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Operative Techniques in
Orthopaedics

Multimodal Analgesia for Spinal Surgery – What Is the Gold Standard?

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Pain control for spine surgery has fundamentally changed in the last decade as new medications and pain techniques have been broadly adopted. Enhanced recovery protocols are the new standard of care, allowing for shorter hospital stays and more rapid patient recovery. Adequate analgesia in the perioperative setting is paramount in achieving these goals and the use of narcotics alone is inadequate. A multimodal approach to perioperative pain management in spinal surgery begins in the preoperative setting, with gabapentin or pregabalin, Celebrex, and acetaminophen. These medicines also play a large role in the multimodal approach for postoperative analgesia with suggested usage being continued while inpatient. Ketorolac remains a useful postoperative adjunctive medication with minimal downside for fusion. Local and intravenous (IV) steroid application also play an important role to decrease nerve irritation and pain related to local inflammation at the surgery site and should be utilized regularly. The use of local anesthetic must also be used at the surgery site in all cases with great improvement in immediate opiate needs and pain scores. Other techniques have had mixed results with both Ketamine and IV lidocaine showing some promise, but further research needs to be done to understand their exact role. To practice spine surgery requires the use of a multimodal approach including nonsteroidal anti-inflammatory drugs, local and IV steroid, local anesthetic, and neuromodulatory agents beginning prior to an incision and continued through the recovery process.
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The goal of perioperative pain management in spine surgery is to promote enhanced recovery and function, shorter hospital stays, and reduce risks associated with opiate medications.[1,2] With the advent of enhanced recovery protocols being adopted by most institutions such as early ambulation, immediate evaluation by physical and occupational therapy, and appropriate preoperative counseling, shorter hospital stays, and improved early recovery and function are being achieved.[3-5] Pain management is critical for achievement of these goals, but can come at great cost with opiates being the traditional postoperative management technique.[6] Opiates are known to cause serious adverse effects such as dependence, ileus/constipation, somnolence, respiratory depression, and a delay in wound healing.

In order to provide optimal pain care while promoting patient recovery and reducing harmful effects, improved modes of pain control are becoming standard. The methods for this multimodal approach (MMA) are focused on addressing the pain sources directly and pre-emptively to avoid sensitizing the central nervous system and reducing inflammation. A growing body of literature supporting MMA in the perioperative setting and immediate postoperative setting has emerged demonstrating improved effectiveness, patient satisfaction, and lower opioid requirements.[7] While there is a difficulty in spine surgery gaining consensus for a "gold standard," there are several principles which spine surgeons can follow that will allow for these goals to be achieved. To assist in formulating a standardized plan, it is best to understand the pain control for each phase of the perioperative period.

Preoperative Analgesia

Perioperative pain control begins prior to the patient arriving in the operating suite. In order to decrease intra- and postoperative narcotics and anesthetic requirements, a variety of agents exist that can have lasting effects on the sensitization

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of the nervous system as well as reducing inflammation. The 2 most well-known and widely used nerve stabilizing agents are gabapentin and pregabalin. Both of these act at the alpha 2-delta subunit of voltage-gated calcium channels found predominantly in the cell membranes of neurons.[8] By binding at these sites, it reduces the likelihood of an action potential (desensitizes the membrane) being generated and thus limits the propagation of a neuronal signal to the brain which can be perceived as pain, numbness, or tingling. This desensitization is what can have lasting effects long after the noxious stimuli (the surgery) has occurred. (Table 1)

Pregabalin at the dose of 150 mg administered 1 hour prior to surgery demonstrated reduced need for opioid rescue and reduced morphine consumption up to 48 hours after spinal fusion.[9] This same study further demonstrated that the 75 mg of pregabalin did not have this benefit, and no differences were found between the side effects. In a study of preoperatively administered pregabalin 150 mg with celecoxib 200 mg vs placebo, Visual Analog Scale (VAS) and total postoperative morphine consumption were significantly lower.[10] Khan et al described the use of gabapentin reducing narcotic consumption, whereby they compared gabapentin give pre- and postincision and found a threshold of 900 mg or higher led to decreased total morphine consumption and decreased pain scores.[11] Due to the significance of the findings in this study, it was a primary driver for meta-analysis data showing improved pain control and decrease in total morphine consumption following gabapentin administration.[12] Similarly, Pandey et al who demonstrated a dose effect threshold at 600 mg of gabapentin administered preoperatively with a decrease in immediate postoperative fentanyl consumption as well as VAS scores.[13]

An earlier meta-analysis demonstrated that pregabalin and gabapentin both effective for decrease VAS and total morphine consumption up to 24 hours when administered preoperatively as well.[14] A single Randomized Control Trial (RCT) study on 1200 mg of gabapentin administered prior to surgery also demonstrated improved pain scores in the immediate postoperative period (up to 4 hours) as well as total decrease in morphine consumption.[15] In a head-to-head comparison, pregabalin showed an improvement compared to placebo in functional outcomes such as Oswestry Disability Index (ODI) when administered at a dose of 75 mg preoperatively, however, this same study was unable to show gabapentin administered at 300 mg having the same effect against placebo.[16]

Nonsteroidal anti-inflammatory drugs (NSAIDs), specifically selective COX-2 inhibitors, have been extensively studied for preoperative administration. Many surgical specialties regularly utilize these medications with great effectiveness. Most spine surgeons, however, have concerns about the effects they can have on both fusions and bleeding. Nonetheless, they remain an excellent, if underutilized adjunct for postsurgical pain as little evidence exists to support the risk of nonunion.

Several prospective trials have been done on this topic, including a randomized blinded trial comparing parecoxib, ketorolac, and placebo given 30 minutes prior to lumbar fusion incision demonstrated no increase in bleeding, and a decrease in numerical pain scores, however no difference in immediate 24-hour morphine consumption.[17] A separate study looked at celecoxib with gabapentin vs gabapentin vs no medication, showing a decrease in 24-hour morphine consumption and improved VAS scores in the combination group compared to the other 2 groups with no difference between the gabapentin group and no medication group.

Regarding pre- vs postoperative administration of NSAIDs, one study demonstrated that the administration timing whether preoperative or intraoperatively of 40 mg of parecoxib both were equally effective at lowering postoperative pain and morphine consumption.[18] These studies further demonstrate the effectiveness of a selective COX-2 inhibitor prior to surgery while minimizing the side effects and potential risks of the nonselective NSAIDS. There is less research looking at the use of the nonselective inhibitors such as ibuprofen and naproxen.

Acetaminophen has a long history as a safe and effective pain modulator. With its mechanism of action being placed a central modulator of COX enzymes, it does not carry with it the same potential adverse effect profile as the NSAIDS. While there are no specific studies looking at its preoperative use in either oral or intravenous (IV) form in spine surgery, there are excellent studies within orthopaedic surgery and other surgical subspecialties domains detailing its use.[19-21] With a daily dosage limit of acetaminophen of 3 g per day, it is most efficacious if administered as 1 g preoperatively along with the other adjunctive medications.

The above information serves as a guideline prior to making an incision and the summary below is the authors recommended preoperative medication regimen. It should be noted that no medication can replace appropriate preoperative education, counseling, and expectation management with the patient. This "human" aspect of surgery is an understudied and often overlooked component in todays pressured world of medicine. Nonetheless, it is this factor coupled with excellent pharmaceutical agents that can help create an environment of multimodal analgesia prior to any pain stimuli ever being experienced.

Table 1 Preoperative Spine Cocktail Regimen

Gabapentin 600 mg or Lyrica 150 mg
Celecoxib 200 mg or Parecoxib 40 mg
Acetaminophen 1000 mg
Preoperative counseling

Intraoperative Analgesia

There are several adjunctive measures which can be taken during an operation that can decrease postoperative pain, need for narcotic pain medication, and accelerate recovery. These methods focus on the use of local anesthetics, local steroid application, and IV anesthetic administration.

Local anesthetics have been present for nearly 150 years with the first documented use in the spine for intrathecal anesthesia before the 20th century with the well-known drug cocaine.[22] While this has fallen out of favor for medicinal use, its cousins are still playing a pivotal role in pain

control. Recent iterations of the drugs have found their way into use due to preparations that allow them to act over a longer period of time. While most surgeons are familiar with the traditional usage of bupivacaine due to the longer duration of action then lidocaine, liposomal bupivacaine is newer to market.

Liposomal bupivacaine, known as Exparel (Pacira Bioscience, Inc) in its commercial formulation, is released over a 72-hour period using a lipid structure that breaks down slowly over this time frame to release the drug in local tissues. A case control series looking at the use of 40 mL of a 50:50 mixture of liposomal bupivacaine administered prior to closing in single-level lumbar Translaminar Interbody Fusion surgeries demonstrated decreased total morphine consumption in the first 3 days postoperatively.[23] It also demonstrated a reduction in acute pain service consults, although this impact was modest and may be reflective of norms specific to the study site.

Other data published seem to show minimal difference when comparing liposomal administration to traditional 0.25% bupivacaine HCl administration even when compared to saline in one study (also did not change length of stay).[24] Further articles could not show a difference in posterior lumbar or posterior cervical patients who received the liposomal formulation demonstrating no differences in time to discharge, total morphine equivalents or decrease in VAS scores.[24-26] While none of these studies demonstrated any increase in complications or adverse events, strong evidence is lacking demonstrating marked advantages of local anesthetic in this formulation.

While strong evidence supporting novel liposomal bupivacaine administration is lacking, it should be noted that use of local anesthetic in the musculature is suggested for all cases of lumbar spine surgery as well as posterior cervical surgery. A well done meta-analysis demonstrated significant impact from local anesthetic infiltration prior to closure with decreased VAS scores and opiate usage in the first 24 hours.[27] This early decrease in pain is crucial for early patient mobility and satisfaction which is associated with improved outcomes and lower rates of complications, including reduced perioperative constipation.

IV administration of traditional local anesthetics (such as lidocaine, bupivacaine, etc) has gained popularity amongst general surgeons due to the avoidance of the issues with narcotics and post bowel surgery ileus, and shorter hospital stays.[28,29] Lumbar spine surgery also has a risk of ileus especially in cases of increased blood loss, lumbar correction, and fusion procedures. Interest constipation and ileus avoidance following lumbar surgery has sparked several studies investigating this novel technique. A trial comparing continuous IV lidocaine at 2 mg/kg/h with placebo in complex adult spine surgery patients showed superiority over placebo for pain scores and noninferiority for morphine consumption.[30] This same study also measured complications and outcomes, with improved outcomes at 1 and 3 months on the SF-12 and no difference in complications. However, in a blinded trial against placebo with IV lidocaine administered did not demonstrate superiority. In this study, it was given with a 1.5 mg/kg bolus and then 1.5 mg/kg/h infusion during posterior spinal fusion; at no point in the 24-48 hours period postoperatively did the IV lidocaine group have less morphine requirement.[31] Other outcome measures such as complications (nausea/vomiting/ileus), SF-12, and time to discharge also did not differ. In a study of posterior cervical fusion patients receiving subfascial infusions postoperatively with 0.5% bupivacaine to a matched control group, the study group had better pain control and reduced opioid consumption in the first 4 days.[32] However, the study design demonstrating this result is inadequate to truly compare as the control group did not have any placebo catheter in place.

In an RCT performed In the pediatric scoliosis literature, a single study comparing a continuous post-operative IV bupivacaine to placebo showed a decrease in 24-hour continuous morphine consumptions but did not otherwise differ from control protocols.[33] Based on current literature, IV lidocaine and bupivacaine appear to have a favorable complication profile, however, purported benefits are mixed. Given advantages reported in general surgery literature with a reported decrease in ileus, faster time to bowel movement and shorter hospital stays, IV administration of local anesthetic warrants additional investigation in spine surgery patients.

Use of intraoperative steroids remains a mainstay of surgery with benefits for both anesthesia and surgical teams. Most steroids are administered intravenously with benefits for airway edema, postoperative nausea, and vomiting as well as reductions of postoperative inflammation and radiculitis. A meta-analysis looking at spine fusion patients (both cervical and lumbar) and the use of IV steroids demonstrated lower VAS scores up to 48 hours following spine surgery.[34] The studies were heterogeneous in the dosing however with some giving a single dose of 80 mg of dexamethasone and others 3 doses of 20 mg of dexamethasone given over 24 hours.[35,36] Despite this heterogeneity, subset analysis of some of these studies in the analysis revealed decreased morphine consumption, shorter hospital stays and improved nausea control all reaching significance. The benefit for IV steroids is clear but there is no single best dosing regimen. Based on the studies, a recommendation for the use of a minimum of 20 mg of dexamethasone given between 1 and 3 times over the first 24 hours is where one should likely consider to achieve the desired benefits.

Recently the literature on this topic has shifted with increasing interest to the application of local steroids. While the application of this technique has been dysphagia reduction in the setting of anterior cervical discectomy and fusion, there is significant benefit that has been purported for postoperative pain reduction in lumbar surgery as well. The most comprehensive literature on the topic was a systematic review published in 2014 and while significant heterogeneity limited any meta-analysis, it examined patients undergoing discectomy who received steroids applied directly to the dura or exposed nerve root.[37] The results from this were quite conclusive with 9 of 11 studies demonstrating significant reduction in early postoperative pain which included up to 2 weeks. Outcomes after 2 weeks did not demonstrate a clear benefit with more heterogeneity among the studies. Further takeaways from this systematic review revealed 7 of 9 trials with

a significant reduction in morphine consumption. No evidence of increase in complications could be determined from the review as well which should be quite convincing to its safety. It should be noted that this systematic review did not examine any lumbar fusion cases or cervical cases and looked only at laminectomy and microdiscectomy. The largest driver of this systematic review was a randomized blinded study which enrolled 200 patients into 4 different groups. In one group, an epidural paste was saturated with 80 mg of methylprednisolone and in one of the combination groups included morphine. The morphine alone group though did not show any benefit and only the 2 groups containing the 80 mg of methylprednisolone demonstrated the benefit of decreased immediate postoperative pain.[38]

With application of local steroids, the exact amount and nature of application varied between trials, however, studies typically used between 40 and 80 mg of methylprednisolone. Some authors have recommended direct local application of an aqueous solution bathing the nerve root, other apply the steroids to a collagen or fat matrix and then place it directly so as to minimize dispersion.[39-41] The evidence for adjunctive steroid use in nonfusion lumbar cases is convincing and should be considered. While the dosing and method of delivery will vary between institution and surgeon, those factors do not appear to heavily influence the benefit and can be left to surgeon preference with assurance of an improved pain experience for the patient.

The final intraoperative adjunct of Ketamine is a powerful dissociative agent with pain properties. This is administered intravenously as part of the anesthetic plan and requires coordination and discussion with our anesthesia. Several studies have looked at the efficacy of intraoperative ketamine administration on the effect of postoperative pain control. The number of patients in each of these studies is low, nonetheless, in 2008, Yamanuchi demonstrated a beneficial effect of an intraoperative 1 mg/kg dose of ketamine bolus followed by 83 ug/kg/h infusion during the case reduced postoperative morphine consumption in cervical patients, but did not reach significance in lumbar surgery patients.[42] The other trial which compared placebo to both intraoperative and intraoperative and postoperative ketamine administration provides the most insight into ketamine's role. This study showed that intraoperative ketamine by itself was inferior to the group who also received it postoperatively at the same rate of 1 ug/kg/h infusion, which decreased total postoperative morphine consumption.[43] This is consistent with the final study which suggested that intraoperative ketamine administered solely during the operation did not alter acute postoperative pain medication requirements during pediatric scoliosis surgery.[44] Thus, while ketamine is a powerful tool to be considered, the next section will examine more closely its role in the immediate postoperative setting where it appears to have better efficacy.

Postoperative

Pain management in the postoperative period has undergone a significant shift in the last 10 years. Previously, it was believed that IV patient-controlled analgesia (PCA) narcotic pumps allowed for superior pain control, satisfaction, and early recovery. In fact, the opposite was true, with PCA having been associated with longer hospital stays and no improvement in postoperative pain scores.[45,46] These challenges are thought to be due to the short acting nature of IV medication coupled with the subsequent difficulty in transitioning patients to oral methods of pain control. The shift away from PCA has led to most patients utilizing oral narcotics as a mainstay of postoperative pain control. The author's preferred postoperative narcotic regimen in the table below. (Table 2)

Postoperative NSAID use continues to be one of the most controversial topics in spinal fusion surgery. However, few strict contraindications exist for the use of NSAIDs following spinal surgery. Indeed, severe renal dysfunction and bleeding concerns in the setting of obligate pharmaceutical blood thinning medications remain reasons to avoid NSAIDs following surgery. However, for most patients undergoing spine surgery the evidence for the use of NSAIDs is overwhelming based on efficacy in both RCTs and in meta-analyses.[47-49]

One of the most commonly used postsurgical NSAIDs is the nonselective IV drug ketorolac. Data have been mixed on the potential adverse effects on fusion for this NSAID with animal studies suggesting the inhibitory effect of ketorolac.[50] Further, a retrospective study conducted in the early 1990s suggested a significant detrimental effect of ketorolac with an approximately 5-fold nonunion rate.[51] Since this time, fusion techniques have improved and our knowledge about proper ketorolac administration has evolved. However, an ongoing randomized RCT in spinal fusion patients is currently being performed and likely will help answer the question about the inhibitory function of ketorolac on fusion.[52] Other evidence exists examining the COX-2 selective NSAIDS mentioned earlier suggests celecoxib in animal studies did not demonstrate any inhibitory effect on fusion compared to a control group whereas in the same study indomethacin demonstrated a 50% decrease in fusion rate.[47,53]

The benefit of postoperative NSAIDS is undeniable with evidence for 40 mg of parecoxib IV every 12 hours demonstrating reduced opioid use and improved patient satisfaction.[49] In a trial of multilevel laminectomy, regularly administered 15 mg of ketorolac, postoperatively decreased total morphine consumption had significantly lower VAS scores up to 16 hours postoperatively with the benefit not being seen at 24 and 36 hours.[54]

As mentioned in the previous section, ketamine also needs to be discussed for its role in the postoperative setting. The most

Table 2 Postoperative Narcotic Regimens

	Narcotic Naïve*	Narcotic Tolerant*
Nonfusion cases	Hydrocodone 5-10 mg every 4 hours	Oxycodone 5-10 mg every 4 hours
Fusion cases	Oxycodone 5-10 mg every 4 hours	Oxycodone 10-15 mg every 4 hours

*Promethazine given every 8 hours (for nausea and narcotic potentiator).

comprehensive work done on the subject is a systematic review done in 2018.[55] It demonstrated that ketamine when administered intraoperatively and postoperatively decreased total morphine consumption up to 24 hours, but this effect was now found to be significant at 36 hours. The dosing of the studies varied in the postoperative setting from 0.1 to 3 mg/kg/h. Not only was morphine consumption less in the ketamine groups, but VAS scores from 6 to 24 hours were also decreased. Most studies stopped looking at reduction in pain at 48 hours where there was no difference with some studies showing the ketamine group having more pain at 48 hours that did not reach significance. It is clear ketamine does not provide long-term relief, but does present an option in the short term during the inpatient stay to care for patients. It can be used in select patients with expected severe pain from either narcotic sensitization or those with poor coping skills.

Summary

Multimodal analgesia methods besides opiate medication can greatly reduce a surgeon's dependence on narcotic medications. Several MMA regimens have been examined in the literature to identify optimal preemptive and postsurgical methods that when used in combination to allow patients an enhanced recovery experience.

Kim et al performed an RCT examining a preoperative regimen of celecoxib 200 mg, pregabalin 75 mg, oxycodone-ER 10, and acetaminophen 500 mg for patients receiving an L4/5 fusion. VAS scores were lower at all time points in this RCT for MMA as well as for ODI except for on POD #1. Of note, the authors also found that 75 mg of pregabalin when used alone did not have immediate postoperative benefits.[56] Similarly, Garcia et al compared celecoxib, pregabalin, and oxycodone ER vs IV morphine. VAS and total morphine consumption were significantly lower in the MMA up to 36 hours postoperatively.[7]

These 2 studies are the only RCTs examining MMA in the spine literature and highlight a notable deficiency. However, based on broader review of the literature, the evidence is clear that patients are best served with multimodal vs conventional narcotic driven perioperative analgesia. Table 3 highlights the authors current best practice evidence-based recommendations for MMA in spinal surgery.

Table 3 Recommended Multimodal Analgesia for Spine surgery

Preoperative	Intraoperative	Postoperative
Gabapentin 600 mg	Depo Medrol 80 mg	Oxycodone dosing schedule PRN
Celecoxib 200 mg	Bupivacaine w/Epi (max. allowable dose)†	Ketorolac 15 mg q 8 for 24 hours
Acetaminophen 1000 mg		Gabapentin 300 mg qhs
*Oxycontin 10 mg		Acetaminophen 1000 mg q 8 h

*To be given once preoperatively if desired with risk of opioid induced side effects.

†To be infiltrated in the paraspinal musculature and dermis and subdermal layers.

References

1. Wheeler M, Oderda GM, Ashburn MA, et al: Adverse events associated with postoperative opioid analgesia: A systematic review. J Pain 3:159-180, 2002
2. Lemos P, Pinto A, Morais G, et al: Patient satisfaction following day surgery. J Clin Anesth 21:200-205, 2009
3. Staartjes VE, de Wispelaere MP, Schroder ML: Improving recovery after elective degenerative spine surgery: 5-year experience with an enhanced recovery after surgery (ERAS) protocol. Neurosurg Focus 46:E7, 2019
4. Ali ZS, Ma TS, Ozturk AK, et al: Pre-optimization of spinal surgery patients: Development of a neurosurgical enhanced recovery after surgery (ERAS) protocol. Clin Neurol Neurosurg 164:142-153, 2018
5. Wainwright TW, Immins T, Middleton RG: Enhanced recovery after surgery (ERAS) and its applicability for major spine surgery. Best Pract Res Clin Anaesthesiol 30:91-102, 2016
6. Rudd RA, Aleshire N, Zibbell JE, et al: Increases in drug and opioid overdose deaths—United States, 2000-2014. MMWR Morb Mortal Wkly Rep 64:1378-1382, 2016
7. Garcia RM, Cassinelli EH, Messerschmitt PJ, et al: A multimodal approach for postoperative pain management after lumbar decompression surgery: A prospective, randomized study. J Spinal Disord Tech 26:291-297, 2013
8. Kukkar A, Bali A, Singh N, et al: Implications and mechanism of action of gabapentin in neuropathic pain. Arch Pharm Res 36:237-251, 2013
9. Kim JC, Choi YS, Kim KN, et al: Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. Spine 36:428-433, 2011
10. Kien NT, Geiger P, Van Chuong H, et al: Preemptive analgesia after lumbar spine surgery by pregabalin and celecoxib: A prospective study. Drug Design Dev Ther 13:2145-2152, 2019
11. Khan ZH, Rahimi M, Makarem J, et al: Optimal dose of pre-incision/post-incision gabapentin for pain relief following lumbar laminectomy: A randomized study. Acta Anaesthesiol Scand 55:306-312, 2011
12. Liu B, Liu R, Wang L: A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. Medicine 96:e8031, 2017
13. Pandey CK, Navkar DV, Giri PJ, et al: Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: A randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol 17:65-68, 2005
14. Yu L, Ran B, Li M, et al: Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: A systematic review and meta-analysis. Spine 38:1947-1952, 2013
15. Turan A, Karamanlioglu B, Memis D, et al: Analgesic effects of gabapentin after spinal surgery. Anesthesiology 100:935-938, 2004
16. Khurana G, Jindal P, Sharma JP, et al: Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. Spine 39:E363-E368, 2014
17. Siribumrungwong K, Cheewakidakarn J, Tangtrakulwanich B, et al: Comparing parecoxib and ketorolac as preemptive analgesia in patients undergoing posterior lumbar spinal fusion: A prospective randomized double-blinded placebo-controlled trial. BMC Musculoskel Disord 16:59, 2015
18. Moonla R, Threetipayarak A, Panpaisarn C, et al: Comparison of preoperative and postoperative parecoxib administration for pain control following major spine surgery. Asian Spine J 12:893-901, 2018
19. Hansen RN, Pham AT, Boing EA, et al: Comparative analysis of length of stay, hospitalization costs, opioid use, and discharge status among spine surgery patients with postoperative pain management including intravenous versus oral acetaminophen. Curr Med Res Opin 33:943-948, 2017
20. Khalili G, Janghorbani M, Saryazdi H, et al: Effect of preemptive and preventive acetaminophen on postoperative pain score: A randomized, double-blind trial of patients undergoing lower extremity surgery. J Clin Anesth 25:188-192, 2013

21. Doleman B, Read D, Lund JN, et al: Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: Systematic review and meta-analysis. Reg Anesth Pain Med 40:706-712, 2015
22. Bier A: Versuche über Cocainisirung des Rückenmarkes. Deutsche Zeitschrift f Chirurgie 51:361-369, 1899
23. Tomov M, Tou K, Winkel R, et al: Does subcutaneous infiltration of liposomal bupivacaine following single-level transforaminal lumbar interbody fusion surgery improve immediate postoperative pain control? Asian Spine J 12:85-93, 2018
24. Brown L, Weir T, Koenig S, et al: Can liposomal bupivacaine be safely utilized in elective spine surgery? Global Spine J 9:133-137, 2019
25. Grieff AN, Ghobrial GM, Jallo J: Use of liposomal bupivacaine in the postoperative management of posterior spinal decompression. J Neurosurg Spine 25:88-93, 2016
26. Puffer RC, Tou K, Winkel RE, et al: Liposomal bupivacaine incisional injection in single-level lumbar spine surgery. Spine J 16:1305-1308, 2016
27. Perera AP, Chari A, Kostusiak M, et al: Intramuscular local anesthetic infiltration at closure for postoperative analgesia in lumbar spine surgery: A systematic review and meta-analysis. Spine 42:1088-1095, 2017
28. Harvey KP, Adair JD, Isho M, et al: Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. Am J Surg 198:231-236, 2009
29. Marret E, Rolin M, Beaussier M, et al: Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. Br J Surg 95:1331-1338, 2008
30. Farag E, Ghobrial M, Sessler DI, et al: Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. Anesthesiology 119:932-940, 2013
31. Dewinter G, Moens P, Fieuws S, et al: Systemic lidocaine fails to improve postoperative morphine consumption, postoperative recovery and quality of life in patients undergoing posterior spinal arthrodesis. A double-blind, randomized, placebo-controlled trial. Br J Anaesth 118:576-585, 2017
32. Elder JB, Hoh DJ, Liu CY, et al: Postoperative continuous paravertebral anesthetic infusion for pain control in posterior cervical spine surgery: A case-control study. Neurosurgery 66:99-106, 2010. discussion -7
33. Ross PA, Smith BM, Tolo VT, et al: Continuous infusion of bupivacaine reduces postoperative morphine use in adolescent idiopathic scoliosis after posterior spine fusion. Spine 36:1478-1483, 2011
34. Wang F, Shi K, Jiang Y, et al: Intravenous glucocorticoid for pain control after spinal fusion: A meta-analysis of randomized controlled trials. Medicine 97:e10507, 2018
35. Jeyamohan SB, Kenning TJ, Petronis KA, et al: Effect of steroid use in anterior cervical discectomy and fusion: A randomized controlled trial. J Neurosurg Spine 23:137-143, 2015
36. Aminmansour B, Khalili HA, Ahmadi J, et al: Effect of high-dose intravenous dexamethasone on postlumbar discectomy pain. Spine 31:2415-2417, 2006
37. Jamjoom BA, Jamjoom AB: Efficacy of intraoperative epidural steroids in lumbar discectomy: A systematic review. BMC Musculoskel Disord 15:146, 2014
38. Diaz RJ, Myles ST, Hurlbert RJ: Evaluation of epidural analgesic paste components in lumbar decompressive surgery: A randomized double-blind controlled trial. Neurosurgery 70:414-423, 2012. discussion 23-4
39. Debi R, Halperin N, Mirovsky Y: Local application of steroids following lumbar discectomy. J Spinal Disord Tech 15:273-276, 2002
40. Rasmussen S, Krum-Moller DS, Lauridsen LR, et al: Epidural steroid following discectomy for herniated lumbar disc reduces neurological impairment and enhances recovery: A randomized study with two-year follow-up. Spine 33:2028-2033, 2008
41. Lundin A, Magnuson A, Axelsson K, et al: The effect of perioperative corticosteroids on the outcome of microscopic lumbar disc surgery. Eur Spine J 12:625-630, 2003
42. Yamauchi M, Asano M, Watanabe M, et al: Continuous low-dose ketamine improves the analgesic effects of fentanyl patient-controlled analgesia after cervical spine surgery. Anesth Analg 107:1041-1044, 2008
43. Hadi BA, Daas R, Zelko R: A randomized, controlled trial of a clinical pharmacist intervention in microdiscectomy surgery—Low dose intravenous ketamine as an adjunct to standard therapy. Saudi Pharm J 21:169-175, 2013
44. Engelhardt T, Zaarour C, Naser B, et al: Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. Anesth Analg 107:1170-1175, 2008
45. Parvizi J, Miller AG, Gandhi K: Multimodal pain management after total joint arthroplasty. J Bone Jt Surg Am 93:1075-1084, 2011
46. Sinatra RS, Torres J, Bustos AM: Pain management after major orthopaedic surgery: Current strategies and new concepts. J Am Acad Orthop Surg 10:117-129, 2002
47. Cassinelli EH, Dean CL, Garcia RM, et al: Ketorolac use for postoperative pain management following lumbar decompression surgery: A prospective, randomized, double-blinded, placebo-controlled trial. Spine 33:1313-1317, 2008
48. Jirarattanaphochai K, Jung S: Nonsteroidal antiinflammatory drugs for postoperative pain management after lumbar spine surgery: A meta-analysis of randomized controlled trials. J Neurosurg Spine 9:22-31, 2008
49. Jirarattanaphochai K, Thienthong S, Sriraj W, et al: Effect of parecoxib on postoperative pain after lumbar spine surgery: A bicenter, randomized, double-blinded, placebo-controlled trial. Spine 33:132-139, 2008
50. Martin Jr. GJ, Boden SD, Titus L: Recombinant human bone morphogenetic protein-2 overcomes the inhibitory effect of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), on posterolateral lumbar intertransverse process spine fusion. Spine 24:2188-2193, 1999. discussion 93-4
51. Glassman SD, Rose SM, Dimar JR, et al: The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine 23:834-838, 1998
52. Claus CF, Lytle E, Tong D, et al: The effect of ketorolac on posterior thoracolumbar spinal fusions: A prospective double-blinded randomised placebo-controlled trial protocol. BMJ Open 9:e025855, 2019
53. Long J, Lewis S, Kuklo T, et al: The effect of cyclooxygenase-2 inhibitors on spinal fusion. J Bone Jt Surg Am 84:1763-1768, 2002
54. Duttchen KM, Lo A, Walker A, et al: Intraoperative ketorolac dose of 15 mg versus the standard 30 mg on early postoperative pain after spine surgery: A randomized, blinded, non-inferiority trial. J Clin Anesth 41:11-15, 2017
55. Pendi A, Field R, Farhan SD, et al: Perioperative ketamine for analgesia in spine surgery: A meta-analysis of randomized controlled trials. Spine 43:E299-e307, 2018
56. Kim SI, Ha KY, Oh IS: Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: A randomized controlled trial. Eur Spine J 25:1614-1619, 2016