

Review

An Update of Evaluation of Intravenous Sedation on Diagnostic Spinal Injection Procedures

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Background: Intravenous (IV) sedation analgesia is often employed in patients with chronic spinal pain undergoing diagnostic spinal injection procedures. The drugs used for intravenous sedation analgesia produce varying degrees of sedation, amnesia, anxiolysis, muscle relaxation, and analgesia. The very nature of these pharmacologic effects in altering the patient's level of consciousness, awareness, or response to a particular diagnostic stimulus invokes a sense of uncertainty about the results or response obtained from the diagnostic procedure. There is an ongoing controversy regarding the validity of controlled diagnostic blocks due to variability in sensitivity, specificity, and accuracy. Moreover, there is no consensus with regards to the use of sedation analgesic measures prior to controlled diagnostic blocks and their influence on the accuracy and validity of a diagnosis.

Objective: To assess and update the clinically significant effects sedation analgesia procedures have on the diagnostic accuracy and validity of interventional spinal techniques.

Methods: A comprehensive literature search using PubMed, EMBASE, and Cochrane Library review databases up to September 2012 was performed. The search included systematic and narrative review articles, prospective and retrospective studies, as well as cross-referencing of bibliographies from notable primary and review articles and abstracts from scientific meetings and peer-reviewed non-indexed journals. The search emphasized the effects of sedation analgesia on diagnostic spinal interventions.

Conclusion: Based on a review of the available evidence, it appears that the administration of mild to moderate sedation does not confound the results or diagnostic validity of spinal injection procedures. Specifically, immediate pain relief after cervical and lumbar facet joint controlled nerve blocks is not enhanced by IV sedation with midazolam or fentanyl. This is especially true if stringent outcome criteria are employed, such as at least 75% pain relief combined with an increase in range of motion for pain limited movements.

Key words: Conscious sedation, procedural sedation, intravenous sedation, analgesia, hypnotics, sedatives, anxiolytics, opioids, chronic spinal pain, spinal injections, epidural injections, controlled diagnostic nerve blocks, zygapophyseal or facet joint blocks, selective nerve root blocks, provocation discography, sacroiliac joint injections, outcomes

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Procedural sedation analgesia (PSA) is the use of anxiolytic, sedative, hypnotic, analgesic, and/or dissociative medication(s) to attenuate anxiety, pain, and/or motion. These agents are administered in order to facilitate amnesia or decrease awareness

and/or increase patient comfort and safety during a diagnostic or therapeutic procedure (1-4). PSA is administered worldwide by a diverse group of practitioners to patients of all ages in a variety of clinical settings, both inside and outside the

operating room (4). Practice guidelines for sedation and analgesia may vary in different regions of the world (5). The American Society of Anesthesiologists (ASA) has developed such guidelines for use by physicians who are not anesthesiologists. The society considers sedation to be a continuum, and defines 3 levels of sedation: minimal, moderate, and deep (Table 1). Minimal sedation provides a drug-induced state of anxiolysis during which patients respond normally to verbal commands. Moderate sedation analgesia, or conscious sedation, is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands when aroused by the sound of a voice or light tactile stimulation. No interventions are required to maintain a patient airway, during conscious sedation. Deep sedation or analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after the administration of repeated or painful stimulation.

Ventilatory function may be impaired during deep sedation or analgesia. Certain invasive or painful procedures require this level of sedation (5).

The drug classes utilized for anxiolysis and analgesia include benzodiazepines, opioids, and other agents (6). Drugs within this class possess varying degrees of pharmacologic potential to produce sedation, amnesia, anxiolysis, muscle relaxation, and analgesia. The very nature of these pharmacologic effects in altering the patient's level of consciousness, awareness, or response to a particular diagnostic stimulus invokes a sense of uncertainty about the results or response obtained from the diagnostic procedure. Table 2 illustrates the spectrum of pharmacologic effects exhibited by the various drugs typically used for PSA (7). Midazolam and fentanyl are more frequently used intravenous (IV) drugs for intraoperative sedation and analgesia due to the short duration of action combined with rapid onset of action. Midazolam is a short-acting benzodiazepine with central nervous system (CNS) depressant activity. The CNS depressant effects of midazolam depend on the dose administered, the route of administration, and the presence or absence of other medications with CNS depressant activity. Midazolam is 3 to 4 times more potent than diazepam. Fentanyl is an opioid 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. When given intravenously, fentanyl has an almost immediate onset of action. Propofol is another drug commonly used to provide IV sedation. Compared to IV midazolam, it provides statistically significant faster onset of sedation scores, lower mean anxiety scores, and a more rapid recovery with less impairment of recall (8).

Table 1. Description of levels of sedation.

Minimal sedation Patient is in drug-induced state of anxiolysis Patient responds normally to verbal commands
Conscious sedation Patient has drug-induced depression of consciousness Patient responds purposefully to voice or tactile stimulation No interventions are needed to maintain a patient airway should
Deep sedation Patient has drug-induced depression of consciousness Patient cannot be easily aroused Patient responds purposefully after repeated or painful stimulation Ventilatory function may be impaired

Source: Jones DR, et al. Videos in clinical medicine. Conscious sedation for minor procedures in adults. N Engl J Med 2011; 364:e54 (5).

Table 2. Comparative spectrum of pharmacologic effects.

Drug	Anxiolysis*	Sedation	Hypnosis	Analgesia	Amnesia	Anesthesia	Dependency
Methohexital	0	+	+	0	+	+	+
Diazepam	+	+	+	0	+	+	+
Midazolam	+	+	+	0	+	+	+
Propofol	0	+	+	0	+	+	+
Ketamine	0	0	0	+	+	+/D	0
Fentanyl	0	+	+	+	0	+	+
Remifentanyl	0	+	+	+	0	+	+
Dexmedetomidine	0	+	+	+	+	S	0/A

Key: * Possessing receptor specificity for effect; + = Produces effect; 0 = No effect; S = Anesthetic-sparing effects; A = Attenuates withdrawal symptoms from barbiturates, benzodiazepines, and opioids; D = Dissociative anesthetic state.

The most serious complications of conscious sedation are respiratory and cardiovascular depression, which occurs when a patient becomes deeply sedated. Because respiratory and cardiovascular compromise can lead to death, it is vitally important to 1) obtain written consent from the patient, 2) ensure adequate preparation and careful monitoring, and 3) have qualified personnel administer it (9).

The terminology and definitions for sedation related adverse effects were developed by The World Society of Intravenous Anaesthesia (SIVA) International Sedation Task Force (ISTF), after considering and incorporating elements from Institute of Medicine (IOM) (10), World Health Organization (WHO) (11), European Medicines Agency (EMA) (12,13), and United States Food and Drug Administration (FDA) (14) definitions. The ISTF is comprised of 26 physicians from 10 specialties and 11 countries with clinical expertise, a research commitment to the sedation of adults and children, or both. ISTF defines sedation-related adverse effects as: "Unexpected and undesirable response(s) to medication(s) and medical intervention used to facilitate procedural sedation and analgesia that threaten or cause patient injury or discomfort" (4). The Task Force has developed an Adverse Effect Sedation Outcome tool, configured in a check box form, and suitable for use on a web page or paper document, or as part of an electronic medical record. According to this tool, each adverse effect is characterized across 3 domains: description, intervention, and outcome. The specific features within each domain define the severity or clinical importance of the adverse effect: sentinel, moderate, minor, or minimal. Sentinel adverse effects are the most serious and represent those critical enough to pose a real or major imminent risk of patient injury. Once recognized, they warrant immediate and aggressive rescue interventions. Although there are no specific descriptions that alone define a moderate adverse effect, adverse effects are labeled moderate only if they are associated with a moderate intervention or outcome, Minor adverse effects are those encountered periodically in most sedation settings that pose little threat or danger of permanent harm to the patient, given appropriate sedation care, provider skills, and monitoring. Minimal adverse effects are those that alone present no danger of permanent harm to the patient (4). The Adverse Effect Sedation Outcome Tool has not yet been validated in interventional pain management settings.

1.0 INDICATIONS FOR PROCEDURAL SEDATION ANALGESIA

IV sedation analgesia is inconsistently employed across interventional pain settings. In one survey of pain practices, 46% of respondents employed IV sedation for lumbar epidural steroid injections and 53% used it for cervical epidural steroid injections (15). Most practice guidelines discourage the routine use of sedation for interventional pain procedures. There are, however, patients who are unable to cooperate with the procedure for various reasons and for whom sedation may be indicated to control patient anxiety or apprehension and allow for safe and satisfactory conduct of the procedure/intervention. In these instances, providing appropriate sedation goes beyond being humane; it is required in order to perform the procedure safely and effectively. It has been shown that the pre-procedural anxiety level correlates with the post-procedural level of patient comfort. One study compared the anxiolytic effect of midazolam and droperidol, administered prior to epidural catheterization, on post-procedural memories and comfort level between 12 and 20 hours and showed that patients receiving midazolam reported significantly less pain and anxiety (16).

Every possible effort should be made to allay the anxiety and apprehension of the patient before a decision is made to employ IV sedation. The indications and justification for sedation must be clearly documented. It is recommended that the patient must remain sufficiently alert and awake to report any unexpected sensations that may warn of an impending complication. At no time, and under no circumstance should the patient be deeply sedated for the spinal injection procedure. This is even more important for diagnostic procedures such as discography, when the patient may need to describe the pain provocation response or need to be awake and mobile immediately after the procedure to assess the analgesic response. For certain therapeutic procedures, the urge to use sedation analgesia to the extent of producing a deep level of conscious sedation should be tempered, as the risks far exceed the potential benefit. Rathmell et al (17) examined the ASA closed claims database between 2005 and 2008, and compared claims arising from cervical pain procedures with all other chronic pain claims. Claims related to cervical interventions represented 22% of chronic pain treatment claims. Of the claims involving cervical procedures, 59% had traumatic spinal cord damage. Furthermore, spinal cord injuries were more common

in patients who received sedation or anesthesia (17). Hence, the need for sedation analgesia must be carefully evaluated. When these techniques are employed, they must be tailored to the comfort and reassurance level of an individual patient, without impairing the accuracy and validity of the diagnostic test.

2.0 SPINAL INTERVENTIONAL TECHNIQUES AND PROCEDURAL SEDATION ANALGESIA

Multiple evaluations in interventional pain management describe patients with chronic pain and psychiatric comorbidity who have also been exposed to opioid analgesics (18-36). Among chronic pain disorders, the majority of problems stem from pain arising from various structures of the spine (28). In most of these patients, the source of pain or the structure causing pain cannot be identified by standard diagnostic methods, i.e., history and physical examination, laboratory tests, imaging studies, electrophysiologic studies, or histopathology. Because there is no known biomarker for pain, physicians employ anesthetic blocks of the target structure (joint, nerve) in a controlled manner to identify the structure/s causing pain (28-36). Some of the commonly performed diagnostic interventional techniques include selective nerve root injections, facet joint nerve blocks, discography, and sacroiliac joint injections. In patients with chronic low back pain, controlled blocks have demonstrated that the prevalence of facet joint pain is 25% to 45% (32), discogenic pain is 26% to 42% (36), and sacroiliac joint pain is 10% to 62% (35). Similarly, in patients with chronic neck pain, facet joint pain occurs in 36% to 60% (33) and discogenic pain in 16% to 53% of patients (31). Nearly 34% to 48% of patients with chronic thoracic pain have facet joint pain (34).

When associated with diagnostic injections, the placebo effect may result in false positive rates. In multiple studies, false positive rates for controlled and uncontrolled diagnostic blocks have been estimated to range from 27% to 63% for cervical facet joint nerve blocks (33), 42% to 58% for thoracic facet joint nerve blocks (34), 17% to 50% for lumbar facet joint nerve blocks (32), and 20% for sacroiliac joints injections (35). Accordingly, Carragee et al (37-40), and others (41-44) have questioned the validity of precision diagnostic blocks. Some of the plausible explanations given for these false-positive responses include use of IV sedation, placebo response to diagnostic injections, liberal use of local anesthetic to infiltrate superficial soft tissues, and the spread of injectate beyond the target structure to anesthetize adjacent structures (41-44).

Cohen and Raja (41) 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, Frölich et al (45), in a recent evaluation assessing the effect of sedation on pain perception, showed that in fact, sedation may increase pain perception. They also showed that the effect of sedation on pain perception is agent- and pain type-specific. In this assessment of 83 healthy volunteers randomly assigned to receive one of 3 sedative drugs, which included midazolam, propofol, or dexmedetomidine, midazolam increased cold, heat, and electrical pain perception significantly; propofol reduced ischemic pain; and dexmedetomidine reduced both cold and ischemic pain significantly. Consequently, midazolam, most commonly utilized as a sedative for interventional pain procedures, does not demonstrate any pain relieving effect, but does increase pain perception. On the other hand, Manchikanti et al (46-49) found that sedation with midazolam exerts minimal effect on the diagnostic accuracy of cervical and lumbar facet joint controlled blocks. The value and validity of diagnostic facet joint blocks (50-53) and accuracy also have been exemplified by therapeutic interventions (54-58).

Psychological factors such as patient mood and motivation to get well can bias patient response. In some cases, the drugs used may interfere with the interpretation of the analgesic response and confound the results of diagnostic blocks. Psychiatric comorbidity such as depression, anxiety, and excessive somatic symptoms are known to actively contribute to the perception of pain (18-24,59-68). Clinically, a diagnosis of depression correlates with increased pain (66-68) and anxiety decreases a patient's pain threshold and tolerance (59). In chronic pain patients, the prevalence of current major depression and anxiety ranges from 15% to 59%, and is significantly higher than the rate of 5% to 10% in persons without pain in the general population (21-23,59). One study showed that preprocedural anxiety levels are predictive of verbal pain intensity ratings following a clinical pain stimulus (20). Manchikanti et al (19,24) evaluated the effect of depression and anxiety on the diagnostic validity of disc and facet joint injections in chronic pain patients and found that these variables did not significantly influence false positive rates. They also studied the effect of prior exposure to opioids (18) on diagnostic blocks and found no significant effect on the diagnostic validity of controlled comparative local

anesthetic blocks in patients with chronic spinal pain. The role of the placebo effect has been extensively discussed and its role in diagnostic blocks is undetermined (69-118). Local anesthetic blocks have been shown to modulate pain responses (102). However, nocebo effects are not well recognized (77,98,103-107). The role of local anesthetic also has been debated and misinterpreted (108-134). Local anesthetics have been demonstrated to provide long-term relief (54,57,58,135-166).

At this time, the issue of providing procedural sedation in interventional pain management specifically for diagnostic techniques has not been satisfactorily resolved. 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 review is an update to a previous review published in 2009 (29).

3.0 STUDIES ON ASSESSING SEDATION ANALGESIA IN INTERVENTIONAL PAIN MANAGEMENT

Of the available studies on procedural sedation in interventional pain management, 2 studies (by the same group) described patient preference for IV sedation and anxiety control (167,168). Four studies prospectively evaluated the influence of sedation on post procedure pain ratings: one was an audit of patients treated with epidural steroid injections (169) and 3 studies (by the same group of authors) evaluated changes in pain scores and range of motion after diagnostic medial branch blocks (46-48).

According to one survey, the majority of patients undergoing spinal injection procedures request sedation before the procedure, when given the option. However, in a survey of 500 patients undergoing lumbar, thoracic, and/or cervical spinal injections, only 17% patients requested sedation before an injection and 28% indicated that they would request sedation if they were to receive a second injection (167). A second study by the same group did not replicate these results and in fact found that more than half of the patients preferred to receive sedation prior to their spinal injection procedure (168). In this study, 301 consecutive patients were given a choice of oral diazepam, IV diazepam, or no sedation before the spinal injection. One hundred fifty-seven patients (58%) chose to have IV sedation. After the injection, patients who chose sedation were asked if they were satisfied with their decision on sedation and if their anxiety about the procedure was effectively controlled with IV sedation. Ninety percent of patients

indicated that their anxiety was controlled, while 7% of patients did not feel that their anxiety was adequately controlled. Furthermore, more patients preferred to be sedated for their second procedure, in contrast to 58% of patients requesting sedation for the first injection procedure. These findings are similar to those reported by Manchikanti and Giordano (170). It is possible that the differences in the proportion of patients requesting sedation in the 2 studies reflect a wide variance in the number and type of patients requiring sedation for spinal injection procedures. Physicians must therefore consider the physical and psychological characteristics of each patient, and factor these into their decision regarding the use of sedation in their patients.

A prospective audit of pain patients undergoing treatment with epidural steroid injections demonstrated that mild or moderate sedation did not influence post-procedure pain relief, and that there were no significant differences between mean Visual Analog Scale (VAS) or mean differences in VAS scores between those who did or did not receive IV sedation (169).

Manchikanti et al (46-48) evaluated the effect of sedation on pain relief after diagnostic medial branch blocks for cervical facet joints and lumbar facet joints (Table 3) in 3 studies that utilized identical methodology and compared pain relief and ability to perform painful movements in patients who received midazolam or fentanyl with a placebo group. There were no significant differences noted either among the groups (IV sodium chloride, midazolam, or fentanyl) or between regions (cervical vs. lumbar). Based on these results, the authors concluded that IV sedation with fentanyl or midazolam does not alter the diagnostic validity of controlled comparative local anesthetic blocks in the cervical or lumbar spine (18). They recommended employing strict outcome criterion such as $\geq 80\%$ pain relief and an increase in range of previously painful movements. The false-positive rates were 7% and 8% (for lumbar and cervical medial branch blocks) when these criterion standards were employed as compared to 13% and 27% when these standards were relaxed to 50% pain relief. Based on limited data, the authors concluded that IV sedation either with midazolam or fentanyl did not adversely affect the diagnostic validity of facet joint nerve blocks in either the cervical spine or lumbar spine, provided strict criterion standards are used. The authors did not include a group that received both midazolam and fentanyl (as is common practice), and therefore it is not known if co-administration of the 2 drugs will lead to similar or different outcomes.

Table 3. Descriptive characteristics of sedation for interventional techniques.

Study/Methods	Participants	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Manchikanti et al, 2004 (46) Randomized, double-blind	180 patients with cervical facet joint pain	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	80% pain relief and ability to perform previously painful movements	Pain relief of > 80% was noted in 5% of the patients in Group I, 8% in Group II, and 8% in Group III. However, > 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 that were painful prior to injection.	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 > 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.
Manchikanti et al, 2004 (47) Randomized, double-blind	180 patients with lumbar facet joint pain	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	80% pain relief and ability to perform previously painful movements	Pain relief of > 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 > 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.	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, are 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.
Manchikanti et al, 2006 (48) Randomized, double-blind	60 patients with combined cervical facet joint pain and lumbar facet joint pain	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	80% pain relief and ability to perform previously painful movements	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 (2 reported 80%) with the ability to perform prior painful movements.	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.

Also there is no study that evaluated the influence of IV sedation on other diagnostic injection procedures such as discography and sacroiliac joint blocks.

Discography is a diagnostic interventional procedure performed for the purpose of confirming or refuting a clinical assessment that a specific intervertebral disc is the prominent source of a patient's spinal pain. Provocative discography implies that the procedure provokes a level of discomfort to the pa-

tient in order to identify the pain generator. Most studies concerning provocative discography, however, usually do not indicate whether or not sedation analgesia is employed for the procedure. The potential confounding pharmacologic influence imposed by sedation analgesia coupled with the inherent variability and subjectivity in discography techniques and diagnostic criteria can affect the validity of the results (171).

4.0 LIMITATIONS

This review is limited by a paucity of studies on this topic in general, and by the absence of data on the influence of sedation, with or without opioids, in diagnosing discogenic pain and sacroiliac joint pain. In addition, 2 groups conducted all of the available studies. One group evaluated overall patient preference for IV sedation prior to spinal injections, while the other group studied the effect of sedation on the diagnostic validity of facet joint nerve blocks in neck and low back pain. The studies by Manchikanti et al (46-48) were placebo-controlled, randomized, double-blind, and evaluated pain relief and pain limited movements. These authors however, did not evaluate the effect of co-administering midazolam and fentanyl, which is the norm for sedation in most interventional pain practices. These studies also did not evaluate the effect of a variable drug dose (midazolam and or fentanyl) on diagnostic validity, i.e., the minimum effective dose to control anxiety and improve patient comfort without significantly altering outcome variables of diagnostic procedures. Future studies should describe the characteristics of patients requiring sedation; compare outcomes in patients receiving oral benzodiazepines or antihistamines (Benadryl) with IV sedation; compare IV sedation to self hypnosis, breathing, or other behavioral diversion strategies; and provide guidelines on optimal drug and dosing combinations.

5.0 CONCLUSION

Most interventional diagnostic spinal procedures are inherently stressful and discomfoting to the patient. The ultimate goal is to employ sedation analgesia techniques adapted to the comfort and reassurance level of the patient based upon the expected degree of invasiveness and extent of mental anguish to be evoked

by the diagnostic procedure, without impairing the accuracy and validity of the diagnostic test. The essential features that the clinician seeks in a diagnostic test are accuracy, safety, and reproducibility. The general parameters of accuracy are described as the specificity and sensitivity of the diagnostic test. There is no completely reliable "gold standard" with which to compare a diagnostic test or injection in conditions wherein the presence or absence of pain is the end point (172). The potential for compromising the diagnostic criteria for procedural results seems apparent. This narrative review, however, has not found any significant evidence for the influence of sedation with either midazolam or fentanyl in the evaluation of cervical and lumbar facet joint pain with controlled facet joint nerve blocks. There remains a paucity of evidence in the literature to show whether or not other sedation analgesia regimens affect the diagnostic accuracy of various spinal interventional techniques, such as selective nerve root blocks, facet joint injections, sacroiliac joint injections, provocation discography, and spinal cord lead placement trials.

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