Article type : Review

Prevention and treatment of postoperative pain after lumbar spine procedures: a systematic review.

Sergio Terracina MD[1], Chiara Robba MD[2], Anna Prete MD[1], Paola G. Sergi MD[1], Federico Bilotta MD, PhD.[1*]

[1] Department of Anesthesiology, Critical Care and Pain Medicine, 'Sapienza' University of Rome, Rome, Italy

[2] Neurosciences Critical Care Unit, Cambridge University Hospitals NHS Foundation Trust, UK.

Funding sources: None declared.

Conflicts of interest: None declared.

*Address correspondence and reprint requests to Federico Bilotta, MD, PhD, University of Rome "La Sapienza", Department of Anesthesiology and Critical Care. Via Acherusio 16, Rome, 00199 Italy. Phone: 3393370822

E-mail: bilotta@tiscali.it

Category of submission: Review

Key words: Electrical stimulation therapies, lumbar surgery, neuroanesthesia, postoperative pain, prevention, spine procedures, treatment.

Running Head: Postoperative Pain Control

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/papr.12684

Funding sources: None declared

Conflicts of interest: None declared

ABSTRACT

Background and Objective: In the last decades, in developed countries, spine procedures (surgical and percutaneous) had the highest absolute increase in case volume trend. Optimal approach to prevent and treat postoperative pain is continuously evolving. This systematic literature review presents evidence on safety and efficacy of pharmacological and non-pharmacological therapies to prevent and treat postoperative pain after lumbar spine procedures.

Databases and Data Treatment: Publications listed in PUBMED and EMBASE were considered to identify randomized clinical trials suitable for inclusion in this systematic review. Key words for literature search were selected, with authors' agreement, using the PICOS approach.

Results: Fifty-nine randomized clinical trials (involving a total of 4238 patients, with age range 18-86 years) published between January 2012 and September 2017 were retrieved. Data are presented according to the timing of therapy administration.

Conclusion and Recommendations: Clinical evidence on perioperative pain management in patients undergoing spine procedures have significantly evolved after the review published in 2012. Aim of this systematic review is to report the latest evidence published. These include: the preoperative use of dexamethasone, that showed to be able to reduce pain at mobilization but not pain at rest and total morphine consumption; the use of gabapentinoids as part of a multimodal analgesic approach; safety and effectiveness of intraoperative use of ketamine,

dexketoprofen, and tramadol. Finally, electrical nerve stimulation is gaining interest and is potentially suitable for the clinical needs.

Introduction

Spine surgery has had the highest absolute increase in case volume trend in the last decades, with a 7-fold increase in the USA (from 54,000 in 1993 to > 350,000 in 2007).[1] This trend in the 1990-2010 period is related to an "epidemic" of low back pain that –in developed countries- is among the leading causes of disability-adjusted life-years.[2,3] In up to 80% of patients undergoing lumbar spine procedures, postoperative pain subsides over the first 3 days after the operation, thus making its prevention and treatment a clinical priority for anesthesiologists.[4-6] Postoperative pain after spine procedures can be due to intrinsic and extrinsic mechanisms, which include chronic preoperative root or nerve compression and inflammation, duration and extent of the procedure, and multiple vertebral levels.[7,8] Clinical relevance of optimal pain management in these patients is further complicated by the risk of postoperative worsening of symptoms as consequence of chronic abuse of analgesics.[9-11] Furthermore, in this setting, postoperative pain control is one of the major determinants of the quality of health care delivered and it can contribute to improve functional recovery, to facilitate early mobilization and rehabilitation, and to warrant efficient resource utilization.[12-17] As lumbar surgery procedures continue to grow so will the number of patients suffering from failed back surgery syndrome.[18] After the review published in 2012 new evidence have been reported and should be implemented in the clinical practice.[19]

This systematic review has been designed to report evidence -from randomized controlled trials (RCTs), published between January 2012 and September 2017- about safety and efficacy of pharmacological (systemic and local) and non-pharmacological (electrical

stimulation) therapies for the prevention and treatment of postoperative pain after lumbar spine procedures.

Materials and methods

Search strategy: This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations and the study was registered in the International Prospective Register Of Systematic Review (PROSPERO registration number: CRD42015017759).[20,21] Publications listed in PUBMED and EMBASE were considered to identify RCTs suitable for inclusion in this systematic review.[22,23] Key words for literature search were selected, with authors' agreement, using the PICOS approach: participants, interventions, comparisons, outcomes, and study design.[24] The following key words were used: spine surgery AND analgesia; opioids AND spine surgery; morphine AND spine surgery; analgesics AND spine surgery; pregabalin gabapentin AND spine surgery; spine procedures AND analgesia, methadone AND lumbar surgery, nonsteroidal anti-inflammatory drugs AND lumbar surgery, ketamine AND lumbar surgery, local anesthetics AND lumbar surgery, steroids AND lumbar surgery, anesthesia AND laminectomy, anesthesia AND discectomy, anesthesia AND spinal fusion.

Study selection and inclusion criteria: Inclusion criteria were: RCTs published between January 2012 and September 2017 in adult population (older than18 years old) about analgesia in lumbar spine procedures (i.e. including studies accomplished after both open and percutaneous procedures, microdiscectomy, percutaneous endoscopic lumbar discectomy, spine fusion and laminectomy) were included. Only full papers in English language were considered for eligibility. Abstracts and meeting/symposium proceedings were excluded. Studies reporting evidence on pharmacological (systemic and local drug administration) and

non-pharmacological therapies were considered suitable for this systematic review. Studies related to other forms of postoperative pain (in particular sore throat) were excluded.

Data extraction and data analysis: Three authors (ST, CR and PGS) independently screened and assessed titles, abstracts and full-text papers to identify eligible articles, with FB and AP acting as arbiters. Details of study population, type of interventions, outcomes and other information were extrapolated using standardized data extraction form that included: study design, eligibility and exclusion criteria, duration of follow-up, randomization, blinding, number and characteristics of patients, type of surgery, drug dosage and way of administration. We reported the efficacy of tested analgesic therapy according to the pain scale adopted in the individual study as primary outcome. Secondary outcomes measures were related to safety and clinical complications as recorded in the selected clinical trials. We reported as significant efficacy those treatments that are related to $p < 0.05$.

Risk of bias: Risk of bias was assessed according to Cochrane Collaboration's criteria for RCTs that include 6 types of bias: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessor; incomplete outcome data; selective outcome reporting; and "other criteria" that include differences between the study and the control group in baseline characteristics) and categorized as: high, low or unclear (http://handbook.cochrane.org). Level of evidence and Class of recommendation were categorized according to the criteria listed by Oxford center for evidence-based medicine (OCEBM, http://www.cebm.net/ocebm-levels-of-evidence). In the selected RCTs, two approaches have been used to evaluate the severity of postoperative pain: pain-rating scales and the consumption of opioid/non-opioid analgesics. Pain scales in the RCTs included: VAS and numerical rating scale (NRS) scored at rest and on movement (with a 0 to 10 mm range: 0 mm-no pain to 10 mm-worst pain imaginable) and questionnaires (McGill Pain). Duration of follow-up ranged from the immediate postoperative period to 12 months after surgery. As

secondary outcomes measures, the quality of postoperative sleep, length of hospital stay, and postoperative nausea and vomit (PONV) were recorded.

Results

Literature search led to retrieve a total of 2426 studies; after the initial screening for eligibility, 2367 studies were excluded as they did not match the inclusion criteria. A total of 59 RCTs (involving a total of 4238 patients, with age range 18-86 years), were selected and the risk of bias was evaluated for each study included (Fig. 1 and Table 1). Selected RCTs were categorized according to the timing of provided therapy into 3 groups: "preoperative therapies", when the first dose/treatment was administered between 12 hours before the surgery and intraoperative patient positioning (23 studies, Table 2); "intraoperative therapies", when the first dose/treatment was administered between the end of patient positioning and the end of the surgery (29 studies, Table 3); and "postoperative therapies", when the first dose/treatment was administered after skin closure (7 studies, Table 4). Within each group, evidence supported by the largest number of studies or by the largest number of recruited patients, will be presented first.

Preoperative therapies

The 23 RTCs that tested therapies administered in the preoperative period, included: systemic pharmacological therapies (14 studies),[25-38] locoregional therapies (7 studies),[39-45] and electrical stimulation (2 studies)[46,47] (Table 2).

Systemic pharmacological therapies: Of the 14 RCTs that evaluated systemic pharmacological therapies to prevent and treat postoperative pain after lumbar spine procedures, pregabalin was tested in 7 RCTs,[25-31] non-steroidal anti-inflammatory drugs

(NSAIDs) in 2 RCTs[32,33] and other drugs (dexamethasone, minocycline, propofol, sevoflurane, paracetamol, naproxen, ketamine, clonidine) in the remaining 5 RCTs.[34-38] Of the 7 RCTs that tested pregabalin, 4 demonstrated that pregabalin alone or in association with other drugs is more effective than placebo, 1 that it is as effective as placebo and 2 that it is more effective than morphine in preventing postoperative pain.[25-31] The 2 RCTs that tested NSAIDs showed that parecoxib, ketorolac and etoricoxib are more effective than placebo in preventing postoperative pain.[32,33] Dexamethasone, paracetamol and the combination of ketamine-clonidine led to positive results on postoperative pain prevention, furthermore propofol proved to be as effective as sevoflurane, while minocycline use led to controversial results.[34-38]

Locoregional anesthesia: Of the 7 RCTs that studied drugs locoregionally administered to prevent and treat postoperative pain after lumbar spine procedures, 4 studies tested the combination of bupivacaine with other drugs,[39-42] while in 2 cases the effectiveness between epidural and general anesthesia was compared[43,44] and finally in 1 case the efficacy of ropivacaine was evaluated.[45] Of the 4 RCTs that tested bupivacaine, 1 demonstrated that bupivacaine is able to effectively reduce postoperative pain similarly to levobupivacaine, 1 showed that bupivacaine is more effective when combined to fentanyl and intrathecal magnesium sulphate ($MgSO_4$), 1 proved that it is less effective than dexmedetomidine in reducing pain, and 1 proved the supremacy in postoperative pain prevention when administered as spinal injection instead of epidural or combined administrations.[39-42] The 2 RCTs that compared epidural and general anesthesia found that epidural anesthesia is the best alternative in terms of pain management, surgeons' and patients' satisfaction and costs.[43,44] Ropivacaine was effective in reducing pain.[45]

Non-pharmacological strategies: Two RCTs studied electrical stimulation systems for pain control, evaluated with visual analog scale (VAS) and verbal rating score (VRS) from 4 to 24 hrs, demonstrating a good efficacy of this technique in the management of postoperative pain.[46, 47]

Intraoperative therapies

The 29 RTCs that tested therapies administered during the intraoperative period, included: systemic pharmacological therapies (19 studies)[48-66] and locoregional anesthetic drugs (10 studies)[67-76] (Table 3).

Systemic pharmacological therapies: Of the 19 RCTs that studied systemic pharmacological therapies to prevent and treat postoperative pain after lumbar spine procedures, 5 studies tested the use of dexmedetomidine,[48-52] 5 the use of ketamine,[53-57] 2 the use tramadol,[58,59] 2 the use of paracetamol,[60,61] 2 the use of lidocaine,[62,63] and finally ketorolac, fentanyl and non-steroidal anti-inflammatory drugs (tenoxicam) were tested in one study for each.[64-66] Of the 5 RCTs that tested dexmedetomidine,[48-52] in 2 cases the use of dexmetomedine did not guaranteed lower postoperative pain scores but was able to reduce opioid consumption when compared to placebo or midazolam; in 2 other studies it did not reduce postoperative pain when compared to the control group, and in 1 it was more effective than remifentanil in reducing postoperative pain and patient-controlled analgesia (PCA) consumption. Of the 5 RCTs that tested ketamine,[53-57] 4 studies proved that this drug can reduce opioid consumption but not pain scores when compared to placebo, while one study[54] found that low dose ketamine has lower pain scores but higher opioid consumption when compared to fentanyl. The 2 RCTs that tested tramadol, found that it is not able to reduce pain scores but it is more effective than placebo and less effective than fentanyl in reducing

opioid consumption.[58,59] The 2 RCTs that tested paracetamol, found that it is more effective than placebo and less effective than dexketoprofen in reducing pain scores.[60,61] The RCTs that tested systemic lidocaine, ketorolac and non-steroidal anti-inflammatory drugs (tenoxicam) led to controversial results.[62-64,66] Upton et al. found that fentanyl administered maintaining Analgesia Nociception Index > 50 with boluses of 50 μg (in patients < 50 years) or 25 μg (in patients > 50 years) was more effective than the "classic" administration.[65]

Locoregional delivery: Of the 10 RCTs that studied drugs locoregionally administered to prevent and treat postoperative pain after lumbar spine procedures, 5 tested morphine in various combinations and dosages,[67-71] in 2 ropivacaine was tested,[72,73] in 1 levobupivacaine,[74] in 1 fentanyl[75], and in 1 $MgSO_4$ injection.[76] Of the 5 RCTs that tested morphine, in 4 cases morphine administration led to a reduction of analgesics consumption when compared to the control group,[67-70] while Yen et al. found that there is no difference in opioid consumption between extended release epidural morphine 10 mg and 15 mg.[71] Ropivacaine effectively reduced pain intensity and proved to be more effective when combined with dexamethasone caudal than systemic dexamethasone.[72,73] Levobupivacaine, epidural fentanyl and MgSO4 injection led to positive results on postoperative pain prevention and treatment.[74-76]

Postoperative therapies

The 7 RTCs that tested therapies administered in the postoperative period, include: systemic pharmacological therapies (2 studies),[77,78] local delivery (4 studies)[79-82], and electrical stimulation (1 study)[83] (Table 4).

Systemic pharmacological therapies: The 2 RCTs that administered a small postoperative dose of intravenous ketamine evaluated its efficacy and safety compared to other drugs in a total of 111 patients.[77,78] Ketamine proved to be more effective than placebo and morphine in reducing either postoperative pain scores or opioid consumption.

Local delivery: In the 4 RCTs that evaluated the role of locally administered drugs to prevent and treat postoperative pain after lumbar spine procedures: Singh et al. proved the superiority of continuous wound infiltration of 0.25% levobupivacaine compared to continuous epidural infusion of 0.25% levobupivacaine and PCA of 1mg morphine;[79] either epidural steroids, after percutaneous endoscopic lumbar discectomy, or levobupivacaine combined with tramadol, after lumbar spine surgery, proved to be effective in reducing postoperative pain;[80,81] controversial results were obtained with postoperative administration of bupivacaine.[82]

Non-pharmacological strategies: In a RCT, that tested various types of trans-cranial current stimulation (tDCS) therapies, there were reported no differences in PCA morphine consumption and VAS at rest and after movement up to 48 hours.[83]

Discussion

In this systematic review, we report an update on safety and efficacy of pharmacological (systemic and local) and non-pharmacological (electrical stimulation) therapies for the prevention and treatment of postoperative pain after lumbar spine procedures. Compared to a systematic review by Sharma et al.,[19] dealing with the same topic and published in 2012, new evidence has been published: intraoperative infusion of ketamine and paracetamol, whose effectiveness was controversial, are now established as safe and effective therapies in lumbar

spine procedures; ketamine, dexketoprofen, and tramadol proved to have their highest efficacy in the management of postoperative pain as a single postoperative agent; furthermore, preoperative dexamethasone proved to be associated with a reduction of pain scores in mobilization and PONV, but not with VAS at rest and total morphine consumption (Table 5).

The NSAIDs often represent a foundational component of multimodal analgesic strategies but these results confirmed that their effect on pain management strictly depends on the single drug used. The choice of the drug to use and the administration depends on several factors and considerations such as costs, route of administration, risk of complications including renal toxicity, bleeding risk, and cardiac complications and should be assessed case by case. Epidural approach provides better early pain control, with less PONV events and lower request for supplemental analgesics, suggesting that as long as patients are selected carefully, spinal anesthesia may be a safer and a more economical alternative;[43,44] however, locoregional anesthesia can be precluded in some cases of coagulopathy.[84] In the last years, authors focused on the use of systemic drugs combinations: our results showed that gabapentinoids may have their greatest impact as part of a multimodal analgesic approach and pose the question on the use of analgesic efficacy of pregabalin / gabapentin as a single drug in the treatment of postoperative pain following lumbar spine procedures, especially in preemptive approach.[25-31] As confirmed by a recent meta-analysis studies about the efficacy of pregabalin to reduce postoperative pain have several limitations (number of studies and the sample size), and therefore a multicenter RCT is needed to accurately identify the effects and optimal dose of pregabalin for reducing acute pain after spine surgery.[85] Differently from the previous review, preoperative bupivacaine alone proved to be as effective as levobupivacaine in reducing both opioid consumption and pain scores, and showed to be more effective when combined with intrathecal $MgSO_4$. The effectiveness of combinative use

of systemic analgesic has been also confirmed also in a recent meta-analysis on the use of opioids for the prevention and treatment of pain after spine surgery, that reported how a combination of acetaminophen with either an NSAID or nefopam is superior to most analgesics other than morphine used alone, in reducing morphine consumption.[86] Furthermore, electrical nerve stimulation has shown to be potentially suitable for the clinical needs because of its non-invasiveness, low cost, and the absence of side effects.

Limitations: There are several limitations in this study that need to be mentioned. Firstly, we have not defined, in our search strategy, a minimum number of enrolled patients in the source studies, differently from the previous systematic review. This may have led to the inclusion of studies with small number of patients with positive or negative outcomes that have limited statistical power and/or clinical predictive value. Nevertheless, we considered important to present the entire systematically retrieved spectrum of trials. To balance this limitation, we reported the number of studied patients to reflect more accurately the trials' impact of clinical characteristics and within our outcomes summary (Table 2-4). Other factors that may have confounded the analgesic outcomes across these trials include: patient's individual analgesic preoperative history, type and amount of intraoperative opioids administered, and variations in the pain score threshold that triggered administration of rescue analgesic(s). Of interest, selected studies have substantial differences in the methods used to evaluate the severity of postoperative pain, including the timing and modality of assessment of the pain- at rest or at movement- as well as differences based on the intraoperative anesthesia, such as the use of short acting opioids. Despite these limitations and variations in study design, several new trends and insights have emerged through the 59 selected RCTs. These new information can help in building an evidence-based strategy to prevent postoperative pain after lumbar spine procedures and to design future trials.

Conclusions, recommendations and "future directions"

The "ideal" strategy for clinical management of pain after lumbar spine surgery remains a clinical challenge because of the limitations and potential drawback associated with single drug therapy. Compared to the review previously published in 2012,[19] this systematic review reports new insights on safety and efficacy of pharmacological and non-pharmacological therapies to prevent and treat postoperative pain after spine procedures, and allows to deliver further evidence-based recommendations. In particular, the preoperative use of gabapentinoids (as part of a multi-drug approach), or dexamethasone, or electrical stimulation, are effective and should be implemented in therapeutic protocols dedicated to prevent postoperative pain (Table 5). Intraoperative systemic injection of low dose ketamine, or tramadol - when used as single therapy- or the use of NSAIDs (parecoxib, ketorolac and etoricoxib), paracetamol, locoregional use of epidural morphine, wound infiltration -when combined in a multidrug/multimodal approach- have a proven analgesic efficacy and therefore should be considered as part of a therapeutic work-out (Table 5). The intraoperative systemic infusion of lidocaine is also associated with effective reduction of postoperative pain, but it remains uncertain the optimal dosing schedule.

In the future, prevention and management of postoperative pain after lumbar spine surgery will potentially involve the development of new therapies as well as new combinations of existing drugs. In this context, the use of non-pharmacological therapies, such as electrical stimulation, have the potential to provide promising results and might have a role in the pre-, intra- and postoperative settings.

Acknowledgements

None declared

Author contributions

All authors contributed equally to the study protocol, search strategy and screening of articles. ST, CR and PGS extracted data with FB and AP acting as arbiters for any disagreement. First draft was written by ST, FB and CR. All authors contributed to discussion section.

References

1.- Hughey AB, Lesniak MS, Ansari SA, Roth S. What will anesthesiologists be anesthetizing? trends in neurosurgical procedure usage. *Anesth Analg* 2010;110:1686-1697.

2.- Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med* 2013;3694:48-57.

3.- Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. *J Clin Neurosci* 2015;22:930-8.

4.- Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013;118:934-44.

5.- Bajwa SJ, Haldar R. Pain management following spinal surgeries: An appraisal of the available options. *J Craniovertebr Junction Spine* 2015;6:105-10.

6.- Rivkin A, Rivkin MA. Perioperative nonopioid agents for pain control in spinal surgery. *A J Health System Pharm* 2014;71:1845-57

7.- Tsaousi GG, Logan SW, Bilotta F. Postoperative pain control following craniotomy: a systematic review of recent clinical literature. Pain Pract 2017;17(7):968-981.

8.- Golob AL, Wipf JE. Low back pain. *Med Clin North Am* 2014;98:405-28.

9.- Mathiesen O, Dahl B, Thomsen BA, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. *Eur Spine J* 2013;22:2089-96.

10.- Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology* 2014;120:1237-45.

11.- Dolgun H, Turkoglu E, Kertmen H, et al. Gabapentin versus pregabalin in relieving early post-surgical neuropathic pain in patients after lumbar disc herniation surgery: a prospective clinical trial. *Neurol Res* 2014;36:1080-5.

12.- Hussain A, Erdek M. Interventional pain management for failed back surgery syndrome. *Pain Pract* 2014;14:64-78.

13.- Becker JA, Stumbo JR. Back pain in adults. *Prim Care* 2013;40:271-88.

14.- White AP, Arnold PM, Norvell DC, Ecker E, Fehlings MG. Pharmacologic management of chronic low back pain: synthesis of the evidence. *Spine* 2011;36:131-43.

15.- Armaghani SJ, Lee DS, Bible JE, et al. Preoperative opioid use and its association with perioperative opioid demand and postoperative opioid independence in patients undergoing spine surgery. *Spine* 2014;39:1524-30.

16.- Pasternak JJ, Lanier WL. Neuroanesthesiology update. J Neurosurg Anesthesiol 2014;26:109-154.

17.- Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine 2013;38:1947-52.

18.- Taylor RS, Desai MJ, Rigoard P, Taylor RJ. Predictors of pain relief following spinal cord stimulation in chronic back and leg pain and failed back surgery syndrome: a systematic review and meta-regression analysis. Pain Pract 2014;14(6):489-505.

19.- Sharma S, Balireddy RK, Vorenkamp KE, Durieux ME. Beyond opioid patient-controlled analgesia a systematic review of analgesia after major spine surgery. Reg Anesth Pain Med 2012;37:79-98.

20.- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009;6(6):e1000097.

21.- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.

22.- Badenes R, Bilotta F. Neurocritical care for intracranial haemorrhage: a systematic review of recent studies. *Br J Anaesth* 2015; 115 Suppl 2:ii68-74.

23.- Bilotta F, Lauretta MP, Tewari A, et al. Insulin and the brain: a sweet relationship with intensive care. *J Intensive Care Med* 2017;32(1):48-58.

24.- Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.

25.- Qadeer M, Waqas M, Rashid MJ, Enam SA, Sharif S, Murtaza G. Preventive gabapentin versus pregabalin to decrease postoperative pain after lumbar microdiscectomy: a randomized controlled trial. *Asian Spine J* 2017;11(1):93-98.

26.- Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *J Neurosurg Anesthesiol* 2012;24:121-6.

27.- Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. *Spine* 2014;39:363-8.

28.- Choi YS, Shim JK, Song JW, Kim JC, Yoo YC, Kwak YL. Combination of pregabalin and dexamethasone for postoperative pain and functional outcome in patients undergoing lumbar spinal surgery: a randomized placebo-controlled trial. *Clin J Pain* 2013;29:9-14.

29.- Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blinded, placebo-controlled study. *J Pain Res* 2013;6:471-8.

30.- Kim SI, Ha KY, Oh IS. Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial. *Eur Spine J* 2016;25(5):1614-9.

31.- Garcia RM, Cassinelli EH, Messerschmitt PJ, Furey CG, Bohlman HH. A multimodal approach for postoperative pain management after lumbar decompression surgery: a prospective, randomized study. *J Spinal Disord Tech* 2013;26:291-7.

32.- Siribumrungwong K, Cheewakidakarn J, Tangtrakulwanich B, Nimmaanrat S. Comparing parecoxib and ketorolac as preemptive analgesia in patients undergoing posterior

lumbar spinal fusion: a prospective randomized double-blinded placebo-controlled trial. *BMC Musculoskelet Disord* 2015;16:59.

33.- Srivastava S, Gupta D, Naz A, Rizvi MM, Singh PK. Effects of preoperative single dose Etoricoxib on postoperative pain and sleep after lumbar diskectomy: prospective randomized double blind controlled study. *Middle East J Anesthesiol* 2012;21:725-30.

34.- Nielsen RV, Siegel H, Fomsgaard JS, et al. Preoperative dexamethasone reduces acute but not sustained pain after lumbar disk surgery: a randomized, blinded, placebo-controlled trial. *Pain* 2015;156(12):2538-44.

35.- Martinez V, Szekely B, Lemarié J, Martin F, Gentili M. The efficacy of a glial inhibitor, minocycline, for preventing persistent pain after lumbar discectomy: a randomized, double-blind, controlled study. *Pain* 2013;154:1197-2033.

36.- Konstantopoulos K, Makris A, Moustaka A, Karmaniolou I, Konstantopoulos G, Mela A. Sevoflurane versus propofol anesthesia in patients undergoing lumbar spondylodesis: a randomized trial. *J Surg Res* 2013;179(1):72-7.

37.- Polat R, Peker K, Gülöksüz ÇT, Ergil J, Akkaya T. Comparison of the postoperative analgesic effects of paracetamol-codeine phosphate and naproxen sodium-codeine phosphate for lumbar disk surgery. *Kaohsiung J Med Sci* 2015;31(9):468-72.

38.- Nitta R, Goyagi T, Nishikawa T. Combination of oral clonidine and intravenous low-dose ketamine reduces the consumption of postoperative patient-controlled analgesia morphine after spine surgery. *Acta Anaesthesiol Taiwan* 2013;51:14-7.

39.- Attari MA, Najafabadi FM, Talakoob R, Abrishamkar S, Taravati H. Comparison of the effects of 3 methods of intrathecal bupivacaine, bupivacaine-fentanyl, and bupivacaine-

fentanyl-magnesium sulfate on sensory motor blocks and postoperative pain in patients undergoing lumbar disk herniation surgery. *J Neurosurg Anesthesiol* 2016;28(1):38-43.

40.- Salem RA, Darweesh EI, Wanis MA, Mohamed AA. Evaluation of the effects of intrathecal bupivacaine-dexmedetomidine for lumbar spine fusion: a double blinded randomized controlled study. *Eur Rev Med Pharmacol Sci* 2015;19:4542-8.

41.- Gurbet A, Bekar A, Bilgin H, Ozdemir N, KuytuT. Preemptive wound infiltration in lumbar laminectomy for postoperative pain: comparison of bupivacaine and levobupivacaine. *Turk Neurosurg* 2014;24:48-53.

42.- Düger C, Gürsoy S, Karadağ O, et al. Anesthetic and analgesic effects in patients undergoing a lumbar laminectomy of spinal, epidural or a combined spinal-epidural block with the addition of morphine. *J Clin Neuroscience* 2012;19:406-10.

43.- Vural C, Yorukoglu D. Comparison of patient satisfaction and cost in spinal and general anesthesia for lumbar disc surgery. *Turk Neurosurg* 2014;24(3):380-4.

44.- Ezhevskaya AA, Mlyavykh SG, Anderson DG. Effects of continuous epidural anesthesia and postoperative epidural analgesia on pain management and stress response in patients undergoing major spinal surgery. *Spine* 2013;38:1324-3010.

45.- Kang H, Jung HJ, Lee JS, Yang JJ, Shin HY, Song KS . Early postoperative analgesic effects of a single epidural injection of ropivacaine administered preoperatively in posterior lumbar interbody spinal arthrodesis: a pilot randomized controlled trial. *J Bone Joint Surg Am* 2013;95:393-9.

46- Aydoğan S, Er U, Ozlü O. Effectiveness of preemptive analgesia using a frequency rhythmic electrical modulation system in patients having instrumented fusion for lumbar stenosis. *Asian Spine J* 2014;8:190-6.

47.- Unterrainer AF, Uebleis FX, Gross FA, Werner GG, Krombholz MA, Hitzl W. TENS compared to opioids in postoperative analgesic therapy after major spinal surgery with regard to cognitive function. *Middle East J Anesthesiol* 2012;21:815-21.

48.- Naik BI, Nemergut EC, Kazemi A, et al. The effect of dexmedetomidine on postoperative opioid consumption and pain after major spine surgery. *Anesth Analg* 2016;122(5):1646-53.

49.- Peng K, Liu HY, Liu SL, Ji FH. Dexmedetomidine-fentanyl compared with midazolam-fentanyl for conscious sedation in patients undergoing lumbar disc surgery. *Clin Ther* 2016;38(1):192-201.e2.

50.- Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. *BMC Anesthesiol* 2015;15:21.

51.- Bekker A, Haile M, Kline R, et al. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. *J Neurosurg Anesthesiol* 2013;25:16-24.

52.- Song Y, Shim JK, Song JW, Kim EK, Kwak YL. Dexmedetomidine added to an opioid-based analgesic regimen for the prevention of postoperative nausea and vomiting in highly susceptible patients: A randomised controlled trial. *Eur J Anaesthesiol* 2016;33(2):75-83.

53.- Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. *Br J Anaesth* 2013;111(4):630-5

54.- Yeom JH, Chon MS, Jeon WJ, Shim JH. Peri-operative ketamine with the ambulatory elastometric infusion pump as an adjuvant to manage acute postoperative pain after spinal fusion in adults: a prospective randomized trial. *Korean J Anesthesiol* 2012;63:54-8.

55.- Kim SH, Kim SI, Ok SY, Park SY, Kim MG. Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. *Korean J Anesthesiol* 2013;64:524-8.

56.- Pacreu S, Fernández Candil J, Moltó L, Carazo J, Fernández Galinski S. The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. *Acta Anaesthesiol Scand* 2012;56(10):1250-6.

57.- Nielsen RV, Fomsgaard JS, Siegel H, et al. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. *Pain* 2017;158(3):463-470.

58. - Yilmaz MZ, Sarihasan BB, Kelsaka E, et al. Comparison of the analgesic effects of paracetamol and tramadol in lumbar disc surgery. *Turk J Med Sci* 2015;45:438-442.

59.- Lin BF, Ju DT, Cherng CH, et al. Comparison between intraoperative fentanyl and tramadol to improve quality of emergence. *J Neurosurg Anesthesiol* 2012;24(2):127-32.

60.- Tunali Y, Akçil EF, Dilmen OK, et al. Efficacy of intravenous paracetamol and dexketoprofen on postoperative pain and morphine consumption after a lumbar disk surgery. *J Neursurg Anesthesiol* 2013;25:143-147.

61.- Shimia M, Parish M, Abedini N. The effect of intravenous paracetamol on postoperative pain after lumbar discectomy. *Asian Spine J* 2014;8:400-4.

62.- Dewinter G, Moens P, Fieuws S, Vanaudenaerde B, Van de Velde M, Rex S. 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* 2017;118(4):576-585.

63.- Kim KT, Cho DC, Sung JK, et al. Intraoperative systemic infusion of lidocaine reduces postoperative pain after lumbar surgery: a double-blinded, randomized, placebo-controlled clinical trial. *Spine J* 2014;14:1559-66.

64.- Duttchen KM, Lo A, Walker A, et al. Intraoperative ketorolac dose of 15mg versus the standard 30mg on early postoperative pain after spine surgery: A randomized, blinded, non-inferiority trial. *J Clin Anesth* 2017;41:11-15.

65.- Upton HD, Ludbrook GL, Wing A, Sleigh JW. Intraoperative "Analgesia Nociception Index"-guided fentanyl administration during sevoflurane anesthesia in lumbar discectomy and laminectomy: a randomized clinical trial. *Anesth Analg* 2017;125(1):81-90.

66.- Chang WK, Wu HL, Yang CS, et al. Effect on pain relief and inflammatory response following addition of tenoxicam to intravenous patient-controlled morphine analgesia: a double-blind, randomized, controlled study in patients undergoing spine fusion surgery. *Pain Med* 2013;14:736-48.

67.- Diaz RJ, Myles ST, Hurlbert RJ. Evaluation of epidural analgesic paste components in lumbar decompressive surgery: a randomized double-blind controlled trial. *Neurosurgery* 2012;70:414-23.

68.- Kundra S, Gupta V, Bansal H, Grewal A, Katyal S, Choudhary AK. Comparative study of epidural application of morphine versus gelfoam soaked in morphine for lumbar laminectomy. *J Anaesthesiol Clin Pharmacol* 2014;30:46-52.

69.- Offley SC, Coyne E, Horodyski M, Rubery PT, Zeidman SM, Rechtine GR. Randomized trial demonstrates that extended-release epidural morphine may provide safe pain control for lumbar surgery patients. *Neurol Int* 2013;4:51-7.

70.- Wilartratsami S, Sanansilp V, Ariyawatkul T, et al. The effect of epidural low-dose morphine-soaked microfibrillar collagen sponge in postoperative pain control after laminectomy and instrumented fusion: a randomized double-blind placebo-controlled study. *J Med Assoc Thai* 2014;97:62-7.

71.- Yen D, Turner K, Mark D. Is a single low dose of intrathecal morphine a useful adjunct to patient-controlled analgesia for postoperative pain control following lumbar spine surgery? A preliminary report. *Pain Res Manag* 2015;20:129-32.

72.- Kalappa S, Sridhar RB, Nagappa S. Comparing the efficacy of caudal with intravenous dexamethasone in the management of pain following lumbosacral spine surgeries: a randomized double blinded controlled study. *Anesth Essays Res* 2017; 11(2): 416–420.

73.- Kumar S, Palaniappan JM, Kishan A. Preemptive caudal ropivacaine: an effective analgesic during degenerative lumbar spine surgery. *Asian Spine J* 2017;11(1):113-119.

74.- Servicl-Kuchler D, Maldini B, Borgeat A, et al. The influence of postoperative epidural analgesia on postoperative pain and stress response after major spine surgery--a randomized controlled double blind study. *Acta Clin Croat* 2014;53:176-83.

75.- Guilfoyle MR, Mannion RJ, Mitchell P, Thomson S. Epidural fentanyl for postoperative analgesia after lumbar canal decompression: a randomized controlled trial. *Spine J* 2012;12:646-51.

76.- Demiroglu M, Ün C, Ornek DH, et al. The effect of systemic and regional use of magnesium sulfate on postoperative tramadol consumption in lumbar disc surgery. *Biomed Res Int* 2016;2016:3216246.

77.- Garg N, Panda NB, Gandhi KA, et al. Comparison of small dose ketamine and dexmedetomidine infusion for postoperative analgesia in spine surgery-a prospective randomized double-blind placebo controlled study. *J Neurosurg Anesthesiol* 2016;28(1):27-31.

78.- Abrishamkar S, Eshraghi N, Feizi A, Talakoub R, Rafiei A, Rahmani P. Analgesic effects of ketamine infusion on postoperative pain after fusion and instrumentation of the lumbar spine: a prospective randomized clinical trial. *Med Arh* 2012;66:107-10.

79.- Singh A, Jindal P1, Khurana G, Kumar R. Post-operative effectiveness of continuous wound infiltration, continuous epidural infusion and intravenous patient-controlled analgesia on post-operative pain management in patients undergoing spinal surgery. *Indian J Anaesth* 2017;61(7):562-569.

80.- Shin SH, Hwang BW, Keum HJ, Lee SJ, Park SJ, Lee SH. Epidural steroids after a percutaneous

endoscopic lumbar discectomy. *Spine (Phila Pa 1976)* 2015;40(15):E859-65.

81.- Ozyilmaz K, Ayoglu H, Okyay RD, et al. Postoperative analgesic effects of wound infiltration with tramadol and levobupivacaine in lumbar disk surgeries. *J Neurosurg Anesthesiol* 2012;24:331-5.

82.- Choi S, Rampersaud YR, Chan VW, et al. The addition of epidural local anesthetic to systemic multimodal analgesia following lumbar spinal fusion: a randomized controlled trial. *Can J Anaesth*

2014;61(4):330-9.

83.- Dubois PE, Ossemann M, de Fays K, et al. Postoperative analgesic effect of transcranial direct current stimulation in lumbar spine surgery: a randomized control trial. *Clin J Pain* 2013;29:696-7014

84.- Hahnenkamp K, Theilmeier G, Van Aken HK, Hoenemann CW. The effects of local anesthetics on perioperative coagulation, inflammation, and microcirculation. *Anesth Analg* 2002;94(6):1441-7.

85.- Jiang HL, Huang S, Song J, Wang X, Cao ZS. Preoperative use of pregabalin for acute pain in spine surgery: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2017;96(11):e6129.

86.- Martinez V, Beloeil H, MarretE, Fletcher D , Ravaudand P, Trinquart L. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. *Br J Anaesth* 2017;118(1):22-31.

Table 1. Risk of bias of the studies included.

I.D	Sequence generation	Allocation Concealment	Blinding of participants, personnel and outcome assessor	Incomplete outcome data	Selective outcome reporting	Others criteria
PREOPERATIVE						
systemic pharmacological therapies						
Qadeer et al[25]	L	L	L	L	L	U
Gianesello et al[26]	L	L	L	L	L	L
Khurana et al[27]	L	L	L	L	L	L
Choi et al[28]	L	L	L	L	L	L
Kumar et al[29]	L	L	L	U	U	U
Kim et al[30]	L	L	H	U	H	U
Garcia et al[31]	L	L	L	U	L	L
Siribumrungwong et al[32]	L	L	L	L	L	L
Srivastava et al[33]	U	L	L	U	U	U
Nielsen et al[34]	L	L	L	L	L	L
Martinez et al[35]	L	L	L	U	L	U
Konstantopoulos et al[36]	L	L	H	L	L	L
Polat et al[37]	L	L	L	L	L	L
Nitta et al[38]	L	L	L	U	L	L
local delivery						

Attari et al[39]	U	L	L	L	L	L
Salem et al[40]	U	L	L	L	L	L
Gurbet et al[41]	L	L	L	U	L	L
Düger et al[42]	L	L	H	H	L	L
Vural et al[43]	L	L	H	L	L	U
Ezhevskaya et al[44]	L	L	H	H	L	U
Kang et al[45]	L	L	L	L	L	L
non-pharmacological strategies						
Aydoğan et al[46]	L	L	H	U	L	L
Unterrainer et al[47]	L	L	U	U	U	U
INTRAOPERATIVE						
systemic pharmacological therapies						
Naik et al[48]	L	L	L	L	L	L
Peng et al[49]	L	L	L	U	L	L
Hwang et al[50]	L	L	U	L	U	L
Bekker et al[51]	L	U	L	U	U	U
Song et al[52]	L	L	L	L	L	U
Song et al[53]	L	L	L	L	U	U
Yeom et al[54]	L	L	L	L	L	L
Kim et al[55]	L	L	L	L	L	U
Pacreu et al[56]	L	L	L	L	U	U
Nielsen et al[57]	L	L	L	L	L	L
Yilmaz et al[58]	L	L	L	L	L	U
Lin et al [59]	L	L	L	L	L	L

Tunali et al[60]	L	L	L	L	L	L
Shimia et al[61]	L	L	L	U	L	L
Dewinter et al[62]	L	L	L	L	L	L
Kim et al[63]	L	L	L	L	L	L
Duttchen et al[64]	L	L	L	H	U	U
Upton et al[65]	L	L	L	L	U	U
Chang et al[66]	L	L	L	H	L	U
local delivery						
Diaz et al[67]	L	L	L	L	L	U
Kundra et al[68]	L	L	L	U	U	U
Offley et al[69]	U	L	H	U	L	U
Wilartratsami et al[70]	L	L	L	L	L	L
Yen et al[71]	L	L	L	L	U	U
Kalappa et al[72]	L	L	L	L	L	L
Kumar et al[73]	L	L	H	L	L	L
Servicl-Kuchler et al[74]	L	L	U	L	L	U
Guilfoyle et al[75]	L	L	L	L	L	L
Demiroglu et al[76]	U	L	H	L	L	L
POSTOPERATIVE						
systemic pharmacological therapies						
Garg et al[77]	L	L	L	L	L	L
Abrishamkar et al[78]	L	L	L	L	L	U

local delivery						
Singh et al[79]	L	L	L	L	L	U
Shin et al[80]	L	L	L	L	L	L
Ozyilmaz et al[81]	L	L	L	L	L	L
Choi et al[82]	L	L	L	H	H	H
non-pharmacological strategies						
Dubois et al[83]	L	L	L	L	U	U

Table 2. Summary of the studies in the preoperative analgesia section**.**

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
SYSTEMIC PHARMACOLOGICAL THERAPIES						
Pregabalin						
Qadeeret al.[25]	N=78 • pregabalin 75mg /os: N = 39 • gabalin 200mg: N = 39	Preoperative pregabalin or gabapentin one week before surgery twice daily	Postoperative Hours: 24 Weeks: 1	VAS	• Dose • Cost • Pharmacokinetics • Side effects	No difference in preventing postoperative pain
Gianesello et al.[26]	N = 60 • pregabalin 300mg/os: N = 30 • pregabalin 150mg/os: N = 30	Preoperative • 300mg 1 h before surgery Postoperative • 150 mg twice a day for 48 h	Postoperative Hours: 1, 4, 8, 12, 24, 48 Postoperative Months: 3, 12	VAS scores at rest and movement	• Dizziness • PONV	VAS scores at rest and movement in the first 12 h were lower in pregabalin group

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Khurana et al.[27]	N = 90 • gabapentin 300mg: N = 30 • pregabalin 75mg/os: N = 30 • placebo: N = 30	Preoperative • 1 h before surgery Postoperative • Every 8 h for 7 days after surgery	Postoperative Hours: 0, 3, 6, 12, 24, 36, 48, 72 Postoperative Days: 7, 21, 90	VAS score at rest	PONV	• VAS score at rest was lower in gabapentinoids groups up to 72 h • pregabalin at 3 months was more effective in reducing pain than gabapentin

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Choi et al.[28]	N = 108 • pregabalin 150mg/os + placebo: N = 36 • pregabalin 150mg/os + dexamethasone 16mg: N = 36 • placebo: N = 36	Preoperative • dexamethasone before anesthesia induction • pregabalin: 1 h before surgery Postoperative • pregabalin every 12 h for three days (8 doses)	Postoperative Hours: First 72 Postoperative Months: 6	• VAS score • Additional rescue analgesic lower	PONV lower in pregabalin / dexamethasone group	The combination pregabalin / dexamethasone was effective in reducing VAS 24 h and 6 months, additional rescue analgesic and PONV

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Kumar et al.[29]	N = 75 • tramadol 100mg/os: N = 25 • pregabalin 150 mg/os: N = 25 • placebo: N = 25	Preoperative • 1 h before surgery	Postoperative Hours: 1, 2, 4, 6	• VAS • rescue analgesia	• PONV • Drowsiness	• Pain scores and rescue analgesia were lower in tramadol group • PONV and VAS scores were lower in pregabalin group than placebo group

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Kim et al.[30]	N = 80 • celecoxib 200mg + pregabalin 75mg/os: N = 40 • control: N = 40	Preoperative • 1 h before surgery Postoperative • Twice daily during the postoperative period. • celecoxib once daily after surgery.	Postoperative Days: 1, 2, 4, 7	Pain scores (VAS and ODI)	Major complications	Pain scores were lower at every time point

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Garcia et al.[31]	N = 22 • celecoxib 200mg + pregabalin 75mg/os: N = 10 • control: N = 12	Preoperative • 1 h before surgery Postoperative • twice daily until hospital discharge	Postoperative Hours: 0, 4, 8, 12, 16, 24, 36	• VAS • morphine requirements	• Major complication • Earlier solid food intake	Associated to celecoxib and oxycodone, pregabalin is more effective than morphine alone in the prevention of postoperative pain
non-steroidal anti-inflammatory drugs						
Siribumrungwong et al.[32]	N = 96 • parecoxib 40mg/IV: N = 32 • ketorolac 30mg/IV: N = 32 • placebo: N = 32	Preoperative • All drugs 30 minutes before surgery	Postoperative Hours: 0, 1, 2, 3, 4, 6, 12, 18, 24	VNRS at rest	Complications	Parecoxib was as effective as ketorolac and both were more effective than placebo in preventing postoperative pain at rest at 24h

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Srivastava et al.[33]	N = 43 • etoricoxib 120mg/os: N = 21 • control: N = 22	Preoperative • 1 h before surgery	Postoperative Hours: First 24	• VAS score at rest and movement • fentanyl consumption	• Sleep • Episodes of respiratory depression • Episodes of sedation	Eterocoxib was more effective than placebo in reducing pain at rest and movement, and opioid consumption, and ensuring better night sleep in the first 24h
Other drugs						
Nielsen et al.[34]	N=153 • dexamethasone 16 mg: N = 77 • placebo: N = 76	Preoperative • 1 h before surgery	Postoperative Hours: 2, 4, 8, 12, 24, 48	• VAS scores at rest and in mobilization • Total morphine consumption	PONV	• Pain scores in mobilization and PONV events were lower in dexamethasone group • VAS at rest and total morphine consumption were similar

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Martinez et al.[35]	N = 85 • minocycline 100mg: N = 43 • placebo: N = 42	Preoperative • 100mg 12 h before surgery Postoperative • 100mg twice a day for 8 days after surgery	Preoperative Hours: 24 Postoperative Hours: 48 Postoperative Months: 3	NRS at rest and in movement	Opioid consumption in the first 24 h	• Minocycline showed no efficacy in reducing pain or opioid consumption
Konstantopoulos et al.[36]	N=70 • sevoflurane 8%: N = 35 • propofol 2,5 mg/kg IV: N = 35	Preoperative • For induction of anesthesia •	Postoperative Hours: 0, 3, 6, 24	VAS at rest and at cough	PONV	There were no significant differences in all the parameters

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Polat et al.[37]	N=60 • naproxen sodium 550 mg/os + codeine phosphate30 mg: N = 20 • paracetamol 300 mg + codeine phosphate 30 mg: N = 20 • control: N = 20	Preoperative • All drugs 30 minutes before surgery	Postoperative Hours: 0, 1, 2, 6, 12, 24	• VAS • tramadol consumption	The hemodynamic values, Ramsey sedation scores, and PONV	• Pain was equally lower in paracetamol and naproxen groups compared with control group • tramadol consumption was lower in paracetamol and naproxen groups compared with control group, and lower in paracetamol group than naproxen group • No differences in PONV

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Nitta et al.[38]	N = 49 • morphine 2mg IV + clonidine 4µg/kg: N = 13 • morphine 2mg IV + ketamine 10mg • morphine 2mg IV + ketamine 2mg/kg/h : N = 12 • morphine 2mg IV: N = 12 • morphine 2mg IV + ketamine 2mg/kg/h + clonidine 4µg/kg: N = 12 •	Preoperative • clonidine 4µg/kg before surgery Intraoperative • 10mg ketamine during induction anesthesia • 2mg/kg/h ketamine during surgery	Postoperative Hours: First 60	• VAS score at rest and at movement • Cumulative morphine requirement	• PONV • Request of additional analgesia.	• VAS score at rest in morphine group and morphine ketamine group was lower • VAS score at movement had no differences • Cumulative morphine requirement was lower in MCK group • No differences in PONV
LOCAL DELIVERY						
Bupivacaine						

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Attari et al.[39]	N=105 • hyperbaric bupivacaine 15 mg + fentanyl 25 mg IV: N = 35 • hyperbaric bupivacaine 15 mg + fentanyl 25 mg IV + $MgSO_4$ 50 mg: N = 35 • control: N = 35	Preoperative • Immediately before the correct positioning	Postoperative Hours: 2, 4, 6, 12, 24	• Time to complete recovery of motor function • VAS • Total morphine consumption • Time of first analgesic requirement	Complications	• Pain and Total morphine consumption were less in $MgSO_4$ group • Time to complete recovery of motor function and analgesic requirement were longer in MgSO4 group

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Salem et al.[40]	N=52 • dexmedetomidine 5 μg: N = 26 • control: N = 26	Immediately before the correct positioning	Postoperative Hours: 24	• Quality of the operative field with mean ACS score • Total dose of ketorolac during the first 24 h postoperatively	• Patients' satisfaction • Intraoperative blood loss • Surgeons' satisfaction • Time of first requirement of analgesia	• ACS and total dose of ketorolac were lower in dexmedetomidine group • Surgeons and patients in dexmedetomidine group were more satisfied with their control of pain • Time of first requirement of analgesia was longer in dexmedetomidine group
Gurbet et al.[41]	N = 56 • levobupivacaine 0.25% 20ml + 40mg methylprednisolone: N = 19 • bupivacaine 0.25% 20ml + 40mg methylprednisolone: N = 18 • placebo: N = 19	Intraoperative • Infiltration applied to the surgery site paravertebral muscles	Postoperative Hours: 1, 2, 4, 8, 12, 16, 24	• VAS at movement and rest • Morphine consumption	First analgesic requirements	• VAS and morphine consumption were similarly lower in the 2 groups when compared to the control group • First analgesic requirement was shorter in control group

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Duger et al.[42]	N = 65 SA: N = 22 • bupivacaine 0.5% 10mg + • morphine 0.1mg EA: N = 21 • bupivacaine 0.5% 50mg + • morphine 2mg; CA: N = 21 • bupivacaine 5mg 0.5% and morphine 0.05mg in the intrathecal space • bupivacaine 0.5% 30mg • morphine 2mg in the epidural space.	Preoperative Procedures were done before surgery	Postoperative Hours: First 24	• VAS score • Total morphine consumption	• Sedation scores • PONV and other complications • satisfaction scores	• VAS score and total morphine consumption were higher in SA group • Satisfaction scores were similarly in EA and CA groups and lower than in SA group • No differences in sedation scores and complications
Epidural versus general anesthesia						

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Vural et al.[43]	N=66 • thiopental 6 mg/kg + fentanyl 1.5 µgr/kg: N = 33 • hyperbaric bupivacaine15 mg 0.5%: N = 33	Preoperative • Immediately before the correct positioning	Postoperative Hours: 0, 1, 3, 6, 12, 24	• VAS • Request of supplemental analgesic • Patient satisfaction • Total cost	• PONV • Hospital length stay	• In hyperbaric bupivacaine group there were lower VAS, less additional dose of fentanyl intraoperatively request and higher patients' satisfaction • PONV and hospital length stay were similar • Local analgesia is more economical

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Ezhevskaya et al.[44]	N = 85 Bolus: N = 40 • ropivacaine (0.375% - 0.75% 3-10ml) + fentanyl 100µg • fentanyl 0.002 mg/kg/hr + sevoflurane 2 MAC Epidural anesthesia: N = 45 • ropivacaine 0.2% • fentanyl 2µg/ml • epinephrine 5/10ml h • trimeperidine IV 4-5 mg/hr	Preoperative • Bolus before surgery Postoperative Analgesia of 2-3 days	Postoperative Hours: First 36	NRS at rest, while turning in bed, while standing, while coughing, and while walking	Opioid analgesics requirement	• NRS was lower in epidural group • No opioid analgesics requirement in epidural group
Other drugs						
Kang et al.[45]	N = 66 • ropivacaine 0.1% 10 ml: N = 32 • placebo: N = 34	Preoperative • 20 minutes before surgery	Postoperative Hours: 48	• NRS • Opioids consumption (PCA and rescue analgesia)	PONV	Pain scores, opioid consumption and PONV events were higher in control group
NON-PHARMACOLOGICAL STRATEGIES						

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours)	Time Observation	Primary Endpoint: Efficacy	Secondary Endpoint: Safety	Key message
Aydogan et al.[46]	N = 40 • FREMS: N = 20 • placebo: N = 20	Preoperative FREMS was given in five sessions (every 20-30 minutes) and the last session was applied just before surgery	Postoperative Hours: 24	• VAS and verbal rating score (VRS) • Supplementary analgesics	• PONV and other complications • Patient satisfaction	• VAS, VRS and supplementary analgesics were lower in FREMS group • Patient satisfaction was higher in FREMS group • No differences in PONV
Unterrainer et al.[47]	N = 35 • TENS: N = 17 • placebo: N = 18	Preoperative • TENS therapy 30 minutes before operation Postoperative • TENS therapy 24 h after surgery	Postoperative Hours: 24	Postoperative fatigue	• None	Postoperative fatigue was less in TENS group

Table 3. Summary of the studies in the intraoperative analgesia section**.**

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration (h = hours; min = minutes)	Time of Observation	Primary Endpoint	Secondary Endpoint	Key message
SYSTEMIC PHARMACOLOGICAL THERAPIES						
Dexmedetomidine						
Naik et al.[48]	N=131 • dexmedetomidine 1 μg/kg load followed by a continuous infusion of 0.5 μg/kg/h: N = 63 • placebo: N = 68	After transitioning to the prone position and start of the treatment for analgesia maintenance	Postoperative Hours: 2, 6, and 12 hours	• VAS • Opioid consumption	PONV	• No differences in pain intensity and opioid consumption • Dexmedetomidine group had more PONV events
Peng et al.[49]	N=60 • dexmedetomidine 0.5 mg/kg/h + fentanyl 1 mg/kg: N = 30 • midazolam 0.05μg/kg/h + fentanyl 1 mg/kg: N = 30	After transitioning to the lateral position until the end of the surgery	Time points: before sedation; skin incision; 15 minutes after the beginning of surgery; 30 minutes after the beginning of surgery; skin	• VRS • Fentanyl total consumption	• Adverse events • Postoperative hospital length of stay • Patients' satisfaction	• No differences in pain intensity, adverse events, length of stay and satisfaction • Dexmedetomidine group had lower fentanyl consumption

			closure; entering the PACU; 15 minutes in the PACU 2 h after surgery; 6 h after surgery; 12 h after surgery; 18 h after surgery; 24 h after surgery			
Hwang et al.[50]	N = 37 • remifentanil 0.01-0.2 μg/kg/min: N = 18 • dexmedetomidine 0.01-0.02 μg/kg/min: N = 19	• TIVA with propofol and remifentanil started prior intubation and discontinued on completion of skin closure. • TIVA with propofol and dexmedetomidine started rior intubation and discontinued at the start of skin closure	Hours Post PACU Discharge: 2, 8, 24, 48	• VAS • Amount of PCA requirement	PONV	Pain intensity, PCA requirement and PONV events were lower in dexmedetomidine group

Bekker et al.[51]	N=54 • dexmedetomidine infusion 0.5 μg/kg/h: N = 26 • control: N = 28	Infusion begins before surgery and stopped 20 min before end of surgery	Postoperative Hours: 24, 48, 72, 96	• NRS • Quality of recovery (QoR40 and FFS)	Fatigue	• Dexmedetomidine reduced fatigue and improved quality of recovery • No differences in pain
Song Y et al.[52]	N=105 • dexmedetomidine 0.5μg kg^{-1} i.v and 10 μg kg^{-1}: N = 53 postoperatively • control: N = 52	• 30 min before the completion of surgery • First 48 hours postoperatively	Postoperative Hours: 1, 3, 6, 12, 24, 36, 48	VAS at rest and with movement	• Opioid consumption and rescue of anaesthesia • PONV	• Dexmedetomidine group had lower fentanyl consumprion and less intense PONV events • No difference in VAS scores
Ketamine						
Song JW et al.[53]	N=49 • ketamine 0,3 mg kg^{-1} IV+ 3 mg kg^{-1} in 180 ml: N = 24 • control: N = 25	immediately after induction of anesthesia	Postoperative Hours: 6, 12, 24, 36, and 48	VAS at rest or with movement	• Opioid consumption • PONV	• Ketamine reduces opioid consumption • No differences in pain intensity and overall PONV events
Yeom et al.[54]	N = 40 • ketamine 30μg/ml/kg: N = 20 • control: N = 20	Loading dose with fentanyl 1μg/kg and ketamine 0.2 μg/kg, 1 hour after incision, followed by PCA infusions.	Postoperative Hours: 1, 24, 48	• NRS score at rest • Total amount of opioid consumption	Side effects	Ketamine reduced NRS scores but not the opioid consumption and PONV
Kim et al.[55]	N = 52	• ketamine	Postoperative	• VAS at	• Advers	• Ketamine

	• ketamine infusion 1 μg/kg/min following bolus of 0.5mg/kg: N = 18 • ketamine infusion 2μg/kg/min following bolus of 0.5mg/kg: N = 17 • control: N = 17	infusion following bolus dose started before skin incision intraoperatively • Continued until 48 h postoperatively	Hours: 1, 6, 24, 48	rest and with movement • Total amount of fentanyl consumption	e effects • Patients ' satisfaction	2μg/kg/mhad the lower opioid consumption • no difference in pain intensity, adverse effects or patients' satisfaction were found
Pacreu et al.[56]	N=20 • ketamine preoperative bolus 0.5 mg/kg + methadone 0.5 mg in methadone group: N = 10 • control: N = 10	• ketamine 0.5 mg/kg after tracheal intubation • ketamine infusion during the post-operative period (24–48 h after operation) • methadone infusion during the post-operative period (24–48 h after operation)	Postoperative Hours: at 24 and 48	• NRS at rest and on movement • Opioid consumption	Complications and side effects	Ketamine reduced opioid consumption but did not influenced pain intensity or side effects
Nielsen et al.[57]	N=147 • S-ketamine bolus 0.5 mg/kg followed by infusion of S-ketamine 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$: N = 74 • placebo: N = 73	S-ketamine bolus 0.5 mg/kg immediately after induction of anesthesia followed by infusion of S-ketamine 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$	Postoperative Hours: up to 24 Months: 6	• VAS at rest and movement • Opioid consumption	PONV	• Ketamine reduced opioid consumption • No differences in VAS up to 24h and PONV • Back pain at 6 months was higher in ketamine group

Tramadol						
Yilmaz et al.[58]	N = 60 • paracetamol 1g IV: N = 30 • tramadol 1.5mg/kg (loading dose) and PCA bolus of 20mg: N = 30	paracetamol • 1g 30 min before end of surgery • 1g at 6 h intervals for 1 day. tramadol • bolus dose 1.5mg/kg in the reanimation unit • PCA bolus of 20mg for 24 h	Postoperative Hours: 1, 2, 4, 6, 12, 24,	VAS scale • Rescue analgesic consumption	• Hemodynamic Parameters • Modified Aldrete Score • Ramsay Sedation Score • PSS	• No pain differences • Analgesic consumption was lower and delayed in tramadol group • PSS was higher in tramadol group
Lin et al.[59]	N = 110 • fentanyl 1 mg/kg: N = 55 • tramadol 1 mg/kg IV: N = 55	fentanyl or tramadol 30 minutes before the expected extubation	Postoperative Hours after extubation: 0, 2, 4, 24, 48, 72	• VAS scale at rest and on movement • Consumption of fentanyl	Complications incidence	• No differences in pain intensity, opioid consumption • Tramadol reduced complications incidence
Paracetamol						
Tunali et al.[60]	N = 56 • paracetamol 1g: N = 18 • dexketoprofen 50 mg IV: N = 18 • placebo: N = 20	• paracetamol bolus at end of surgery and every 6 h • dexketoprofen at end of surgery	Postoperative Hours: 1, 2, 6, 12, 24	• VAS scores • Morphine consumption	Side effects	• Pain scores were lower in dexketoprofen group • No differences in morphine consumption

		and every 8 h • saline group at end of surgery and every 8 h				and side effects
Shimia et al.[61]	N = 52 • paracetamol 1g: N = 24 • control: N = 28	• 1g paracetamol at end of surgery • 100ml saline solution at end of surgery	Postoperative Hours: 1, 6, 12, 18, 24	VAS	• Opioid requirement • Side effects	• VAS scores were lower in paracetamol group • No differences in morphine consumption and side effects
Lidocaine						
Dewinter et al.[62]	N=69 • lidocaine infusion of 1.5mg kg^{-1} h^{-1}: N = 35 • placebo: N = 34	• lidocaine bolus injection of 1.5mg kg^{-1} at induction of anaesthesia, followed by an infusion of 1.5mg kg-1 h-1 which was continued until six h after arrival at the PACU	Postoperative Hours: up to 24	Opioid consumption	• PONV • Length of stay • Quality of life	No differences in all the parameters
Kim et al.[63]	N = 51 • lidocaine infusion following bolus 2mg/kg/h: N = 25 • control: N = 26	• lidocaine infusion was started preoperatively and stopped at the end	Postoperative Hours: 2, 4, 8, 12, 24, 48	• VAS score • Fentanyl consumption	• Length of stay in hospital • Patient satisfaction	Lidocaine reduced pain intensity, fentanyl consumption, length of hospital stay and guaranteed the best

		of surgery • Control group received saline infusion			• Side effects	satisfaction scores
Other drugs						
Duttchen et al.[64]	N=50 • ketorolac IV 15 mg N=25 • ketorolac IV 30mg N=25	At the end of the surgery	Postoperative • At 4h (VAS) • At 8 and 24h (morphine) • Up to 24h (NRS)	VAS	• morphine usage • NRS	There were not statistically important differences in all the parameters between the two groups, but ketorolac 15 mg failed to meet the pre-specified definition of non-inferiority
Upton et al.[65]	N=50 • Fentanyl IV (Analgesia Nociception Index>50) boluses of 50 µg (<50 years) or 25 µg (>50 years) N=24 • control N=26	After anesthetic induction	Postoperative Minutes: from 0 to 90 of recovery room stay	NRS pain scores at rest	• fentanyl request • nausea	The study group had lower NRS scores at rest and less nausea events
Chang et al.[66]	N = 89 • morphine 100mg: N = 32 • tenoxicam 60mg + morphine 100mg: N = 29	• PCA regimen with morphine; • PCA	Postoperative Hours: 12, 24, 36,	NRS at rest or on movement	• Morphine consumption • PCA	No differences in NRS scores and total morphine consumption

	• tenoxicam 20mg + tenoxicam 60mg + morphine 100mg: N = 28	regimen with tenoxicam and morphine; • tenoxicam administered 30 minutes before wound closure in addition to a PCA with morphine and tenoxicam.	48, 72		demand/delivery • Use of rescue analgesics • Adverse events • Levels of inflammatory mediators in drainages	
LOCAL DELIVERY						
Morphine						
Diaz et al.[67]	N = 201 • Epidural methylprednisolone 80mg: N = 51 • morphine sulfate 3-5mg: N = 50 • Epidural methylprednisolone 80mg + morphine sulfate 3-5mg: N = 48 • placebo: N = 52	• Combination paste methylprednisolone and morphine • steroid paste methylprednisolone • morphine paste (morphine) applied at the end of surgery in the epidural space	Postoperative Days: 1, 3, 7 Postoperative Weeks: 3, 6, 8, 12 Postoperative Months: 6, 12	• Analgesic consumption • Pain intensity (McGill Pain Questionnaire)	• Functional scores • Time of ambulation • Time to discharge from hospital	• Combination paste and steroid paste resulted in better pain and analgesic consumption scores • No differences in time of ambulation and to discharging
Kundra et	N = 150	• At end of	Postoperative	Analgesic	• First	Group I showed lower

al.[68]	• 5 x 1cm strip of gelfoam soaked in 5mg morphine in epidural space • control: N = 75	surgery, 5 x 1cm piece of absorbable gelatin sponge soaked in 5mg morphine placed in epidural space • saline soaked gelfoam placed in epidural space and 5 mg morphine installed over the intact epidural space	Hours: 24, 48	consumption	analgesic request • Time of ambulation • Time of discharge from hospital • Advers e effects	analgesic consumption
Offley et al.[69]	N = 98 • EREM 10mg: N = 51 • EREM 15mg: N = 47	At end of surgery, EREM was placed in epidural space	Postoperative Hours: 6, 12, 18, 24, 36, 48	Total analgesics requested	Side effects	No differences in analgesics consumption
Wilartratsa mi et al.[72]	N = 19 • morphine 1mg in MMCS: N = 9 • placebo: N = 10	At end of surgery, MMCS was placed on the surface of dural sac	Postoperative Hours: 4, 24, 48, 72	Total opioid consumption	PONV	MMCS reduced morphine consumption
Yen et al.[71]	N = 32 • intrathecal morphine 3.5μg/kg to a maximum of 350μg: N = 18 • control: N = 14	At end of surgery, morphine or saline were placed into intrathecal space	Postoperative Hours: 4, 8, 24	• Total morphine PCA consumption in the first 24 hours • Pain intensity	• PONV • Length of hospital stay • Time of first ambulation	• Morphine group had lower PCA consumption • No differences in pain intensity, PONV and length of hospital

						stay
Kalappa et al.[72]	N = 96 • 0.2% ropivacaine caudal 25 ml: N = 32 • dexamethasone IV 8 mg (2 ml) + 0.2% ropivacaine caudal 25 ml: N = 32 • 0.2% ropivacaine 25 ml + dexamethasone caudal 8 mg: N = 32	After endotracheal tube and the patient positioning.	Postoperative Hours: 0 (after surgery when the patient had completely recovered and regained consciousness from general anesthesia), 1, 2, 4, 8, 12, 24	VAS scores		The mean VAS was significantly lower in the ropivacaine plus dexamethasone caudal group for up to 24 h when compared to the other groups.
Kumar et al.[73]	N = 60 • ropivacaine 20 mL: N = 30 • control: N = 30	After the administration of general anesthesia	Postoperative Hours: 0, 2, 4, 6, 8, 12, and 24	VAS	• Time to rescue analgesia • PONV • Early mobilization	Ropivacaine reduced pain intensity, analgesia consumption and PONV
Other drugs						
Servicl kuchler et al.[74]	N = 68 • Epidural levobupivacaine 0.125% versus saline solution: N = 33	At end of surgery, epidural bolus of levobupivacaine 0.125% and epidural bolus of	Postoperative Days: First 5 postoperative days	• VAS • Rescue analgesics consumption	• PONV • Length of hospital stay • Time of	Levobupivacaine reduced pain scores, analgesics consumption and PONV events

	• control: N = 35	saline solution	Postoperative Hours: every 6 hours		first defecation	
Guilfoyle et al.[75]	N = 60 • epidural fentanyl 100μg: N = 29 • control: N = 31	Before wound closure, 100μg fentanyl in 10ml saline solution	Postoperative Hours: 24, 48	VAS scores	• Advers e effects • Length of hospital stay	• Epidural fentanyl reduced VAS up to 24h • No differences in VAS at 24 to 48 h, adverse effects and length of hospital stay
Demiroglu et al.[76]	N = 75 • IV $MgSO_4$ 50mg/kg: N = 25 • IM $MgSO_4$ 50mg/kg: N = 25 • control: N = 25	At the stage of suturing	Postoperative Minutes: 5, 15, 30, 45, and 60 Hours: 4, 8, 12, and 24	• Postoperat ive tramadol consumption • NRS	PONV	• IM had the lower tramadol consumption • IV and IM groups similarly showed less PONV events than control group • No difference in NRS

Table 4. Summary of the studies in the postoperative section**.**

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration	Time of Observation	Primary Outcome	Secondary Outcome	Key message
SYSTEMIC PHARMACOLOGIC THERAPIES						
Garg et al.[77]	N = 66 • ketamine bolus 0.25mg/kg and infusion of 0.25 mg/kg/h: N = 22 • dexmedetomidine bolus 0.5 µg/kg and infusion of 0,3µg/kg/h: N = 22 • control: N = 22	Postoperative • Bolus in PACU • Continuous infusion for the first 24 postoperative	Postoperative Hours: First 48	• Pain-free period • NRS scores	• Rescue analgesic requirement • Side effects	Ketamine and dexmedetomidine groups showed the longer pain-free period and the lower pain scores and analgesics consumption
Abrishamkar et al.[78]	N = 45 • ketamine infusion 0.5 mg/kg/h N = 22 • control: N = 23	Postoperative • PACU ketamine infusion • PACU morphine infusion	Postoperative Hours: Every 6 for first 24	• VAS score • Morphine rescue consumption		Ketamine reduced pain intensity and opioid consumption
LOCAL DELIVERY						

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration	Time of Observation	Primary Outcome	Secondary Outcome	Key message
Singh et al.[79]	N=75 • continuous wound infiltration 0.25% levobupivacaine N=25 • continuous epidural infusion 0.25% levobupivacaine N=25 • PCA morphine 1 mg IV N=25	• Starting immediately after the end of the surgery	Postoperative Minutes: 0, 30 Hours: 1, 6, 12, 24, 36, 48	• VAS at rest and on movement • PPS	Postoperative morphine consumption	• Wound infiltration group scored the lowest VAS and PPS values • Morphine consumption was similarly lower in wound infiltration and epidural infusion groups than PCA group
Shin et al.[80]	N=97 • triamcinolone 40 mg: N = 49 • control: N = 48	• Before being taken out from the operating room	Postoperative Weeks: 1, 4, and 26	• Pain intensity (VAS leg and back scores) • ODI score	Length of hospital stay	Steroid group showed lower VAS leg and ODI scores and shorter length of hospital stay

Authors	Number of Patients (N) Tested Drugs / Analgesic Techniques and Doses	Time of Administration	Time of Observation	Primary Outcome	Secondary Outcome	Key message
Ozyilmaz et al.[81]	N = 80 Wound infiltration • levobupivacaine 0.75% 100 mg: n = 20 • tramadol 2mg/kg: n = 20 • TL 2mg/kg + 100mg: N = 20 • Control: N = 20	At end of surgery • levobupivacaine wound infiltration • tramadol wound infiltration	Postoperative Hours: 0, 1, 2, 4, 8, 12, 24	• Postoperative total opioid consumption • VAS scores	Side effects	TL group reduced opioid consumption, VAS score and side effects
Choi et al.[82]	N=38 • bupivacaine 0.1% and hydromorphone 15 µg mL^{-1}: N = 20 • control: N = 18	PACU	Postoperative Hours: First 48	Cumulative opioid consumption		The study group did not effectively reduced opioid consumption
NON-PHARMACOLOGICAL STRATEGIES						
Dubois et al.[83]	N = 59 • Anodal tDCS: N = 20 • Cathodal tDCS: N = 20 • Sham tDCS: N = 19	In PACU 20 minutes of tDCS	Postoperative Hours: 24, 48	• VAS at rest or on movement • PCA morphine consumption		No differences in pain intensity and morphine consumption

Table 5. Comparison of evidence on pain prevention in patients undergoing lumbar spine procedures from 2012 and 2017 SRs.

Evidence from Sharma et al. (2012)	**Evidence from the present SR**
	Preoperative
Gabapentinoids: no overall evidence of benefits	Gabapentinoids are effective, especially when combined to other drugs
NSAIDs: no overall evidence of benefits for most of the drugs tested	NSAIDs efficacy depends on the tested drug (in particular parecoxib and etoricoxib demonstrated to be safe and effective preventive therapies to control pain)
Dexamethasone: no overall evidence of benefits	Dexamethasone reduces pain scores on mobilization and PONV, but not pain at rest and total morphine consumption
Bupivacaine –used for locoregional, epidural anesthesia- is effective, especially when combined to fentanyl or methylprednisolone.	Bupivacaine alone is as effective as levobupivacaine in reducing both opioids consumption and pain scores. Efficacy is further increased when used in association with $MgSO_4$
N/A	Electrical nerve stimulation is suitable for postoperative pain prevention (limited literature)
	Intraoperative
Ketamine reduces opioid consumption after cervical spine procedures (no evidence after lumbar spine procedures)	Ketamine reduces opioid consumption after lumbar spine procedures
Paracetamol is effective when combined with other drugs but has controversial effects when used as a monotherapy	Paracetamol alone is safe and effective
Regional analgesic techniques: no overall evidence of benefits	Locoregional anesthesia techniques are safer, more comfortable and cheaper than systemic analgesia when patients are selected carefully
	Postoperative
Tramadol, administered preoperatively, effectively reduces opioid consumption at 24h	Tramadol, administered postoperatively, safely and effectively prevents postoperative pain
N/A	Dexketoprofen is more effective than paracetamol

Table 1. Diagram of retrieved studies.