Review Article

The Role of Multimodal Analgesia in Spine Surgery

Abstract

Optimal postoperative pain control allows for faster recovery, reduced complications, and improved patient satisfaction. Historically, pain management after spine surgery relied heavily on opioid medications. Multimodal regimens were developed to reduce opioid consumption and associated adverse effects. Multimodal approaches used in orthopaedic surgery of the lower extremity, especially joint arthroplasty, have been well described and studies have shown reduced opioid consumption, improved pain and function, and decreased length of stay. A growing body of evidence supports multimodal analgesia in spine surgery. Methods include the use of preemptive analgesia, NSAIDs, the neuromodulatory agents gabapentin and pregabalin, acetaminophen, and extended-action local anesthetics. The development of a standard approach to multimodal analgesia in spine surgery requires extensive assessment of the literature. Because a substantial number of spine surgeries are performed annually, a standardized approach to multimodal analgesia may provide considerable benefits, particularly in the context of the increased emphasis on accountability within the healthcare system.

Spine surgery typically causes postoperative pain. Adequate postoperative pain control allows for improved mobility, faster rehabilitation, reduced complications, and improved patient satisfaction. Additionally, implementation of pain management standards by The Joint Commission and the Hospital Consumer Assessment of Healthcare Providers and Systems survey has resulted in increased emphasis on adequate postoperative pain control in the assessment of successful outcomes. Historically, postoperative pain control regimens after spine surgery relied heavily on opioid medications provided at intervals in response to patient-reported pain. Although opioids remain the cornerstone for management of severe acute postoperative pain, intermittent opioid use may result in inadequate pain relief and substantial opioid-induced adverse effects. A multitude of notable adverse effects are associated with opioid use, including respiratory depression, cardiovascular stress, altered cognition, delayed wound healing, urinary and gastrointestinal dysfunction, and acquired tolerance.

Preemptive multimodal analgesia (MMA) regimens have been developed as a means of improving postoperative pain management and reducing opioid consumption and its adverse effects. Preemptive analgesia, or analgesia administered before the onset of pain, prevents central sensitization, which is the activation of central neurons and their amplified peripheral neurons in response to noxious stimuli. MMA regimens rely on the synergistic action of nonopioid agents given in lower
A growing body of evidence supports the use of MMA in spine surgery. Here, we provide a comprehensive review of available literature addressing the use of MMA in spine surgery with consideration of the level of evidence of each study. We performed a comprehensive literature search of MEDLINE and PubMed for high-quality studies evaluating the use of individual agents as adjuncts to standard opioid regimens and the use of MMA regimens in patients undergoing spine surgery. Levels of evidence were determined according to the criteria in the Oxford Centre for Evidence-Based Medicine’s Levels of Evidence table.10

Adjuvant Agents

Nonsteroidal Anti-inflammatory Drugs

NSAIDs exert anti-inflammatory and analgesic effects by blocking prostaglandin production via inhibition of cyclooxygenase (COX) isozymes. COX-1 enzymes are ubiquitous throughout the body, whereas COX-2 enzymes are more specific to acute and chronic inflammatory tissues. COX-2 inhibitors were developed to specifically target inflammatory tissues while reducing the effects of COX-1 inhibition and adverse effects on gastric mucosa and platelet function. Spine surgeons have been reluctant to adopt routine use of NSAIDs for perioperative pain management in patients undergoing spinal fusion because of concern for pseudarthrosis, nonunion, and postoperative bleeding. A retrospective study by Glassman et al11 demonstrated statistically significantly greater nonunion rates in patients who received intramuscular ketorolac (17%) compared with patients who received no NSAIDs (4%) after lumbar fusion. In an animal model, Martin et al12 demonstrated a significantly lower rate of posterolateral lumbar fusion with high-dose ketorolac (a nonselective NSAID) compared with saline (35% and 75%, respectively; P = 0.037).

Other investigations have focused on the effect of differing NSAIDs and doses on spinal fusion. A meta-analysis of five retrospective comparative studies demonstrated increased risk of nonunion with the use of high-dose ketorolac after spinal fusion but no detrimental effects of short-term use of NSAIDs (ketorolac, diclofenac, celecoxib, or rofecoxib) at normal doses.13 It is important to note that rofecoxib has been withdrawn from the market. High-dose ketorolac was defined as >120 mg/d. No patients received NSAIDs at any dose for >14 days after spinal fusion. This meta-analysis suggested that NSAIDs had a dose-dependent effect on spinal fusion rates and were safe to use for short-term perioperative analgesia at normal doses. Interestingly, the increased risk of nonunions associated with NSAIDs may be mitigated when selective COX-2 inhibitors are used. Long et al14 compared the fusion rates of 72 rabbits that underwent posterolateral fusion and were given 10 mg/kg of celecoxib (a COX-2 inhibitor), 10 mg/kg of indomethacin, or 1 mL of saline. A significant difference in the fusion rate was found between the rabbits that received indomethacin and those that received saline (41% versus 82%, respectively; P = 0.004), but no difference was identified in the fusion rate between rabbits that received celecoxib and those that received saline (86% versus 82%).

Although the rate of pseudarthrosis may decrease with the use of COX-2 inhibitors, the clinical efficacy remains substantial. A randomized controlled trial (RCT) by Jirattanaphochai et al15 compared the addition of parecoxib (a COX-2 inhibitor) and the addition of a placebo (saline) in the postoperative pain management regimen of patients undergoing lumbar discectomy, decompression, or fusion. The study demonstrated a 39% reduction in opioid use, improved pain control, and higher patient satisfaction in patients who received...
40 mg of parecoxib intravenously 30 minutes before the surgical procedure and additional 40-mg doses every 12 hours for 48 hours postoperatively, compared with the results in patients receiving saline. No difference was found in adverse outcomes, including postoperative bleeding. A meta-analysis of 17 studies comparing the use of adjunctive NSAIDs and the use of opioid pain management alone demonstrated improved pain scores and reduced opioid consumption with the use of adjunctive NSAIDs in patients undergoing lumbar spine surgery. Level I evidence supports the routine perioperative use of NSAIDs to improve pain control and reduce opioid consumption in patients undergoing spine surgery, and the use of selective COX-2 inhibitors or short-term, low-dose nonselective COX inhibitors does not appear to affect spinal fusion rates, although high-dose nonselective COX inhibitors may decrease fusion rates (Table 1).

### Neuromodulatory Agents

Gabapentin and pregabalin are second-generation anticonvulsants used to manage acute and chronic neuropathic pain. These neuromodulatory agents reduce neuronal excitability via inhibition of the α2-δ subunit of calcium-gated channels on presynaptic axons. One RCT demonstrated statistically significant improvement in pain scores at 1, 2, and 4 hours postoperatively in patients undergoing lumbar spine surgery who received a single 1,200-mg dose of gabapentin 1 hour before incision compared with those who received a placebo. The study also demonstrated overall reduction in opioid consumption in the patients who received gabapentin, and significantly more episodes of vomiting and urinary retention in the placebo group, which the authors of the study attributed to greater opioid consumption. Another double-blinded RCT compared total intravenous opioid patient-controlled analgesia use in patients undergoing lumbar fusion who received 75 mg of pregabalin, 150 mg of pregabalin, or a placebo 1 hour preoperatively and 12 hours postoperatively. The total volume of patient-controlled analgesia used was significantly lower in patients receiving 150 mg (but not 75 mg) of pregabalin, compared with that of the placebo group, at 24 (P = 0.025) and 48 hours (P = 0.028) postoperatively, suggesting a dose-dependent analgesic effect of pregabalin. No statistically significant difference was found between the control and treatment groups in the incidence of adverse effects associated with pregabalin, such as dizziness, vertigo, or blurred vision.

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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design (Procedure)</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glassman et al11</td>
<td>Retrospective review (lumbar fusion)</td>
<td>288</td>
<td>Intramuscular ketorolac and opioid analgesics</td>
<td>Nonunion rates were higher in patients who received intramuscular ketorolac than in patients who did not receive NSAIDs.</td>
<td>III</td>
</tr>
<tr>
<td>Jirarattanaphochai et al15</td>
<td>Randomized controlled trial (lumbar diskectomy, decompression, or fusion)</td>
<td>120</td>
<td>Parecoxib (40 mg preoperatively and every 12 hr for 48 hr postoperatively) and morphine</td>
<td>Patients receiving parecoxib had 39% reduction in morphine use, reduced pain at rest, and greater satisfaction.</td>
<td>I</td>
</tr>
<tr>
<td>Jirarattanaphochai and Jung16</td>
<td>Meta-analysis of 17 randomized controlled trials (lumbar spine surgery)</td>
<td>789</td>
<td>NSAIDs and opioid analgesics</td>
<td>Lower pain scores and lower opioid use in patients receiving NSAIDs and opioids than in patients receiving opioids alone.</td>
<td>II</td>
</tr>
<tr>
<td>Li et al13</td>
<td>Meta-analysis of five retrospective comparative studies (spinal fusion)</td>
<td>1,403</td>
<td>High-dose ketorolac defined as &gt;120 mg/d, diclofenac &gt;150 mg/d, celecoxib &gt;600 mg/d, rofecoxib &gt;50 mg/d</td>
<td>Increased risk of nonunion with high-dose ketorolac. No detrimental effects of short-term use of NSAIDs (ketorolac, diclofenac, celecoxib, or rofecoxib [removed from market]) at normal doses.</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Levels of evidence were determined according to the Oxford Centre for Evidence-Based Medicine criteria.10*
In a recent RCT of patients undergoing lumbar discectomy, Khurana et al\textsuperscript{19} demonstrated improved pain intensity and functional outcomes, measured by the Prolo score and Oswestry Disability Index, for up to 3 months postoperatively with perioperative use of pregabalin (75 mg) or gabapentin (300 mg), compared with patients receiving gabapentin (300 mg) or placebo treatment. Patients received a single preoperative dose and repeated doses for 1 week postoperatively. Both treatment groups demonstrated reduced total opioid use. No difference in adverse effects was found between the gabapentin and pregabalin treatment groups. Yu et al\textsuperscript{20} performed a systematic review and meta-analysis evaluating the efficacy of gabapentin and pregabalin in pain management after lumbar spine surgery. Their analysis of seven high-quality trials demonstrated considerable pain reduction and decreased narcotic consumption with use of either gabapentin or pregabalin compared with placebo treatment, without notable adverse effects. Thus, level I evidence supports the addition of the neuromodulatory agents gabapentin or pregabalin in the perioperative pain management of patients undergoing spine surgery (Table 2).

One RCT evaluated the use of amantadine for perioperative pain management in patients undergoing thoracolumbar fusion for correction of idiopathic scoliosis.\textsuperscript{21} Amantadine is an antiparkinsonian medication with an unclear mechanism of action. It is thought to modulate dopaminergic and noradrenergic release and to act as a weak NMDA (N-methyl-D-aspartate) antagonist. Patients who were randomized to receive either 50 mg or 100 mg of amantadine 1 hour before surgery and at specified intervals postoperatively reported reduced pain, required 25% less morphine, and had reduced opioid-induced nausea up to

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**Table 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design (Procedure)</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Level of Evidence\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bujak-Giżycka et al\textsuperscript{21}</td>
<td>RCT (elective spine surgery for management of idiopathic scoliosis)</td>
<td>60</td>
<td>Oral amantadine</td>
<td>Postoperative morphine consumption was lower in amantadine group than in placebo group</td>
<td>I</td>
</tr>
<tr>
<td>Khurana et al\textsuperscript{19}</td>
<td>RCT (lumbar spine surgery)</td>
<td>90</td>
<td>Gabapentin or pregabalin</td>
<td>Lower visual analog scale pain scores, Oswestry Disability Index scores, and rescue opioid use in gabapentin and pregabalin groups than in placebo group. Higher Prolo score at 3 mo postoperatively in gabapentin group than in pregabalin group.</td>
<td>II</td>
</tr>
<tr>
<td>Kim et al\textsuperscript{18}</td>
<td>RCT (elective lumbar fusion)</td>
<td>84</td>
<td>Pregabalin (75 mg or 150 mg)</td>
<td>Patients who received 150 mg of pregabalin used less intravenous patient-controlled analgesia than patients in the placebo group used. No difference in pain intensity or adverse events.</td>
<td>I</td>
</tr>
<tr>
<td>Turan et al\textsuperscript{17}</td>
<td>RCT (lumbar discectomy or fusion)</td>
<td>50</td>
<td>1,200 mg of gabapentin given 1 hr preoperatively</td>
<td>Pain scores at 1, 2, and 4 hr postoperatively were lower in the gabapentin group than in the placebo group. Less morphine use in the gabapentin group than in the placebo group. No difference in adverse events.</td>
<td>I</td>
</tr>
<tr>
<td>Yu et al\textsuperscript{20}</td>
<td>Systematic review/meta-analysis (lumbar spine surgery)</td>
<td>705</td>
<td>Gabapentin or pregabalin</td>
<td>Gabapentin and pregabalin each resulted in decreased opioid use and decreased pain compared with placebo.</td>
<td>I</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Levels of evidence were determined according to the Oxford Centre for Evidence-Based Medicine criteria.\textsuperscript{10}

\textsuperscript{RCT} = randomized controlled trial
48 hours postoperatively, compared with patients who received a placebo.\textsuperscript{21} This single RCT represents level I evidence to support the use of amantadine for perioperative spine analgesia (Table 2). However, this agent should be further studied and its adverse effect profile better defined.

**Acetaminophen**

Acetaminophen exerts antipyretic, anti-inflammatory, and analgesic effects through peripheral and central COX inhibition similar to that of NSAIDs. Several studies have demonstrated improved pain control and reduced opioid use with both oral and intravenous adjunctive acetaminophen in patients undergoing orthopaedic procedures.\textsuperscript{22-24} To the best of our knowledge, no studies have evaluated the efficacy of acetaminophen alone in postoperative pain management after spine surgery. However, acetaminophen remains a cornerstone of described multimodal regimens.

**Neuraxial Blockades**

Neuraxial (epidural or intrathecal) administration of opioids may consist of single-dose or continuous infusion or may be used in patient-controlled analgesia. Neuraxial opioids may decrease postoperative pain and result in less opioid tolerance and fewer systemic adverse effects than are seen with oral and intravenous opioids. Life-threatening adverse effects, including respiratory depression, remain a concern, although the risks are agent dependent and dose dependent and are greater with intrathecal use.\textsuperscript{25} Neuraxial opioid use after lumbar spine surgery has been described. The ease of administration and relatively low adverse effect profile make neuraxial opioid blockade an attractive option for postoperative pain management. Two RCTs of single-dose intrathecal morphine and fentanyl have demonstrated improved postoperative visual analog scale (VAS) pain scores and opioid consumption without notable adverse effects in patients undergoing lumbar spine surgery.\textsuperscript{26,27} One retrospective study of patient-controlled epidural analgesia demonstrated reduction of postoperative VAS pain scores and opioid consumption in patients who underwent lumbar spine surgery.\textsuperscript{28} An RCT by Guilfoyle et al\textsuperscript{29} demonstrated improved early postoperative VAS pain scores after lumbar decompression in patients who received a single 100-µg epidural bolus of fentanyl compared with those who received a placebo. No difference was found in length of stay, although more patients required temporary urinary catheterization in the fentanyl group than in the placebo group. These findings suggest the efficacy and limited adverse effect profile of single-dose neuraxial opioid analgesia in patients undergoing spine surgery. Level I evidence supports the use of single-dose intrathecal opioid analgesia as an adjunct in pain management after spine surgery (Table 3). However, care should be taken regarding the dosage and strength of the chosen agent because motor and parasympathetic blockade can mask serious postoperative complications, such as epidural hematoma.

Epidural steroid injection is often used as an adjunct to other methods of pain management after lumbar discectomy. Direct steroid injection is used to reduce acute inflammation and prevent persistent or recurrent radicular symptoms, and its efficacy is well described.\textsuperscript{30-32} An RCT by Rasmussen et al\textsuperscript{33} demonstrated improved pain and neurologic symptoms in the short term and reduced length of hospital stay in patients receiving an epidural steroid injection after lumbar discectomy. They found no difference in long-term leg or back symptoms at 1 and 2 years postoperatively and similar rates of revision surgery at 2 years postoperatively (7% in the steroid injection group versus 8% in the control group). A systematic review by Jamjoom and Jamjoom\textsuperscript{30} demonstrated strong evidence that intraoperative epidural steroid use reduces early postoperative pain and opioid consumption. Level I evidence supports the use of epidural steroids after lumbar discectomy to improve short-term pain and neurologic symptoms (Table 3).

**Local Anesthesia**

Amino amide local anesthetic agents, such as lidocaine and bupivacaine, provide analgesia through inhibition of voltage-gated sodium channels and depolarization of sensory nerves. These agents may provide substantial postoperative pain relief, especially after procedures requiring extensive soft-tissue dissection and retraction, and their use after orthopaedic procedures is well described.\textsuperscript{9,34} Two retrospective level III studies support the use of continuous infusion of local anesthesia in the postoperative care of the spine patient.\textsuperscript{35,36} In a review of patients who underwent posterior cervical fusion, Elder et al\textsuperscript{35} compared 25 patients who received the standard pain regimen and a continuous infusion of bupivacaine (0.5%) via elastomeric pump with 25 matched control patients who were treated with the standard regimen. Patients who received the continuous bupivacaine infusion had improved pain control and reduced opioid consumption in the first 4 days postoperatively. Reynolds et al\textsuperscript{36} reviewed 87 patients who underwent thoracolumbar fusion for the management of idiopathic scoliosis, 62 of whom were treated with the standard pain regimen and continuous infusion of bupivacaine (0.25%) and 25 of whom were treated with the standard regimen. The patients who received local...
anesthesia used 0.5 mg/kg less opioid in the first 24 hours postoperatively.36

**Multimodal Regimens**

MMA regimens rely on the synergistic action of nonopioid agents in postoperative pain management to improve pain control, reduce opioid consumption and adverse effects, and facilitate rehabilitation. The use of MMA regimens after orthopaedic procedures, especially joint arthroplasty,8,9 has gained acceptance, but description of their use after spine surgery is limited. Two retrospective studies demonstrated improved pain control, reduced opioid consumption, earlier mobilization, and reduced opioid-induced adverse effects in patients treated with MMA regimens after spine surgery.37,38 In an RCT by Garcia et al,39 patients undergoing lumbar decompression were randomized to receive intravenous morphine only or a preemptive MMA regimen (a 200-mg preoperative dose of celecoxib followed by 100 mg of celecoxib postoperatively, 15 mg of pregabalin, and 10 mg of extended-release oxycodone given twice daily postoperatively) in addition to morphine. Compared with the patients receiving morphine only, the patients receiving the MMA regimen had lower VAS pain scores at all time points, a 58% reduction in total morphine consumption, and earlier oral intake of solid food. Kim et al40 compared a preemptive MMA regimen (200 mg of celecoxib, 75 mg of pregabalin, 100 mg of intrathecal fentanyl, 15 mg of pregabalin, and 10 mg of extended-release oxycodone given twice daily postoperatively) in addition to morphine.

**Table 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design (Procedure)</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cata et al28</td>
<td>Retrospective review (spinal procedures)</td>
<td>245</td>
<td>Epidural PCA or intravenous PCA</td>
<td>Less morphine use in the epidural PCA group than in the intravenous PCA group</td>
<td>III</td>
</tr>
<tr>
<td>Chan et al27</td>
<td>RCT (lumbar spine surgery)</td>
<td>60</td>
<td>15 μg of intrathecal fentanyl</td>
<td>Lower visual analog scale pain scores and 41% less PCA morphine use in the fentanyl group than in the control group</td>
<td>I</td>
</tr>
<tr>
<td>Guilfoyle et al29</td>
<td>RCT (lumbar decompression)</td>
<td>60</td>
<td>100 μg of intrathecal fentanyl</td>
<td>Lower postoperative visual analog scale pain scores but increased urinary catheterization in fentanyl group than in control group</td>
<td>II</td>
</tr>
<tr>
<td>Jamjoom and Jamjoom30</td>
<td>Systematic review of 16 trials (lumbar spine surgery)</td>
<td>1,310</td>
<td>Epidural steroid infusion</td>
<td>Epidural steroids reduced pain and analgesia consumption at &lt;2 wk postoperatively. No effect on pain at 2 mo to 1 yr postoperatively or LOS. No conclusions were made on postoperative pain control in the intermediate postoperative period.</td>
<td>II</td>
</tr>
<tr>
<td>Rasmussen et al33</td>
<td>RCT (lumbar discectomy)</td>
<td>200</td>
<td>Intraoperative epidural steroid infusion to nerve root</td>
<td>Rates of revision surgery at 2 yr postoperatively were similar (7% in steroid group versus 8% in control group). Neurologic impairment improved at 2 mo but not at 1 or 2 yr postoperatively in steroid group. LOS shorter in steroid group than in control group (6 d versus 8 d). No difference in back pain. No complications from intervention (eg, dural tear, infection, neurologic complications).</td>
<td>I</td>
</tr>
<tr>
<td>Ziegeler et al26</td>
<td>RCT (posterior lumbar fusion)</td>
<td>46</td>
<td>0.4 mg of intrathecal morphine</td>
<td>Lower opioid consumption in morphine group than in placebo group. No adverse effects.</td>
<td>I</td>
</tr>
</tbody>
</table>

LOS = length of stay, PCA = patient-controlled analgesia, RCT = randomized controlled trial

a Levels of evidence were determined according to the Oxford Centre for Evidence-Based Medicine criteria.10

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500 mg of acetaminophen, and 10 mg of extended-release oxycodone administered 1 hour before the surgical procedure and twice daily postoperatively) with an intravenous morphine regimen in patients who underwent single-level lumbar fusion. The MMA group demonstrated improved VAS pain scores at all time points and lower Oswestry Disability Index scores at all time points except postoperative day 1. No difference was found in intraoperative estimated blood loss, drain output, or nonunion rates. No episodes of wound dehiscence, hematoma, or gastrointestinal ulcers were observed in either group. No significant difference in fusion rates was found at 1 year postoperatively between patients in the MMA group (7.5%) and patients in the morphine group (10%). Level II evidence supports the superiority of perioperative MMA regimens over standard opioid regimens in patients undergoing spine surgery (Table 4). The available data do not demonstrate an increased risk of nonunion with MMA regimens.

**Summary**

Among surgical procedures, those involving the spine are often associated with greater postoperative pain. Management of the pain with minimal adverse effects is imperative to ensure postoperative recovery, rehabilitation, patient satisfaction, and acceptable outcomes. Historically, postoperative pain regimens have relied heavily on opioid medications. Although opioids are effective in the management of postoperative pain, they are associated with substantial dose-related side effects, including somnolence, respiratory depression, and urinary and bowel symptoms, that may inhibit the recovery process and mask postoperative complications. Inadequately controlled postoperative pain is the second most common reason for 30-day readmission after lumbar spine surgery (22.4%), behind...
wound complications (38.6%). The Joint Commission guidelines, Hospital Consumer Assessment of Healthcare Providers and Systems surveys, and outcome-based and bundled payment models place increased emphasis on adequate postoperative pain control, reduced length of stay, and decreased readmission rates. Preemptive MMA regimens were developed to improve postoperative pain management and reduce opioid use through the synergistic effects of nonopioid agents. These regimens have shown promising results and have gained recognition for use in other orthopaedic procedures. As demonstrated in this review, a growing body of evidence supports the use of preemptive and MMA regimens in the treatment of patients undergoing spine surgery. These regimens include perioperative use of NSAIDs, acetaminophen, and the neuromodulatory agents pregabalin and gabapentin as adjuncts to the use of opioids. Further high-quality studies are required to determine the optimal agents, dosages, and length of the analgesic regimen and to further clarify the effect on outcomes, including length of stay, perioperative complications, and long-term fusion rates.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 1, 15, 17, 18, 20, 21, 26, 27, and 33 are level I studies. References 16, 19, 29, 30, 34, 39, and 40 are level II studies. References 11, 28, and 35-38 are level III studies. Reference 13 is a level IV study.

References printed in bold type are those published within the past 5 years.


