may be preserved.

Keywords: Chronic low back pain, lumbar facet joint pain, controlled comparative local anesthetic blocks, false-positives, confounding factors, analgesia

Among chronic pain problems, pain emanating from various structures of the lumbar spine remains a major challenge, despite the efforts extended in gathering information, research, prevention, treatment, and rehabilitation (1). Various structures in the lumbar spine, such as facet joints, intervertebral discs, dorsal root ganglia, muscles, and ligaments, are capable of causing low back pain, and lower extremity pain. Facet joints have

been increasingly recognized as a significant source of low back and lower extremity pain. Despite the high prevalence of low back pain, it has been suggested that a specific etiology of back pain can be diagnosed in only about 15% of patients with certainty based on clinical examination alone (2-5).

Bogduk (5) noted that a reductionist approach to chronic low back pain requires an anatomical diagnosis. Bogduk (6) identified four factors necessary for any structure to be deemed a cause of back pain: a nerve supply to the structure; the ability of the structure to cause pain similar to that seen clinically in normal volunteers; the structure's susceptibility to painful diseases or injuries; and demonstration that the structure can be a source of pain in patients using diagnostic techniques of known reliability and validity. In accordance with postulates of Bogduk (6, 7), the lumbar facet joints or zygapophysial joints are innervated, they produce pain in normal volunteers, and relief

of pain has been demonstrated by using diagnostic techniques of known reliability and validity.

Based on the response to controlled diagnostic blocks of lumbar facet joints, in accordance with the criteria established by the International Association for the Study of Pain (8), the prevalence of lumbar facet joint pain has been shown to range from 15% to 45% in patients with chronic low back pain (9-16).

The evidence for lumbar facet joints being a source of chronic low back pain is compelling. Yet, there are no neurophysiologic findings, radiologic findings, physical findings, historical or clinical features that are either clearly indicative or diagnostic of lumbar facet joint pain (2-7, 17, 18). Consequently, it has been postulated that the blocks of the facet or zygapophysial joint can be performed in order to test the hypothesis that the target joint is the source of the patient's pain.

True-positive responses may be secured by performing controlled blocks,

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either in the form of placebo injections of normal saline or comparative local anesthetic blocks, in which the same joint is anesthetized on two separate occasions, but using local anesthetics with different durations of action. The specificity of lumbar medial branch blocks as well as the ability of lumbar medial branch blocks to anesthetize facet joints has been demonstrated (19, 20). However, with single local anesthetic blocks, a significant proportion of patients (22% to 41%) may present with false-positive results (11-16, 21).

Face validity and construct validity of facet joint blocks has been well established (18-20, 22). However, multiple other confounding factors may affect the diagnostic validity of lumbar facet joint blocks. These factors include psychological and behavioral status, as well as administration of anxiolytics, narcotics, and other agents. The issue of confounding factors has been well investigated in provocation discography (23-26). A lack of influence of psychological factors on the validity of controlled comparative diagnostic local anesthetic blocks of facet joints in the low back has been demonstrated (27). A lack of value of provocation was also demonstrated with lumbar zygapophysial joints (28). However, the effects of anxiolytics and narcotics on the validity of diagnosis of lumbar facet joint pain by means of controlled comparative local anesthetic blocks have not been studied.

This evaluation was conducted to evaluate the effect of midazolam and fentanyl on the validity of diagnosis of lumbar facet joint pain. Patients who were proven to have lumbar facet joint pain, demonstrated by fluoroscopically directed controlled comparative local anesthetic blocks of medial branches or L5 dorsal rami and therapeutic measures involving lumbar facet joint nerve blocks with good response, but returning for a repeat treatment after a significant period of symptom relief, were included to evaluate the effect of placebo, midazolam, and fentanyl.

METHODS

The protocol was approved by the Institutional Review Board. The design consisted of a control group (Group I) receiving sodium chloride solution, Group II receiving midazolam, and Group III receiving fentanyl.

The study was undertaken in an in-

terventional 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 document approved by the Institutional Review Board for this study. The informed consent document described the details of the trial.

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 lumbar facet joint pain by controlled comparative local anesthetic blocks of medial branches or L5 dorsal rami, and good response to therapeutic Lumbar facet joint nerve blocks.

Inclusion Criteria

Inclusion criteria consisted of the following:

1. Patients with a history of chronic, function limiting, low back pain of at least two years duration.
2. Patients between ages of 18 and 90 years.
3. Patients with facet joint pain confirmed by controlled, comparative local anesthetic blocks of medial branches or L5 dorsal rami.
4. Patients were treated in the past with lumbar facet joint nerve blocks and were presenting for repeat treatment after a significant period of symptom relief.
5. Patients with the ability to understand the investigation, and/or cooperate with the investigational procedures.
6. Patients with a willingness to participate in the clinical trial.

Exclusion Criteria

Exclusion criteria were as follows:

1. Patients without confirmed evidence of lumbar facet joint pain.
2. Patients with uncontrolled major depression or other psychiatric disorders.
3. Patient who were pregnant or lactating
4. Patients with multiple complaints involving other problems which have overlapping pain complaints

5. Patients unable to achieve appropriate positioning.
6. Patients unable to understand informed consent and protocol.
7. Patients with history of adverse reactions to either midazolam or fentanyl.
8. Patients who were not willing to participate in the study.

Evaluation

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

1. Demographic data.
2. Routine physical and medical evaluation.
3. Confirmed evidence of lumbar facet joint pain by controlled comparative local anesthetic blocks of medial branches or L5 dorsal rami.
4. Significant symptom relief following lumbar facet joint nerve blocks and necessity for repeat treatment.
5. Pain assessment by numeric pain scale.
6. Identification of painful movements.

Study Design and Investigation

All the patients in the three groups were provided identical preparation, along with administration of identical volumes of drugs in unlabeled syringes. The study was performed in the holding area of the ambulatory surgery center by registered nurses experienced with evaluation, administration and monitoring of sedatives and narcotics.

After the patients have agreed to participate in the study, patients in all three groups were brought to the holding area of the surgery center. They were allocated into one of the three groups based upon a computer generated randomization scheme with 5 of 15 patients to each group. Pre-drug administration evaluation included determination of baseline pain on a numeric pain rating scale of 0 to 10, with 0 being no pain and 10 being the worst possible pain such as pain of delivery or a kidney stone in women, or a kidney stone in men. The evaluation also included identification of the painful movements.

Each patient, based on the randomization, received 1 of the 3 solutions in incremental doses of 1 mL with a maximum of 5 mL of NaCl in Group I, 1 mg of midazolam per mL (5 mg per 5 mL) in Group II, or 50 mcg of fentanyl per mL (250 mcg per 5 mL) in Group III. Patient and inves-

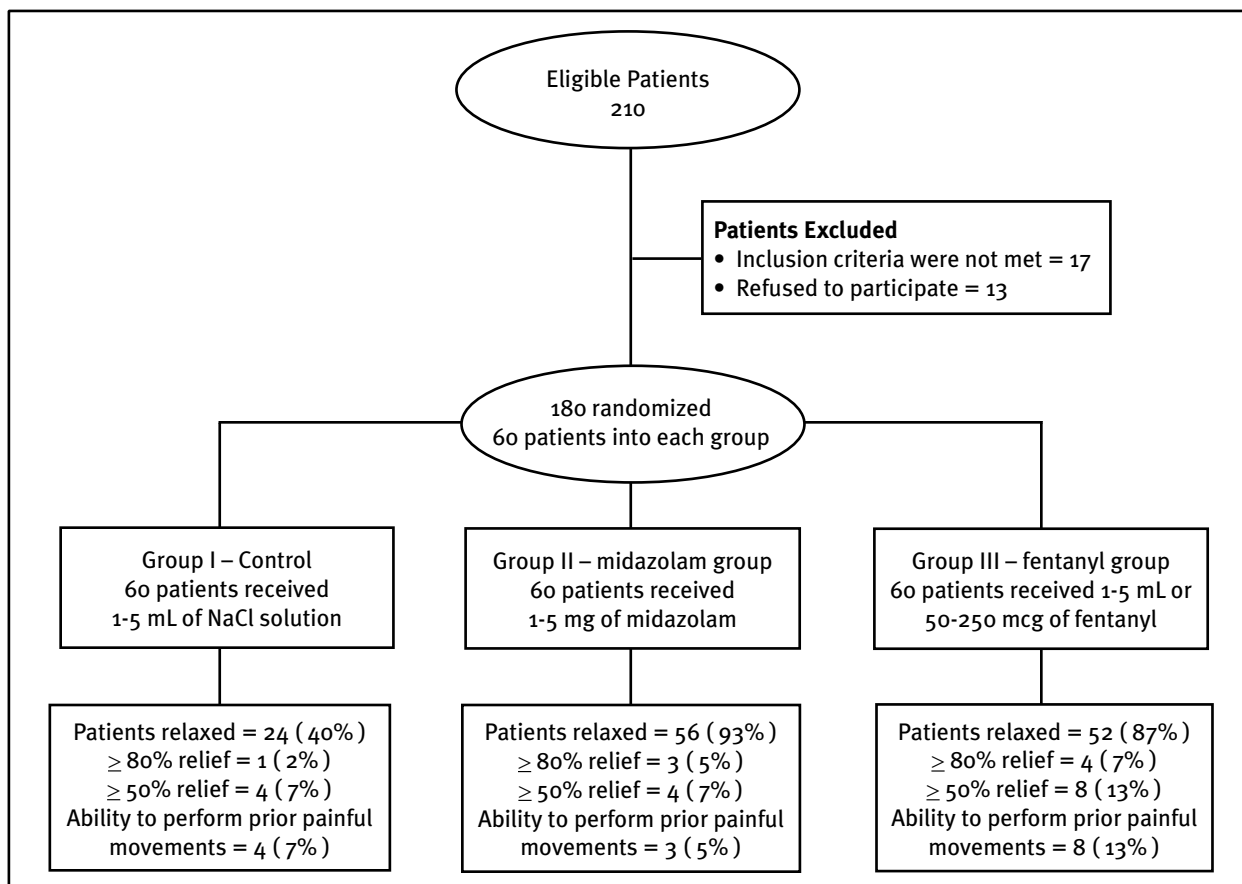


Fig 1. Schematic description of patient flow during the trial

tigator were blinded to the randomized allocation, as well as solution administered, in each and every case.

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 numeric pain scale and ability to perform pre-sedation painful movements were reassessed.

After completion of the evaluation, unblinding was carried out and the amount of sedation administered in Groups II and III were noted on the record.

Outcomes Assessment

Outcomes were assessed at baseline prior to the administration of the solution and after the administration of the solution. Multiple parameters included numeric pain scale, proportion of pain relief, and ability to perform prior pain-

ful movements.

Statistical Methods

Differences in proportions were tested using Chi-Squared test. For comparison of means, one-way analysis of variance was used. After significance was found, the least significant difference (LSD) pairwise 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 over a period of five months extending from February through June of 2004. Patient flow is depicted in Figure 1. From a sample of 210 eligible patients, 180 were randomized with 60 patients in each group.

Demographic Characteristics

Table 1 illustrates the demograph-

Table 1. Demographic characteristics

		Group I (Control)	Group II (Midazolam)	Group III (Fentanyl)
Gender	Male	35% (21)	37% (22)	37% (22)
	Female	65% (39)	63% (38)	63% (38)
Age (yrs)	Range	25 – 77	25 – 77	22 – 83
	Mean ± SD	48 ± 11.9	48 ± 11.7	48 ± 14.5
Height (inches)	Mean ± SD	66 ± 4.1	66 ± 3.8	66 ± 3.8
Weight (lbs)	Mean ± SD	181 ± 54.2	181 ± 50.2	184 ± 43.4
Post Surgery		25% (15)	18% (11)	27% (16)

Table 2. Characteristics of administration of drugs and their effect

		Group I (Control)	Group II (Midazolam)	Group III (Fentanyl)	P Value
Time required for relaxation (in minutes)	Mean ± SD	8.7 ± 2.9	8.6 ± 2.9	8.8 ± 3.0	0.942
	Range	4 – 20	4 – 15	3 – 16	
Amount of solution or drug dosage (in ml)	1 ml	1% (1)	-	1% (1)	0.000
	2 ml	12% (7)	30% (18)	25% (15)	
	3 ml	12% (7)	28% (17)	42% (25)	
	4 ml	10% (6)	19% (11)	13% (8)	
	5 ml	65% (39)	23% (14)	19% (11)	
	Mean ± SD	4.3 ± 1.2	3.4 ± 1.2	3.2* ± 1.1	0.000
Relaxed Status		40% (24)	93%* (56)	87%* (52)	0.000
95% Confidence Interval		28% - 52%	87% - 99%	79% - 96%	

* Indicates significant difference with Group I

ic characteristics of patients included in the study. No significant differences were noted with regards to gender, age, height, weight, and history of previous surgery.

Study Characteristics

Details with regards to time required for relaxation, amount of solution or drug in dosage, and relaxed status are illustrated in Table 2. 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 compared to Group I.

Relaxation status varied in all three groups. Group II, receiving midazolam, had the greatest proportion of patients relaxed with 93%, whereas Group III had 87% of the patients. Both groups significantly differed from Group I with only 40% of the patients relaxed.

Pain Relief

Descriptions of pain measurements prior to and after the administration of appropriate drugs or sodium chloride solution are illustrated in Table 3. There were no differences noted in the baseline or post-study follow-up pain levels among the groups. The proportion of patients receiving significant relief (≥80% or ≥50% relief was similar in all three groups.

Description of pain relief and correlation with ability to perform movements painful prior to injection of solution are illustrated in Table 4. There were no significant differences noted either in the proportion of relief or ability to perform previously painful movements. Figures 2 and 3 illustrate the proportion of patients with pain relief and ability to perform baseline painful movements in post-study follow-up period in each group.

Complications

There were no adverse events or complications during the study.

DISCUSSION

In this randomized, placebo-controlled, double-blind evaluation, we

Table 3. Comparison of pain status by numeric pain scales

Numeric Pain Scale		Group I (Control)	Group II (Midazolam)	Group III (Fentanyl)	P Value
Baseline pain scale	Mean ± SD	7.6 ± 1.5	7.4 ± 1.7	7.5 ± 1.8	0.834
Post-study follow-up	Mean ± SD	6.6 ± 1.8	6.2 ± 2.2	6.0 ± 2.4	0.301
Change on pain scale	Mean ± SD	1.0 ± 1.5	1.3 ± 1.5	1.5 ± 2.0	0.226
Significant relief (≥ 80% relief)		2% (1)	5% (3)	7% (4)	0.400
Significant relief (≥ 50% relief)		7% (4)	5% (3)	13% (8)	0.272

Table 4. Proportion of pain relief and ability to perform movements painful prior to injection of solution

Percent Relief	Group I (Control)		Group II (Midazolam)		Group III (Fentanyl)	
	Number of patients	Ability to perform previously painful movements	Number of patients	Ability to perform previously painful movements	Number of patients	Ability to perform previously painful movements
100%	0	0	2	2	2	2
90%	0	0	0	0	0	0
80%	1	1	1	1	2	2
70%	1	1	0	0	2	2
60%	0	0	0	0	0	0
50%	2	2	0	0	2	2
<50%	56	0	57	0	52	0
Total	60	4	60	3	60	8

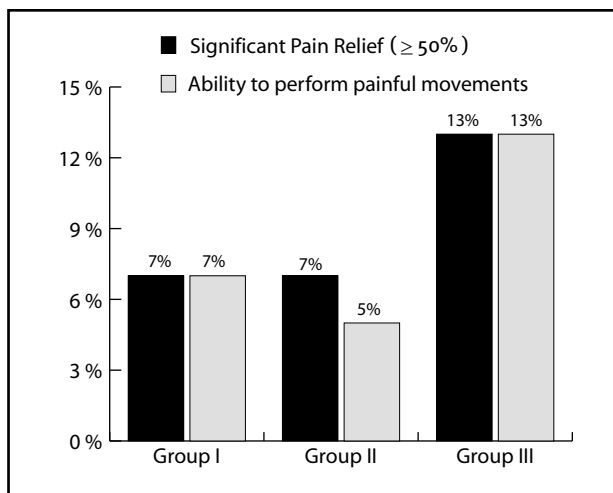


Fig 2. Illustration of significant pain relief (≥ 50%) and ability to perform baseline painful movements in post-study follow-up period in each group

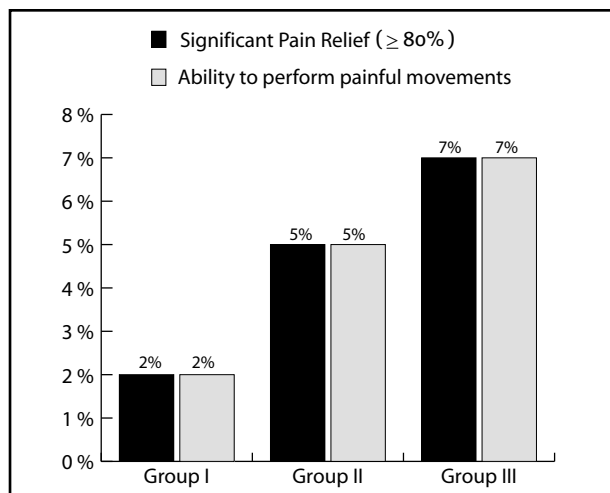


Fig 3. Illustration of significant pain relief (≥ 80%) and ability to perform baseline painful movements in post-study follow-up period in each group

demonstrated that an insignificant proportion of patients with 2% in Group I (placebo group – NaCl solution), 5% in Group II (midazolam group), and 7% in Group III (fentanyl group) had experienced ≥80% pain relief and were able to perform movements painful prior to the administration of intravenous sodium chloride, midazolam, or fentanyl in patients with chronic low back pain of lumbar facet joint origin. Further, evaluation of significant relief of ≥50% relief with ability to perform baseline painful movements in post follow-up period was seen in 7%, 5%, and 13% of the patients in Groups I, II, and III. Significant differences were only noted with regards to the relaxation status with 40% in Group I, 93% in Group II, and 87% in Group III. This study showed no significant differences between the pain relief, and ability to perform painful movements in any of the groups.

These observations represent progress in the understanding of confounding factors in the diagnosis of lumbar facet joint pain. Based on the results of this study, an insignificant proportion of patients in all the three groups were able to report significant pain relief or had ability to perform movements which were painful prior to administration of solution. The only significant improvement was seen in the relaxation status in patients receiving sedation compared to placebo. Surprisingly, 40% of the patients in placebo group also were relaxed.

An intravenous preoperative seda-

tive dose of an anxiolytic such as midazolam or a short-acting narcotic such as fentanyl is no more likely to cause a patient to report false-positive pain relief with active motion testing than placebo. This proportion is smaller when the criterion standard of ≥80% pain relief and ability to perform painful movements is utilized instead of significant pain relief of ≥50% with ability to perform painful movements. Since fentanyl is administered only in patients who are not relaxed and potentially combative, it appears that most patients who receive fentanyl may not be impacted adversely by diluting the diagnostic value of controlled comparative local anesthetic blocks.

Among the various drugs utilized for anxiolysis and analgesia during interventional procedures, midazolam and fentanyl are common. Midazolam is a short-acting benzodiazepine affecting the central nervous system depressant activities. The effects of midazolam on the central nervous system are dependent on the dose administered, the route of administration, and the presence or absence of other medications.

Fentanyl is a narcotic analgesic. The principle actions of fentanyl are analgesia and sedation. The onset of action of fentanyl is almost immediate when the drug is given intravenously.

The results of this study confirm that some patients obtain relaxation and pain relief with ability to perform prior painful movements with sodium chloride solution, midazolam, and fentanyl.

However, this appears to be in an insignificant proportion of patients whether they are receiving sodium chloride solution, midazolam, or fentanyl, specifically if one considers as the criterion standard of ≥80% relief with ability to perform previously painful movements. Thus, administration of sedation either with midazolam or fentanyl to achieve a relaxed status appears to be safe, with minimal effect on the diagnostic validity of lumbar facet joint nerve blocks.

This evaluation has some potential drawbacks and consequently, may be criticized. First, there was no additional group with combined midazolam and fentanyl. Second, it may be argued that inclusion criteria were flawed as sedation was given to patients after the diagnosis of facet joint pain was already established. Third, it may be argued that we retrospectively inferred the validity of the primary diagnosis. Fourth, the study may be criticized for conducting the evaluation in patients already exposed to the drugs utilized in the study.

First, the study was placebo-controlled, randomized, double-blind, with 60 patients in the each group, with appropriate evaluation of outcome parameters of pain relief and ability to perform prior painful movements. The question about an additional group with midazolam and fentanyl appears to be clinically important. However, the Institutional Review board felt that the administration of the two drugs in a safe manner would be extremely difficult, specifically limiting the

total dosage to 5 mL with 50% midazolam and 50% fentanyl. Since the drugs cannot be mixed reliably and uniformly, they may have to be provided in two separate syringes. Such a scenario will not provide a double blind evaluation. Consequently, the combined effect of midazolam with fentanyl was not evaluated.

The second issue relates to the inclusion criteria. We employed strict inclusion criteria, with history of chronic, function limiting, low back pain of at least two years of duration, prior confirmed evidence of facet joint pain by controlled comparative local anesthetic blocks. Consequently, all the patients included in the study were treated in the past and were presenting for repeat treatment after a period of symptom relief.

The third question is related to the inference of the validity of the primary diagnosis retrospectively rather than the evaluation of the effect of sedation while performing the primary diagnostic blocks. The effect of sedation was used to evaluate the validity of diagnosis thus, it is not a retrospective study. Thus, the methodology used in this study appeared to be ideal. However, one may argue that to answer this question, this study would have needed to actually give the sedation prior to the controlled comparative local anesthetic blocks performed for the purpose of diagnosis. We believe that such a study will not offer any additional information and could introduce further confounding factors.

Fourth, the study was conducted in patients who were previously exposed to the study drugs. One may argue that the tolerance and the response may confound the results. We do acknowledge that patients do develop tolerance and the response may be attenuated in patients with prior exposure. However, in interventional pain management settings, this situation would be difficult to avoid as most patients have already been exposed to opioids and benzodiazepines prior to presenting for evaluation. Thus, we do not believe that tolerance and a history of exposure to the drugs would have altered the results. Due to randomization, we believe that there should not be any difference among the groups. This study

also showed that 65% of the patients in Group I, 23% of the patients in Group II, and 19% of the patients in Group III received 5 mL (the total dosage) to achieve a relaxed status. Others, even though they were aware that they could receive the maximum dosage or additional medication, felt they were relaxed, and no further drug was administered. Thus, tolerance, if any, did not appear clinically significant.

However, we do acknowledge the limitations of this study. The results of this evaluation should not be generalized. They can only be utilized when the controlled comparative local anesthetic blocks are performed under strict criteria with 0.5 mL of anesthetic for each nerve, under fluoroscopic visualization, along with application of strict criteria of significant pain relief with ability to perform movements which were painful prior to administration of sedation.

CONCLUSION

This placebo-controlled, double-blind evaluation showed that the administration of sedation with midazolam or fentanyl could be a confounding factor in the diagnosis of lumbar facet joint pain in patients with chronic low back pain, nevertheless, in a small proportion of patients. This study shows that an intravenous preoperative sedative dose of a narcotic such as fentanyl or an anxiolytic such as midazolam is no more likely to cause a small proportion of patients to report false positive pain relief with active motion testing than sodium chloride placebo. This study suggests that the prudent administration of midazolam and fentanyl to patients who are not relaxed, may not have any significant adverse effect on the diagnostic validity of controlled comparative local anesthetic blocks.

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