2009

Systematic review of the role of sedation in diagnostic spinal interventional techniques

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Background: There is ongoing controversy regarding the validity of controlled diagnostic blocks due to variability in sensitivity, specificity, and accuracy. Consequently, identification of false-positive rates, false-negative rates, and placebo responses is crucial. The reasons described for false-positive responses to diagnostic anesthetic blocks are many; however, sedation and psychological factors have been implied as causes. Further, there is no consensus with regards to sedation prior to controlled diagnostic blocks and their influence on the accuracy and validity of a diagnosis.

Study Design: A systematic review of the literature evaluating the influence of sedation on diagnostic spinal interventional techniques.

Objectives: To systematically assess the quality of clinical studies evaluating the diagnostic accuracy of controlled diagnostic blocks in the diagnosis of chronic spinal pain.

Methods: A comprehensive evaluation of the literature relating to sedation in diagnostic interventional techniques was performed. The methodologic quality assessment of the studies was carried out by utilizing Agency for Healthcare Research and Quality (AHRQ) methodologic quality criteria with scores of 50 or higher included in the assessment of the level of evidence. Level of evidence was based on the U.S. Preventive Services Task Force (USPSTF) criteria for the assessment of accuracy of diagnostic studies.

Limitations: All 3 of the studies were produced by one group of authors. Thus paucity of the literature on the subject of facet joint pain and the lack of literature on the subjects of discogenic pain and sacroiliac joint pain are major limitations.

Results: Three studies were identified which met inclusion and methodologic assessment quality criteria. Sedation can be a confounding factor in a small population of patients specifically if fentanyl is employed and non-stringent criteria are followed. Based on the 3 randomized double-blind trials with stringent criteria utilizing 80% pain relief and the ability to perform prior painful movements without any significant pain following the diagnostic injection in evaluation of facet joint pain, the indicated evidence is Level II-1.

Conclusion: This systematic review provides no significant evidence of the influence of sedation either with midazolam or fentanyl in the evaluation of cervical and lumbar facet joint pain with controlled cervical and lumbar facet joint nerve blocks with an indicated evidence of Level II-1, with application of stringent criteria of at least 80% pain relief and the ability to perform previously painful movements after the diagnostic blocks.

Key words: Sedation, chronic spinal pain, anxiolytics, analgesics, controlled diagnostic nerve blocks, opioids, benzodiazepines, zygapophysial or facet joint blocks, provocation discography, sacroiliac joint injections
Evolution and phenomenal growth of interventional pain management (IPM) (1-5) has led almost all interventional pain physicians to encounter patients with chronic, persistent spinal pain with psychological problems who also have been exposed to opioids (6-11). Among chronic pain disorders, pain arising from various structures of the spine constitutes the majority of the problems (6). However, due to the inability of physical examination, clinical symptoms, radiologic evaluation, and nerve conduction studies to provide a reliable diagnosis of the structural origin of pain in a patient with chronic pain without disc herniation and radiculitis, controlled diagnostic blocks are considered the only means of reliable diagnosis of spinal pain (6,8,12-16). The most commonly performed diagnostic interventional techniques include diagnostic facet joint nerve blocks, discography, and sacroiliac joint injections (6). Based on the controlled evaluations, lumbar facet joint pain has been demonstrated in 15% to 45% of the patients, with a false-positive rate of 17% to 50% (17-29), discogenic pain has been demonstrated in 26% to 39% (17,30), with a significant alleged false-positive rate (31), with a prevalence of sacroiliac joint pain in 10% to 26% with a false-positive rate of 20% to 22% (17,32,33). Similarly in the cervical spine, facet joint pain was determined in 36% to 67% of the patients with chronic neck pain with a false-positive rate of 27% to 63% (18,20,28,34-39) with a reported prevalence of cervical discogenic pain in 16% to 20% of the patients (39,40). However, while there is no data available on the thoracic spine for prevalence of discogenic pain (41), facet joints were shown to be involved in 34% to 48% of patients with chronic thoracic pain with a false-positive rate of 42% to 58% (18,20,42,43).

There is ongoing controversy regarding the validity of controlled diagnostic blocks of facet joints. In general, precision diagnostic techniques are variable in sensitivity, specificity, and accuracy. Thus, identification of false-positive rates, false-negative rates, and placebo responses is crucial. Numerous reasons have been described for false-positive responses to diagnostic anesthetic blocks, including placebo response to diagnostic injections, use of sedation, liberal use of superficial local anesthetic, and the spread of injectate to pain generating structures other than those targeted (44-46). False-positive responses may also be due to the psychological status of the patient and the effects of various drugs have been suggested to affect false-positive rates by interfering with the interpretation of the analgesic response to controlled diagnostic blocks. Further, psychological variables such as depression, anxiety, and excessive somatic symptoms are recognized as actively contributing to a patient’s perception of pain (47-52). In addition, a diagnosis of depression correlates with increased pain (53-55) and anxiety decreases a patient’s pain threshold and tolerance (56). In samples evaluating chronic pain patients, rates of current major depression and anxiety ranged from 15% to 59%, significantly higher than the rate of 5% to 10% in persons without pain found in the general population (57-63).

Consequently, there is ongoing controversy regarding the validity of controlled diagnostic blocks. Carragee et al (64-67), and others (44-46,68) have raised numerous questions about the value of controlled diagnostic blocks. Cohen and Raja (44) described that both opioids and sedatives, such as midazolam, can lead to false-positive responses by producing general analgesia and/or muscle relaxing-properties that interfere with analgesic responses of controlled diagnostic blocks. However, Manchikanti et al (11,69,70) showed that psychological factors may not have significant influence on the diagnostic validity of interventional techniques in discogenic and facet joint pain. Manchikanti et al (71-74) have also shown that midazolam sedation exerts only a minimal effect on the diagnostic accuracy of controlled blocks of the cervical and lumbar facet joints in the diagnosis of facet joint pain. In addition, Manchikanti et al (75) have also demonstrated that prior exposure to opioids has no significant effect on the diagnostic validity of controlled comparative local anesthetic blocks in the diagnosis of chronic pain of spinal origin.

Consequently, the issue of providing procedural sedation in interventional pain management specifically for diagnostic techniques remains controversial. Further, there is no consensus with regards to sedation prior to controlled diagnostic blocks and the influence of sedation on the accuracy and validity of the diagnosis.

This systematic review was undertaken to review the literature to arrive at appropriate recommendations for utilization of sedation for controlled diagnostic blocks in evaluation of chronic spinal pain.
METHODS

Literature Search
A literature search included multiple databases including PubMed, EMBASE, and databases of multiple journals, Cochrane Reviews, systematic and narrative reviews, Clinical Trials Registry, cross references, and letters to the experts. A search was conducted from 1966 through November 2008.

The search terminology included interventional techniques, controlled diagnostic blocks, controlled comparative local anesthetic blocks, role of sedation for diagnostic blocks, role of opioids, role of anxiolytics, provocation discography, facet or zygapophysial joint nerve blocks.

Inclusion Criteria
Inclusion criteria concentrated on clinical relevance with types of studies concentrating on the role of sedation, anxiety on the diagnosis of spinal facet, discogenic, or sacroiliac joint pain.

Exclusion criteria included abstracts, publications in non-peer reviewed journals, technical reports, expert opinions, general review articles, and single case reports.

Review Methods
Study Selection
Studies were selected if they met inclusion criteria.

Data Extraction
Relevant data on methodology and outcomes were collected.

Methodologic Quality Assessment
The Agency for Healthcare Research and Quality (AHRQ) criteria for diagnostic testing (76) as reported in Table 1 were used for methodologic quality assessment. Based on the weighted scoring system developed and revised by consensus of the Guidelines Committee of the American Society of Interventional Pain Physicians

Table 1. Modified AHRQ methodologic assessment criteria for diagnostic interventions.

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>Weighted Score (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Population</td>
<td>15</td>
</tr>
<tr>
<td>• Subjects similar to populations in which the test would be used and with a similar spectrum of disease</td>
<td></td>
</tr>
<tr>
<td>2. Adequate Description of Test</td>
<td>10</td>
</tr>
<tr>
<td>• Details of test and its administration sufficient to allow for replication of study</td>
<td></td>
</tr>
<tr>
<td>3. Appropriate Reference Standard</td>
<td>30</td>
</tr>
<tr>
<td>• Appropriate reference standard (gold standard) used for comparison</td>
<td>15</td>
</tr>
<tr>
<td>• Reference standard reproducible</td>
<td>15</td>
</tr>
<tr>
<td>4. Blinded Comparison of Test</td>
<td>30</td>
</tr>
<tr>
<td>• Evaluation of test without knowledge of disease status, if possible</td>
<td>15</td>
</tr>
<tr>
<td>• Independent, blind interpretation of test and reference</td>
<td>15</td>
</tr>
<tr>
<td>5. Avoidance of Verification Bias</td>
<td>15</td>
</tr>
<tr>
<td>• Decision to perform reference standard not dependent on results of test under study</td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>100</td>
</tr>
</tbody>
</table>

Adapted and modified from West et al. Systems to Rate the Strength of Scientific Evidence, Evidence Report, Technology Assessment No. 47. AHRQ Publication No. 02-E016 (76).
(ASIPP) (12), a total of 100 total points may be award-
ed for each study. This system has been employed in
other systematic reviews (41,42). Only studies scoring
50 or above were used in the analysis. Each study was
scored independently by 2 reviewers. Any discrepancies
or conflicts were arbitrated by a third author to reach
a consensus agreement. Any disagreement among the
reviewers was resolved by discussion and consensus. If
there was a conflict of interest with the reviewed man-
uscript with authorship or any other type of conflict,
the involved authors did not review the manuscript for
quality assessment or evidence synthesis.

Qualitative Analysis of Evidence

Qualitative analysis was conducted using 5 levels
of evidence, ranging from Level I to III with 3 subcat-
ergories in Level II, as illustrated in Table 2 (77).

RESULTS

Literature Search
Methodologic Quality Assessment

Figure 1 illustrates the search results. The search
yielded 107 articles for review, of these, only 6 were
relevant to the study question, with 2 studies evaluat-
ing role of sedation for non-specific intervention tech-
niques (78,79), and 4 studies evaluating the role of
sedation for diagnostic interventional techniques (71-
74). Methodologic quality assessment of the 6 relevant
studies (71-73) met the inclusion criteria for methodo-
logic quality assessment. Two studies (78,79) were not
included as they were not related specifically to diag-
nostic interventions and also the role of sedation and
its influence on diagnostic value and validity was not
evaluated. Further, one study (74) was the evaluation
of the role of placebo and nocebo effects of periop-
erative administration of sedatives and opioids in in-
terventional pain management on the data obtained
from the previous controlled studies (71-73).

Table 3 illustrates the methodologic quality as-
essment of studies evaluating the effect of sedation.
There were no studies available evaluating the influ-
ence of sedation on diagnostic value or validity of ei-
ther discogenic pain or sacroiliac joint pain.

Study Methods

In 2 studies (71,72), there were 60 patients in each
group. In the third study (73) there were 20 patients
in each group. Each patient, based on the randomiza-
tion, received 1 of the 3 solutions in incremental doses
of 1 mL with a maximum of 5 mL in all groups; 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 investigator
were blinded to the allocation sequence, as well as the
solution administered, in all cases. The solutions were
administered slowly based on the patient's response
with relaxation and/or a 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 the ability to perform
pre-sedation painful movements were reassessed. Af-
fer completion of the evaluation, unblinding was car-
rried out and the amount of sedation administered in
Groups II and III were noted on the record.

Outcomes Assessment

In all studies, the outcomes were assessed at
baseline prior to the administration of the solution
and after the administration of the solution. Multi-
ple parameters included numeric pain scale, percent
of pain relief, and ability to perform prior painful
movements.

<table>
<thead>
<tr>
<th>I:</th>
<th>Evidence obtained from at least one properly randomized controlled trial or multiple well-conducted diagnostic studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-1:</td>
<td>Evidence obtained from well-designed controlled trials without randomization or at least one well-controlled diagnostic study of adequate size</td>
</tr>
<tr>
<td>II-2:</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group or evidence obtained from at least one properly designed small diagnostic accuracy study</td>
</tr>
<tr>
<td>II-3:</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence</td>
</tr>
<tr>
<td>III:</td>
<td>Opinions of respected authorities, based on clinical experience descriptive studies and case reports or reports of expert committees</td>
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Adapted from the U.S. Preventive Services Task Force (USPSTF) (77).
Fig. 1. The flow diagram of the selection process of the literature.
Descriptive characteristics of these 3 studies are included in Table 4. All 3 studies (71-73) were performed by the same group utilizing the same methodology. Manchikanti et al (71) performed a randomized, placebo-controlled, double-blind study and demonstrated that 2% of the patients 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 baseline painful movements in the post follow-up period 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 the 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. Thus, this study showed no significant differences in any of the groups between pain relief or the ability to perform painful movements and the type of sedation.

Manchikanti et al (72) performed a randomized, prospective, double-blind, placebo-controlled evaluation on the effect of sedation in the diagnostic validity of cervical facet joint pain. Pain relief of ≥ 80% was noted in 5% of the patients in Group I, 8% in Group II, and 8% in Group III. However, pain relief of ≥ 50% was noted in 8% of the patients in Group I, 13% in Group II, and 27% in Group II (72).

In the study by Manchikanti et al (73), 50% to 100% of the patients reported relaxation, and as many as 10% of the patients experienced significant pain relief (80% or greater) and were able to perform movements that were painful prior to the administration of intravenous sodium chloride, midazolam, or fentanyl. There were no significant differences noted either among the groups or between regions (cervical vs. lumbar). Significant differences were noted only with regards to relaxation status, with 50% reported in Group I and 100% in Groups II and III. Thus, overall this study showed no significant differences in any of the groups between pain relief or the ability to perform painful movements and the type of sedation

Based on the results of a randomized, placebo-controlled evaluation, 13% to 30% of all the patients receiving either sodium chloride solution, midazolam, or fentanyl reported a placebo response (74). 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 con-

### Table 3. Methodologic quality assessment and scoring

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<tbody>
<tr>
<td>Manchikanti et al 2004 (72)</td>
<td>15</td>
<td>0</td>
<td>_</td>
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<tr>
<td>Manchikanti et al 2004 (71)</td>
<td>15</td>
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<tr>
<td>Manchikanti et al 2006 (73)</td>
<td>15</td>
<td>0</td>
<td>_</td>
<td>15</td>
<td>_</td>
<td>15</td>
</tr>
</tbody>
</table>

(-) weighted item score

Methodological criteria and scoring adapted from West et al. Systems to Rate the Strength of Scientific Evidence, Evidence Report, Technology Assessment No. 47. AHRQ Publication No. 02-E016 (76).
Sedation for Interventional Techniques

included 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.

In all the studies (71-73), Manchikanti et al concluded that prudent administration of 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. These studies suggested that the prudent administration of midazolam and fentanyl to patients who are not relaxed may not have any significant adverse effect on the diagnostic valid-

<table>
<thead>
<tr>
<th>Study/Methods</th>
<th>Participants</th>
<th>Intervention(s)</th>
<th>Outcome(s)</th>
<th>Result(s)</th>
<th>Conclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchikanti et al (72) 2004</td>
<td>180 patients with cervical facet joint pain</td>
<td>Randomization into 3 equal groups (60/group); titration of agent 1 mL at a time; relaxed or 5 mL max given. Group I - NaCl Group II - midazolam Group III - fentanyl</td>
<td>80% pain relief and ability to perform previously painful movements</td>
<td>Pain relief of &gt; 80% was noted in 5% of the patients in Group I, 8% in Group II, and 8% in Group III. However, &gt; 50% relief was noted in 8% of the patients in Group I, 13% of the patients in Group II, and 27% of the patients in Group III. Overall, 8% of the patients in Group I, 13% in Group II, and 27% in Group III were able to perform movements which were painful prior to injection.</td>
<td>The administration of sedation with midazolam or fentanyl is a confounding factor in the diagnosis of cervical facet joint pain in patients with chronic neck pain. However, if &gt; 80% pain relief with the ability to perform prior painful movements is used as the standard for evaluating the effect of controlled local anesthetic blocks, the diagnostic validity of cervical facet joint nerve blocks may be preserved.</td>
</tr>
<tr>
<td>Manchikanti et al (71) 2004</td>
<td>180 patients with lumbar facet joint pain</td>
<td>Randomization into 3 equal groups (60/group); titration of agent 1 mL at a time; relaxed or 5 mL max given. Group I - NaCl Group II - midazolam Group III - fentanyl</td>
<td>80% pain relief and ability to perform previously painful movements</td>
<td>Pain relief of &gt; 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 &gt; 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.</td>
<td>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 the 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.</td>
</tr>
<tr>
<td>Manchikanti et al (73) 2006</td>
<td>60 patients with combined cervical facet joint pain and lumbar facet joint pain</td>
<td>Randomization into 3 equal groups (20/group); titration of agent 1 mL at a time; relaxed or 5 mL max given. Group I - NaCl Group II - midazolam Group III - fentanyl</td>
<td>80% pain relief and ability to perform previously painful movements</td>
<td>Overall, 50% of the patients were relaxed or sedated in the placebo group, while 100% of the patients in the midazolam and fentanyl groups were relaxed or sedated. As many as 10% of the patients reported significant relief (≥ 80%) with the ability to perform prior painful movements.</td>
<td>Perioperative administration of sodium chloride, midazolam, or fentanyl can confound results in the diagnosis of combined cervical and lumbar facet joint pain. False-positive results with placebo or sedation may be seen in a small proportion of patients.</td>
</tr>
</tbody>
</table>
ity of controlled comparative local anesthetic blocks in the cervical or lumbar spine.

Finally, the previous exposure to the study drugs has been shown not to have any significant effect on the response during diagnostic blockade (75).

Level of Evidence

Based on the 3 studies (71-73) evaluating the influence of sedation on the diagnostic accuracy in the diagnosis of facet joint pain, based on United States Preventive Services Task Force (USPSTF) criteria (77), as shown in Table 2 criteria, the indicated evidence is Level II-1, in the evaluation of cervical and lumbar facet joint pain.

Discussion

Based on the comprehensive evaluation of all the available literature, the lack of influence of sedation on controlled facet joint nerve blocks on the diagnosis of cervical and lumbar facet joint pain, the indicated evidence is Level II-1. All of the studies showed a lack of influence of sedation either with midazolam or even with fentanyl with criterion standard of 80% pain relief and the ability to perform previously painful movements. The false-positive results were obtained in 7% of the patients with lumbar facet joint nerve blocks in Group III receiving fentanyl, whereas it was 8% in patients with cervical facet joint pain. However, the authors have cautioned that with an application of 50% pain relief as the criterion standard, this proportion will increase to 13% with lumbar facet joint nerve blocks, whereas it would increase to 27% in the cervical group. Based on the results of this systematic review it is postulated that appropriate administration of sedation either with midazolam or with fentanyl will not adversely affect the diagnostic validity of diagnostic facet joint nerve blocks either in the cervical spine or lumbar spine. However, 80% pain relief with the ability to perform previously painful movements should be used as a criterion standard. Any other standard is not applicable.

This systematic review showed a significant paucity of literature and multiple methodological challenges in assessing the influence of sedation on diagnostic interventional techniques. We were able to find only 3 manuscripts (71-73) by the same authors evaluating either cervical and/or lumbar facet joint pain. There were no studies evaluating provocation discography or sacroiliac joint blocks. Further, this evaluation has not included patients with combined midazolam and fentanyl. Based on the present systematic review, it appears that a significant proportion of patients may require sedation during the peroperative period of diagnostic interventional techniques (78-80).

In fact, Cucuzzella et al (78) performed a survey of 500 consecutive patients receiving lumbar, thoracic, and/or cervical spinal injections. A 12-item questionnaire assessing patients’ perceived anxiety was administered before a spinal injection. Subjects were also given the questionnaire after their primal injection. Percentages requesting sedation for a first and potential second procedure were assessed. Additionally, anxiety level and pain rating, location of injection, age, sex, and other medication use were analyzed to determine the effect on the request for sedation. Seventeen percent of patients questioned requested sedation before an injection and 28% would request sedation if they were to have a second injection. Cucuzzella and colleagues (78) concluded that routine sedation before diagnostic and therapeutic injections is not necessary as the majority of patients would not request sedation before the procedure when given the option. However, in some patients sedation is indicated, and many patients may benefit from educational material on sedation before the injection.

In another study from the same institution, Kim et al (79) conducted a study with 301 consecutive spinal injection patients given a choice to take oral or IV diazepam, or no sedation before a spinal injection. All participating patients filled in a validated anxiety questionnaire before the injection. Patients were asked after the injection whether they were satisfied with their decision regarding sedation and whether their anxiety was controlled effectively. One hundred fifty-seven patients (58%) chose to have IV sedation. Of those, 141 (90%) indicated that their anxiety was controlled. Eleven (7%) did not think that their anxiety was controlled and 5 (3%) did not provide a response.

As eluded by Manchikanti and Giordano (80), Kim et al (79) showed that 58% of the patients initially chose to be sedated and this number increased after the first intervention. However, in their previous study by Cucuzzella et al (78) only 17% of the patients requested sedation initially reflecting a wide variance. Consequently, it is important to consider the differences in the physical and psychological characteristics of patients as seen by interventional physiatrists and interventional pain physicians.
Multiple drugs utilized for anxiolysis and analgesia during interventional procedures include benzodiazepines, opioids, and other agents (81). Midazolam and fentanyl are more frequently used intravenous drugs for intraoperative sedation and analgesia due to the expected short duration of action combined with rapid onset of action. 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. Clinical experience has shown midazolam to be 3 to 4 times as potent per mg as diazepam.

Fentanyl is a narcotic analgesic. A dose of 100 mcg or 0.1 mg or 2 mL is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine. The principle actions of therapeutic value are analgesia and sedation. The onset of action of fentanyl is almost immediate when the drug is given intravenously.

The present evaluation may be criticized for several potential drawbacks of the included studies (71-73). However, all the studies were placebo-controlled, randomized, double-blind, with 60 patients in the smallest group in 3 groups in 2 studies (71,72), with appropriate evaluation of outcome parameters of pain relief and the ability to perform prior painful movements. The question about an additional group with midazolam and fentanyl may be legitimate. However, administration of the 2 drugs in a safe manner would have been extremely difficult, specifically limiting the total dosage to 5 mL with 50% midazolam and 50% fentanyl. The drugs cannot be mixed reliably and uniformly. Further, they may have to be provided in 2 separate syringes. In such a scenario, the study would not be blind. Thus, the authors explained that the combined effect of midazolam with fentanyl was not evaluated.

This systematic review utilized stringent criteria for inclusion. In the evidence synthesis, we attempted to evaluate all types of diagnostic studies, however only limited data was available. Further, since the publication of this literature, Manchikanti et al (75) have illustrated a significant lack of influence of prior exposure on the diagnostic validity of controlled facet joint injections. Even then, it is prudent to conduct multiple studies not only evaluating the role of sedation in diagnosing facet joint pain, but also in the diagnosis of discogenic and sacroiliac joint pain and all other types of diagnostic interventions. Consequently, the limitations of this manuscript include the paucity of the data in general and the lack of availability of data in evaluation of the influence of sedation, with or without opioids, in the diagnosis of discogenic pain and sacroiliac joint pain.

**Conclusion**

This systematic review provides no significant evidence of the influence of sedation either with midazolam or fentanyl in the evaluation of cervical and lumbar facet joint pain with controlled cervical and lumbar facet joint nerve blocks with indicated evidence of Level II-1. However, the results of this systematic review only apply for cervical and lumbar facet joint blocks under sedation utilizing the criterion standard of 80% pain relief with controlled comparative local anesthetic blocks with the ability to perform prior painful movements by the patient immediately.

**Acknowledgments**

The authors wish to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript; Sekar Edem for assistance in search of literature; and Tonie M. Hatton and Diane E. Neihoff, transcriptionists (Pain Management Center of Paducah), for their assistance in preparation of this manuscript.
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