First described by Kehlet and Dahl in 1993, multimodal analgesia (MMA) is the simultaneous use of multiple analgesic medications that work in a synergistic manner to provide pain control. In recent years, spine surgery has seen the growth of multimodal perioperative protocols for managing pain. Postoperative pain following spinal procedures is a common complaint, with persistent pain even after the immediate convalescent period leading to negative impacts on health. A multidisciplinary approach is essential in reducing postoperative morbidity and complication rates. This review demonstrates the efficacy in the combined use of opioid-alternative medications such as NSAIDs, gabapentinoids, local anesthetics, acetaminophen, and other neuromodulatory pharmacologic agents. Continued research will be essential in the optimization of the MMA protocol for treating patients who undergo spine procedures.
A paradigm shift from the traditionally open to minimally invasive techniques in spine surgery (MIS) has been made possible by technological advancements (15). Open approaches to spine procedures can result in significant intraoperative and postoperative morbidity due to the utilization of large incisions and greater extent of damage to the soft tissues and structures from dissection and retraction (15). On the other hand, decreased surgical duration, intraoperative blood loss, shorter postoperative inpatient stay, and faster recovery following surgery can be achieved by virtue of the narrow incisions and limited tissue trauma sustained during MIS spine procedures (16). MIS procedures have also demonstrated improvements in postoperative pain and decreased narcotics consumption when compared to open techniques (15). Nevertheless, any persistent pain, discomfort, or disability following MIS surgery can contribute to delayed recovery and function (17). Recent evidence also suggests that acute postoperative pain is an important predictor for chronic pain after surgery (18).

As such, a multidisciplinary approach that incorporates help from all members of the healthcare team, including the nursing staff, anesthesia services, and postoperative rehabilitation providers, will be essential in reducing morbidity and complication rates following MIS spine surgery (19).

Prior investigations have demonstrated that postoperative pain following spine surgery may involve multiple pathways including neuropathic, inflammatory, and nociceptive pain responses (20). Post-surgical pain has been determined to be directly related to the number of vertebral levels on which the operation took place, regardless of the spine region involved (21). Surgical incision has been implicated in the etiology of postoperative pain through activation of the inflammatory response resulting from tissue damage at the cellular level (22). Response to injury manifesting as cardinal signs of inflammation such as pain, edema, erythema, and fever are induced by local activation of prostaglandins (23). In turn, this can lead to the overstimulation of peripheral nociceptors, causing an acute pain response known as primary hyperalgesia (24,25). Previous studies have evaluated the major prostaglandins, cytokines, and interleukins (ILs) that play a major role in the induction of the acute pain response, determining prostaglandin E2 (PGE-2) and IL-6 to be the among the predominant agents that induce pain and inflammation (25,26). For instance, a study by Buvanendran et al. determined there to be an increase in the concentration of PGE-2, IL-6, and IL-8 in the serum and cerebrospinal fluid within the first 30 hours after a total hip arthroplasty procedure (22). The severity of inflammation was found to be correlated with the local concentration of tumor necrosis factor alpha (TNF-α), which stimulates the initial release of IL-6 from various cell types at the site of injury, including endothelial and epithelial cells, fibroblasts, and monocytes (25).

The subsequent development of chronic pain can result from activation of the N-Methyl-D-aspartate (NMDA) receptors and prolonged stimulation of the central nervous system, a process known as central sensitization or secondary hyperalgesia (22,23). The ensuing neuroplastic changes that lead to long-term potentiation of pain result from the production of cyclooxygenase (COX) and nitric oxide synthase (NOS), which in turn upregulate prostaglandin synthesis (24). In this context, nonsteroidal anti-inflammatory drugs (NSAIDs) that work by inhibiting the COX pathway and decrease the production of prostaglandins can directly reduce inflammatory fever and pain (20). A meta-analysis of ten studies conducted by Jirarattanaphochai et al. determined that the combined use of NSAIDs and opioid medications following spinal procedures such as discectomy or laminectomy led to decreased total amount of narcotics consumed and postoperative pain when compared to the sole use of opioid medications (27). This finding adds to the growing body of knowledge that the use of pharmacological agents which simultaneously act upon multiple pain pathways can provide a synergistic effect, allowing for reduced amounts of each individual medication utilized and the associated dose-related side effects. However, it is important to note some evidence in the literature suggests NSAIDs that inhibit COX-2 are associated with diminished fusion rates and bone healing (28-30). For instance, while low to normal doses of NSAIDs provided decreased postoperative pain and narcotics consumption without adverse effects, high-dose NSAIDs typically reserved for treating severe pain were associated with higher rates of pseudarthrosis (31). Therefore, it may be advisable for the spine surgeon to practice caution when prescribing NSAIDs for pain management following spinal fusion procedures.

By demonstrating decreased consumption of narcotics and shorter hospital length of stay, preemptive analgesia protocols in MIS spine surgery have proven to be an effective form of pharmacological intervention that targets the nociceptive receptors in addition to inhibiting the inflammatory pathway (20). For example, the preoperative administration of 600–1200 mg of gabapentin or 100–150 mg of pregabalin several hours prior to surgery resulted in decreased pain and narcotics consumption.
on postoperative day 1, as well as reduced likelihood of breakthrough pain from occurring (32,33). Providing 1–2 g of acetaminophen preoperatively has also led to a reduction of morphine required to control postoperative pain (20). Preemptive MMA that combined 75 mg of pregabalin, 500 mg of acetaminophen, 200 mg of celecoxib, and 10 mg of extended-release oxycodone 1 hour before surgery resulted in lower patient reports of pain scores postoperatively when compared to the singular administration of intravenous (IV) morphine (34). Because the nociceptive pain response sustained from surgical trauma is usually localized, temporary, and often improves with time, therapeutic measures delivered intraoperatively or in the immediate postoperative setting can also be effective. For instance, the preoperative distribution of local anesthetics such as lidocaine and epinephrine into the soft tissue surrounding the incision site, followed by wound closure with 30–40 milliliters of 0.5% ropivacaine were found to decrease postoperative pain and narcotics consumption (35,36). Postoperative administration of epidural analgesia also demonstrated improvement of pain, decreased narcotics consumption and postoperative nausea, and faster recovery of bowel function following spine procedures (37,38).

A review of the literature reveals a variety of different MMA protocols utilized by spine surgeons, and the optimal pain management technique remains a topic of continued research. For instance, Singh et al. (the senior surgeon of this review) conducted a retrospective review of 139 patients undergoing a l-level minimally invasive transforaminal lumbar interbody fusion (MIS TLIF) procedure followed by either MMA or patient-controlled analgesia (PCA) protocols (39). Outcomes including patient-reported pain scores in the inpatient setting, narcotics consumption after hospital discharge, duration of hospital stay, surgical complication rates, and opioid-related adverse effects such as postoperative urinary retention and nausea/vomiting were compared between the MMA and PCA cohorts. The MMA protocol, detailed in Table 1, was developed through a collaboration between surgeons and anesthesiologists at our institution. Patients who received MMA demonstrated lower rates of inpatient narcotics consumption, nausea/vomiting, and a reduced duration of hospital stay. However, there were no differences in postoperative narcotics consumption after hospital discharge, inpatient pain scores, or urinary retention. These findings suggest MMA provides comparable pain control to PCA while allowing for a reduction of inpatient narcotics consumption, which in turn may lead to decreased nausea/vomiting and duration of hospital stay. A related review of anesthetic and analgesic techniques for MIS spine surgery by Buvanendran et al. recommended the preoperative implementation of MMA before surgery takes place (40). The article also highlighted the importance of being judicious about precluding patients that may not be suitable candidates for receiving expedited pain protocols in conjunction with same-day MIS spine procedures. Given the challenges associated with the continuous infusion of IV opioid therapy in these “fast-track” MIS spine patients, one potential alternative is

<table>
<thead>
<tr>
<th>Table 1 Multimodal analgesia protocol</th>
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<tbody>
<tr>
<td><strong>Preoperative</strong></td>
</tr>
<tr>
<td>Cyclobenzaprine 10 mg PO</td>
</tr>
<tr>
<td>Pregabalin 150 mg PO</td>
</tr>
<tr>
<td>Oxycodone 10 mg PO</td>
</tr>
<tr>
<td><strong>Intraoperative</strong></td>
</tr>
<tr>
<td>Bupivacaine 0.5% with epinephrine injection (immediately prior to incision)</td>
</tr>
<tr>
<td>&lt;70 kg, 20 cc per side; &gt;70 kg, 30 cc per side</td>
</tr>
<tr>
<td>Propofol induction</td>
</tr>
<tr>
<td>Sevoflurane maintenance</td>
</tr>
<tr>
<td>Acetaminophen 1,000 mg IV</td>
</tr>
<tr>
<td>Ondansetron 4 mg IV</td>
</tr>
<tr>
<td>Famotidine 20 mg IV</td>
</tr>
<tr>
<td>Dexamethasone 10 mg IV</td>
</tr>
<tr>
<td>Fentanyl 1–2 μ/kg IV (titrated to clinical effect)</td>
</tr>
<tr>
<td>Ketamine 50 mg IV at induction</td>
</tr>
<tr>
<td><strong>Postoperative day 0</strong></td>
</tr>
<tr>
<td>Oxycodone IR 5–10 mg PO, q4h PRN pain</td>
</tr>
<tr>
<td>Cryotherapy (ice packs applied to back)</td>
</tr>
<tr>
<td>Pregabalin 75 mg PO, 1 tablet q12h</td>
</tr>
<tr>
<td>Cyclobenzaprine 10 mg PO, 1 tablet q8h</td>
</tr>
<tr>
<td>Hydrocodone/paracetamol 10 mg PO, 1 tablet q4h</td>
</tr>
<tr>
<td>Tramadol 50 mg PO, 1–2 tablets q6h</td>
</tr>
<tr>
<td><strong>Postoperative day 1</strong></td>
</tr>
<tr>
<td>Cyclobenzaprine10 mg, 1 tablet PO PRN</td>
</tr>
<tr>
<td>Hydrocodone/acetaminophen 10/3 mg PO, 1 tablet PRN pain (VAS 1–5); 2 tablets PRN pain (VAS 6–10)</td>
</tr>
</tbody>
</table>

VAS, Visual Analog Scale; PRN, as needed; PO, by mouth; IV, intravenous.
the use of low-dose intraoperative ketamine (an NMDA antagonist), which has been demonstrated to decrease postoperative narcotic requirements (41). Lastly, other investigations in the literature have demonstrated additional benefits of MMA, including quicker return to mobilization, shorter hospital stay, and reduced opioid-associated side effects such as constipation, respiratory depression, somnolence, nausea, and vomiting (17,42).

With rising healthcare costs and increasing emphasis being placed on value-based care in recent years, there has been a movement toward reducing the duration of hospital stay without sacrificing the quality of care delivered to patients (43). As such, growing numbers of MIS spine procedures are being performed in the ambulatory setting with the expectation that discharge will occur on the same or next day. This requires a concomitant dedication to optimizing a safe and effective analgesic protocol that provides adequate pain control, minimizes side effects, and can easily be managed by either the patients themselves or their caretakers even after discharge from the surgery center (44). The conventional use of IV-administered, opioid-based PCA protocols are thus not a reasonable option for pain management following spine surgery in an outpatient center. Additionally, unintended adverse effects of anesthetic and analgesic medications such as insufficient pain control, intractable nausea and vomiting, gastrointestinal and bladder dysfunction, and altered mental status are all factors that can hinder discharge from taking place on the day of surgery (45). MMA protocols successfully implemented by a multidisciplinary team offer a promising solution for reducing postoperative pain and narcotics dependence in patients undergoing MIS spine surgery in the outpatient setting. As summarized in our review, there is a growing body of knowledge that demonstrates the efficacy in the combined use of opioid-alternative medications such as NSAIDs, gabapentinoids, local anesthetics, acetaminophen, and other neuromodulatory pharmacologic agents. Moving forward, continued research will be essential in the optimization of the MMA protocol for treating patients who undergo ambulatory MIS spine procedures.

**Acknowledgments**

None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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