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REVIEW ARTICLE

Pain management after complex spine surgery

A systematic review and procedure-specific postoperative pain management recommendations

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BACKGROUND Complex spinal procedures are associated with intense pain in the postoperative period. Adequate perioperative pain management has been shown to correlate with improved outcomes including early ambulation and early discharge.

OBJECTIVES We aimed to evaluate the available literature and develop recommendations for optimal pain management after complex spine surgery.

DESIGN AND DATA SOURCES A systematic review using the PROcedure SPECific postoperative pain managemenT methodology was undertaken. Randomised controlled trials and systematic reviews published in the English language from January 2008 to April 2020 assessing postoperative pain after complex spine surgery using analgesic, anaesthetic or surgical interventions were identified from MEDLINE, EMBASE and Cochrane Databases.

RESULTS Out of 111 eligible studies identified, 31 randomised controlled trials and four systematic reviews met the inclusion criteria. Pre-operative and intra-operative interventions that improved postoperative pain were paracetamol, cyclo-oxygenase (COX)-2 specific-inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs), intravenous ketamine infusion and regional analgesia techniques including epidural analgesia using local anaesthetics with or without opioids. Limited evidence was found for local wound infiltration, intrathecal and epidural opioids, erector spinae plane block, thoracolumbar interfascial plane block, intravenous lidocaine, dexmedetomidine and gabapentin.

CONCLUSIONS The analgesic regimen for complex spine surgery should include pre-operative or intra-operative paracetamol and COX-2 specific inhibitors or NSAIDs, continued postoperatively with opioids used as rescue analgesics. Other recommendations are intra-operative ketamine and epidural analgesia using local anaesthetics with or without opioids. Although there is procedure-specific evidence in favour of intra-operative methadone, it is not recommended as it was compared with shorter-acting opioids and due to its limited safety profile. Furthermore, the methadone studies did not use non-opioid analgesics, which should be the primary analgesics to ultimately reduce overall opioid requirements, including methadone. Further qualitative randomised controlled trials are required to confirm the efficacy and safety of these recommended analgesics on postoperative pain relief.

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RECOMMENDATIONS

1. Systemic analgesia should include paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase (COX)-2 specific inhibitors administered pre-operatively or intra-operatively and continued post-operatively.
2. Intra-operative intravenous low-dose ketamine infusion is recommended.
3. Epidural analgesia with local anaesthetics alone or combined with opioids are recommended.
4. Opioids should be reserved as rescue analgesics in the postoperative period.

WHY WAS THIS GUIDELINE DEVELOPED?
Complex spine surgery is associated with significant postoperative pain. Effective pain control can affect early postoperative rehabilitation. The aim of this guideline is to provide clinicians with an evidence-based approach to pain management after complex spine surgery to improve postoperative outcomes such as early ambulation and discharge.

WHAT OTHER GUIDELINES ARE AVAILABLE ON THIS TOPIC?
Pain management recommendations for spine surgery have been published. However, they were not specific for complex spine surgery. Secondly, the published reviews on postoperative analgesia for major spine surgery do not critically evaluate available evidence similar to the PROSPECT approach.

HOW DOES THIS GUIDELINE DIFFER FROM OTHER GUIDELINES?
The PROSPECT approach to develop guidelines is unique as the available evidence is critically assessed for current clinical relevance and the use of simple, non-opioid analgesics such as paracetamol and non-steroidal anti-inflammatory drugs as baseline analgesics are considered. This approach reports true clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, as well as balancing efficacy and adverse effects.

Introduction

Complex spine surgery can be defined as thoracolumbar spine surgery with instrumentation, laminectomy at three or more levels, or scoliosis surgery. Complex spine surgery can improve long-term pain and quality of life in patients with symptomatic back diseases such as idiopathic scoliosis. However, complex spine surgery is associated with significant postoperative pain.[1] Effective pain control can affect early postoperative rehabilitation and long-term outcomes.[2] Although previous reviews stated that multimodal analgesia should be preferred for spine surgery,[3,4] insufficient evidence did not allow clear recommendations for certain associations of analgesics.

With significant variations in analgesic protocols, a unified approach is necessary to provide standardised interventions on pain reduction. The PROcedure SPECific postoperative pain managemenT (PROSPECT) Working Group is a collaboration of surgeons and anaesthetists working to formulate procedure-specific recommendations for pain management after common but potentially painful operations. The recommendations are based on a procedure-specific systematic review of randomised controlled trials (RCTs) and meta-analyses. The methodology considers clinical practice, efficacy and adverse effects of analgesic techniques.[5]

The aim of this systematic review was to evaluate the available literature on the effects of analgesic, anaesthetic and surgical interventions on pain after complex back surgery. The primary outcomes sought were postoperative pain scores and analgesic requirements.

Materials and methods

Search strategy

A systematic review of literature associated with analgesia after complex spine surgery was conducted according to the PROSPECT Methodology.[6] The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement was used as a guide for this review. Specific to this study, the Embase, MEDLINE and Cochrane Databases were searched for RCTs published between 1 January 2008 and 18 April 2020. A 10-year period for literature review was chosen because it more likely resembles relevant clinical practice, given that rapid changes occur in peri-operative care including surgical techniques. Of note, the project started in 2018.

The search terms are described in the appendix. Selection criteria for studies include RCTs or systematic reviews of analgesic, anaesthetic and operative interventions, published in the English language assessing pain management for patients undergoing complex spinal surgery. A study was also required to measure pain intensity using a numerical linear scoring system, such as the numerical rating scale (NRS) or visual analogue scale (VAS).

In accordance with the PRISMA checklist, a stepwise process was used, which included screening of abstracts of potential articles. This process was undertaken by two reviewers. Any discrepancies between results were discussed within the working group and a decision was made on inclusion or exclusion by consensus.

Table 1 Relationship between quality and source of evidence, levels of evidence and grades of recommendation

Study type	Study quality assessments Statistical analyses and patient follow-up assessment		Allocation concealment	Jadad scores	Additional assessment of overall study quality required to judge LoE	Level of evidence (LoE)	Grade of recommendation (based on overall LoE, considering balance of clinical practice information and evidence)
Systematic review with homogeneous results	N/A		N/A	N/A	N/A	1	A
Randomised controlled trial (RCT)	Statistics reported and >80% follow-up	AND	A	(1 to 5)	N/A	1	A (based on two or more studies or a single large, well designed study)
			OR				
			B	(3 to 5)	N/A		
			OR				
			B	(1 to 2)	Yes		
Randomised controlled trial (RCT)	Statistics not reported or questionable or <80% follow-up	AND/OR	B	(1 to 2)	Yes	2	B (or extrapolation from one procedure-specific LoE 1 study)
			OR				
			C	(1 to 5)	N/A		
			OR				
			D	(1 to 5)	N/A		
Nonsystematic review, cohort study, case study; (e.g. adverse effects)	N/A		N/A			3	C
Clinical practice information (expert opinion); inconsistent evidence	N/A		N/A			4	D

Grades A to D (A, adequate; B, unclear; C, inadequate; D, not used), based on overall level of evidence, considering balance of clinical practice information and evidence. LoE, levels of evidence; NA, not applicable; RCT, randomised controlled trial.

Criteria employed in the assessment of the quality of eligible studies included allocation concealment, numerical (1 to 5) quality scoring system employed by Jadad to assess randomisation, double blinding and the flow of patients, follow-up of greater or less than 80% of participants, and whether the study met the requirements of the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement.

Summary information for each included study was extracted and recorded in data tables. Unless specified otherwise, it was assumed that the pain scores were assessed at rest. The systematic reviews were used to find additional studies via bibliographic screens as well as aid in formulating recommendations.

The included studies were grouped together based upon the analgesic interventions. Within each group, the studies were further placed into subgroups of pre-operative, intra-operative and postoperative interventions.

Pain intensity scores were used as primary outcome measures. We defined a 10% change as clinically important: more than 10 mm on the VAS or 1 point on the NRS. The effectiveness of each intervention for each outcome was evaluated qualitatively, by assessing the number of studies showing a significant difference between treatment arms ($P < 0.05$ as reported in the study publication). A meta-analysis was not performed due to the limited number of studies with homogeneous design and differences in how results were reported, restricting pooled analysis.

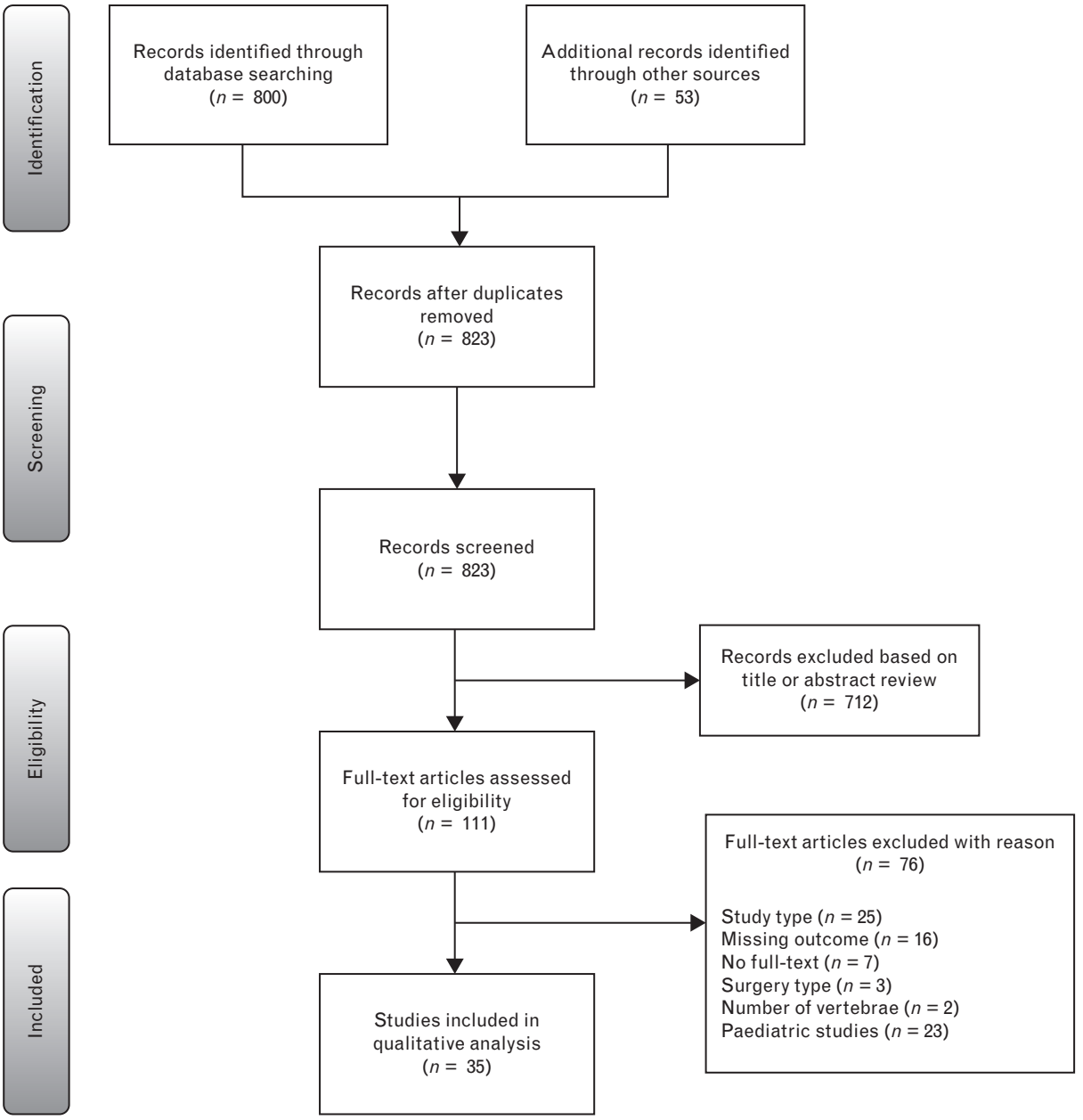
Recommendations are given when at least two congruent studies support an intervention. Recommendations for optimal pain relief are graded A to D according to the overall level of evidence (as determined by the quality of studies included), consistency of evidence and source of evidence (Table 1). The methodology of the PROSPECT group is unique in that it aims to synthesise clinical evidence while considering risks and benefits of interventions, as well as taking into account study design. Specifically, the group seeks to determine the relevance of study interventions in current peri-operative care practice, and critically evaluate the baseline pain treatment.

The proposed recommendations were sent to the PROSPECT Working Group for review and comments. A panel discussion took place, which included several rounds of individual comments followed by round-table discussions. Following a round of discussion during the face-to-face meeting, the Working Group unanimously agreed with the proposed recommendations.

Results

The PRISMA flow chart depicting the search strategy is shown in Fig. 1. We included 31 RCTs and four systematic reviews. The methodological quality assessments of the 31 RCTs included for final qualitative analysis are summarised in Supplementary Table 1, http://links.lww.com/EJA/A489. The characteristics of the included studies are shown in Supplementary Tables 2, http://

Fig. 1 PRISMA flowchart



links.lww.com/EJA/A490 and 3, http://links.lww.com/EJA/A491.

Analgesic interventions

Pre-operative interventions

The benefit of NSAIDs and COX-2 specific inhibitors was investigated in three studies. Pinar *et al.*[7] compared 800 mg of intravenous (i.v.) ibuprofen 30 min prior to incision versus placebo in patients undergoing multilevel posterior lumbar interbody fusion (PLIF) surgery. The VAS scores and morphine consumption were significantly lower in the ibuprofen group in the first 48 h postsurgery. In a placebo-controlled study, Jirarattanaphochai *et al.*[8] compared placebo with the effect of 40 mg parecoxib 30 min before induction of anaesthesia and then every 12 h for 48 h in patients who underwent PLIF surgery. Total morphine requirements over the first 48 h and postoperative pain scores were significantly reduced in the parecoxib group. In a third RCT, the effect of tenoxicam was assessed by Chang *et al.*[9] They compared morphine PCA 1 mg ml^{-1} vs. PCA morphine 1 mg ml^{-1} + tenoxicam 0.6 mg ml^{-1} vs. a loading dose of 20 mg tenoxicam 30 min before wound closure and a morphine + tenoxicam PCA. The PCA devices were programmed to deliver a loading dose of 0.05 ml kg^{-1}, a continuous infusion of 0.005 ml kg^{-1} h^{-1} and a bolus dose of

0.02 ml kg^{-1} with a 10 min lock-out period. The pain scores were not significantly different, but morphine consumption was reduced in both tenoxicam groups. Two meta-analyses support the use of NSAIDs. Zhang *et al.*[10] included eight studies in a meta-analysis, with a total of 408 patients, comparing NSAIDs with placebo after lumbar spine surgery. The mean difference of pain scores between NSAIDs and placebo groups was significant during the first 24 h. The meta-analysis by Jirarattanaphochai *et al.*[11] included 17 RCTs and 789 patients, and compared pain scores in patients who underwent lumbar spine surgery and received either NSAIDs in addition to opioids, or opioids alone. The NSAIDs group experienced significantly less pain and had lower morphine consumption. No significant difference was found regarding side effects.

Kim *et al.*[12] compared placebo with two doses of oral pregabalin (75 or 150 mg), 1 h before and 12 h after surgery. Differences in pain scores were not significant, but cumulative morphine i.v. PCA consumption was reduced in the pregabalin 150 mg group after 24 h. The meta-analysis by Yu Lin *et al.*[13] demonstrated that, compared with placebo, both gabapentin and pregabalin significantly reduced the postoperative narcotic consumption and postoperative pain scores.

Intra-operative interventions

Murphy *et al.*[14] found a positive analgesic effect of methadone 0.2 mg kg^{-1} at the start of surgery compared to hydromorphone 2 mg at surgical closure for spinal fusions. Median hydromorphone consumption was significantly reduced in the methadone group and pain scores were lower. This effect was also seen by Gottschalk *et al.*[15] when they compared methadone 0.2 mg kg^{-1} before surgical incision to a sufentanil bolus and continuous infusion in patients undergoing multilevel thoracolumbar spine surgery: following methadone, there was a reduced postoperative opioid requirement by 50% at 48 and 72 h after surgery. Pain sores were also lower by approximately 50% in the methadone group at 48 h postsurgery.

A placebo-controlled trial from Farag *et al.* showed that i.v. lidocaine infusion (2 mg kg^{-1} h^{-1}) reduced morphine requirements in the first 48 h, but the differences in mean VRS pain scores between the two groups were less than 10%.[16] Ibrahim *et al.*[17] also compared i.v. lidocaine infusion (2 mg kg^{-1} loading and 3 mg kg^{-1} h^{-1} infusion) with placebo. Lidocaine significantly reduced the pain scores in the first 48 h postsurgery, the morphine consumption in the first 24 h and the time to the first request for additional analgesia.

The efficacy of ketamine was investigated in six studies.[18–23] None of the studies had adequate basic analgesia.[6] Bolus doses ranged from high (0.5 mg kg^{-1})[18,20–21,23] to low (0.1 to 0.2 mg kg^{-1})[19,22] and continuous infusion doses ranged from high (up to 10 μg kg^{-1} min^{-1})[18–20] to low (1 to 2 μg kg^{-1} min^{-1}).[19,21–23] In patients undergoing major lumbar spinal surgery, Loftus *et al.*[20] demonstrated morphine-sparing effects of intra-operative high-dose ketamine, with decreased pain scores postoperatively and at 6 weeks. Similarly, in patients undergoing lumbar posterior fusions, low-dose ketamine continued for 24 h postoperatively had analgesic, but not opioid-sparing effects.[22] Two studies investigated ketamine against the backdrop of intra-operative remifentanil-based analgesia. Hadi *et al.*[19] found that patients undergoing scoliosis surgery under remifentanil maintenance benefited from ketamine with lower pain scores, reduced morphine consumption and prolonged time to first rescue analgesic. Similarly, Pacreu *et al.*[21] demonstrated methadone-sparing effects when ketamine infusion was superimposed on a remifentanil maintenance regimen. In chronic pain patients undergoing major spine surgery, Nielsen *et al.*[18] reported opioid-sparing effects, and reduced opioid-induced sedation, of high-dose ketamine. Sumramaniam *et al.*[23] did not observe additional analgesic benefit of ketamine in patients with pre-operative opioid intake when epidural bupivacaine was used as basic analgesia. Side effects were described by three studies[18,20,23]: two of these studies found no increase in side effects with ketamine[20,23] and one study found decreased sedation in the ketamine group.[18] We conclude that intra-operative ketamine has a significant opioid-sparing effect in patients undergoing complex spinal surgery, especially in chronic pain patients.

Dexmedetomidine infusion (0.01 to 0.02 μg kg^{-1} min^{-1}) was compared with remifentanil infusion (0.01 to 0.2 μg kg^{-1} min^{-1}) in patients undergoing PLIF surgery by Hwang *et al.*[24] The pain scores in the dexmedetomidine group were significantly lower than those in the remifentanil group at the immediate and late postoperative periods (48 h after surgery). The dexmedetomidine group had lower hydromorphone requirements for 48 h after surgery except at time of discharge from PACU. Naik *et al.*[25] reported that dexmedetomidine (1 μg kg^{-1} loading dose followed by 0.5 μg kg^{-1} h^{-1} infusion) reduced the intra-operative, but not the postoperative, opioid consumption when compared with placebo in patients undergoing thoracic and/or lumbar spine surgery at three levels or more. There were no differences in pain scores at 24 h postoperatively. A systematic review from Tsaouisi *et al.*,[26] with 913 patients included, showed that dexmedetomidine was sedative and allowed an opioid-sparing effect intra-operatively. No definite conclusion could be drawn due to the considerable heterogeneity of the available data.

In a study by Jabbour *et al.*,[27] patients given magnesium (50 mg kg^{-1}) and ketamine (0.2 mg kg^{-1} bolus with an infusion of 0.15 mg kg^{-1} h^{-1}) showed a significantly lower average cumulative morphine consumption compared with ketamine alone until 48 h postsurgery. VAS scores

were not significantly different, but quality of sleep and patient satisfaction were better in the magnesium group during the first postoperative night.

Kim *et al.*[28] compared a multimodal analgesia protocol with celecoxib 200 mg, pregabalin 75 mg, extended-release oxycodone 10 mg, acetaminophen 500 mg and IV-PCA morphine with IV-PCA with morphine alone. Pain scores were lower in the multimodal pain management group at all time points (until seven days postoperatively) and opioid consumption was reduced for 48 h after spinal fusion surgery.

A RCT from Maheshwari *et al.*[29] also investigated the use of a multimodal analgesic pathway in patients at high risk of postoperative pain undergoing multilevel spine surgery. They compared pre-operative acetaminophen and gabapentin, combined with intra-operative infusions of lidocaine and ketamine, with placebo. All patients received epidural analgesia or local wound infiltration. Pain scores, quality of recovery and opioid consumption in the multimodal analgesic group were not superior to the placebo group.

Regional analgesic interventions

The efficacy of epidural infusions was assessed in seven studies. Two RCTs, Park *et al.*[30] and Gessler *et al.*,[31] compared the epidural infusion of 0.2% ropivacaine with IV-PCA opioids. Pain scores were significantly lower in the epidural groups and lower doses of postoperative opioids were required. Two studies compared the combined effects of neuraxial local anaesthetics and opioids with IV-PCA opioid. Prasartritha *et al.*[32] found that VAS scores in the epidural groups were less than in the i.v. morphine group up to 48 h postoperatively. On the contrary, Kluba *et al.*[33] concluded that epidural 0.2% ropivacaine and sufentanil did not lower postoperative pain scores and i.v. sufentanil rescue doses compared with an IV-PCA with piritramide. Epidural bupivacaine 0.125% infusion was compared with 0.2% ropivacaine infusion by Pham-Dang *et al.*[34] in patients with degenerative or idiopathic scoliosis undergoing multilevel spinal fusion surgery. The VAS scores on mobilisation were lower within the bupivacaine group. Wenk *et al.*[35] compared an intra-operative epidural infusion of 0.175% bupivacaine and sufentanil 0.5 $\mu g\,kg^{-1}$ with an epidural infusion started after neurological examination on the PACU. They found significantly decreased pain scores in the intra-operative group. Patients in the postoperative group received more intra-operative opioids and postoperative piritramide rescue doses. Early postoperative neurological examination was feasible in all patients in both groups. There was only one placebo-controlled trial by Choi *et al.*[36] comparing PCEA with 0.1% bupivacaine and hydromorphone with a PCEA 0.9% saline infusion. The mean cumulative opioid consumption was less in the active treatment group, but the difference was statistically not significant. This was the only study that did not favour postoperative epidural techniques over i.v. analgesics.

In a RCT from Offley *et al.*,[37] low (10 mg) and high (15 mg) doses of extended-release epidural morphine were compared. Pain scores in the first 48 h were not significantly different, neither was the total postoperative analgesic consumption.

Ziegeler *et al.*[38] compared the effect of 0.4 mg intrathecal morphine over placebo after posterior lumbar interbody surgery. There was a significantly lower cumulative piritramide requirement in the intrathecal morphine group without any serious increase of opioid-associated side effects. VAS scores were only significantly lower in the morphine group at 4 and 8 h after surgery.

Three studies investigated the effects of local anaesthetic techniques. In a placebo-controlled trial, Greze *et al.*[39] compared 0.2% ropivacaine ($8\,ml\,h^{-1}$) local wound infusion through a catheter with normal saline after posterior spinal fusion surgery. No additional analgesia or opioid reduction was provided with continuous wound infiltration. Xu *et al.*[40] compared a continuous local wound infusion of 0.33% ropivacaine with flurbiprofen and pentazocine infusion following thoracolumbar spinal surgery. There were no differences in pain scores and rescue analgesia. Chen *et al.*[41] compared the pre-operative placement of a bilateral single shot, ultrasound-guided, lateral thoracolumbar interfascial plane (TLIP) block with a 30 ml bolus of 0.375% ropivacaine at each side to placebo in patients undergoing lumbar spinal fusion surgery. Opioid and anaesthetic consumption in the peri-operative period decreased significantly in the TLIP group compared with the control group. The VAS scores in the TLIP group were lower at 12, 24 and 36 h postoperatively.

Discussion

This systematic review included 31 RCTs with the majority of studies determined to be of high quality based on the CONSORT statement. The strength of our systematic review stems from the PROSPECT methodology, which goes beyond making recommendations based on the simple statistical analysis of the available evidence. On the basis of available evidence and the PROSPECT approach to providing recommendations, combinations of paracetamol and a NSAID or a COX-2 specific inhibitor are recommended pre-operatively or intra-operatively, and they should be continued postoperatively, unless contraindicated.[42–46] Fixed-time interval analgesia has been shown to provide superior pain relief in comparison with on-demand analgesia.[47,48] For the intra-operative period, we recommend a low-dose i.v. ketamine infusion. Epidural infusion of local anaesthetic alone or combined with opioids are recommended. Opioids may be used as postoperative rescue analgesic.

The analgesic benefits and opioid-sparing effects of simple analgesics such as paracetamol and NSAIDs are well described.[49–52] Earlier literature suggests concerns that NSAIDs inhibit osteogenesis and increase the rate of

nonunion.[53] However, more recent studies have reported that NSAIDs appears to have a dose-dependent and duration-dependent effect on fusion rates and their short-term (< 2 weeks) postoperative use is well tolerated.[54,55] Therefore, short-term use of low-dose NSAIDs around the time of spinal fusion is well tolerated and recommended and does not interfere with osteogenesis or increase the rate of nonunion.[56] Patients undergoing spinal surgery in association with peri-operative NSAIDs do not have an increased risk of bleeding.[57–59]

Intra-operative ketamine infusion is recommended due to its significant opioid-sparing effect, especially in opiate-dependent chronic pain patients.[20–23] Negative psychotropic side effects, such as postoperative hallucinations and nightmares, are demonstrated with increasing ketamine doses compared with placebo in the elderly (≥60 years old). This was demonstrated in the PODCAST trial.[60] There is insufficient evidence that supports the continuation of ketamine infusion in the postoperative period. It is reasonable to suggest that postoperative ketamine infusion could increase the risk of ketamine-related adverse drug effects.[61] We conclude that low-dose ketamine infusions (bolus of 0.2 to 0.5 mg kg^{-1} and continuous infusion of 2 μg kg^{-1} min^{-1}) administered during the intra-operative period improve peri-operative analgesia compared with conventional intra-operative opioid management,[62] but the ketamine infusions should not be continued in the postoperative period.[62]

The use of epidural analgesia with local anaesthetic, with or without opioids, is recommended as a component of multimodal analgesia.[30–32,34] Epidural analgesia with opioids alone is not recommended due to lack of evidence. The epidural catheter should be placed under direct visualisation by the surgeon at the end of surgery. Concerns about the use of epidural catheters are loss of sensory function and motor weakness and the possibility of delayed diagnosis of neurological complications. Therefore, low concentrations of local anaesthetics should be used. There were no major adverse effects reported in the literature.[35] Epidural analgesia is recommended, but its use should be individualised.

Methadone given intra-operatively was superior to hydromorphone and sufentanil for lowering postoperative pain scores and opioid requirement.[14,15] However, the benefits of methadone may be related to the duration of action because it was compared with shorter-acting opioids. Furthermore, the methadone studies did not use nonopioid analgesics, which should be the primary analgesics to ultimately reduce overall opioid requirements, including methadone. Importantly, the safety of methadone in the peri-operative period remains a concern. As reported by Dunn *et al.*,[63] moderate respiratory depressions, defined as eight or less breaths per minute, can occur following a one-time methadone dose of 0.14 ± 0.07 mg kg^{-1} in patients scheduled for elective spinal fusion of two or more levels, although the incidence of severe side effects such as reintubation, hypoxaemia and death were not statistically significant.[64] Therefore, i.v. methadone is not recommended currently.

The intra-operative infusion of dexmedetomidine is not recommended due to limited procedure-specific evidence, although intra-operative dexmedetomidine infusion has been reported to reduce peri-operative opioid use and lower postoperative pain scores.[24,26] When compared with remifentanil, dexmedetomidine showed fewer side effects such as hypotension, shivering, postoperative nausea and vomiting, and bradycardia.[65]

Gabapentinoids are not recommended due to limited evidence, although they have an established role in the management of neuropathic pain, which may be a concern in complex spine surgery.[66–68] Current evidence does not support the routine use of gabapentinoids as part of a multimodal analgesic regimen in complex spine surgery, and there are concerns regarding side effects such as sedation and respiratory depression.[69–72]

Two studies assessed the benefit of intra-operative i.v. lidocaine.[16,17] Only one showed a clinically meaningful reduction in pain scores.[17] In the study by Farag *et al.*,[16] the difference in pain scores was less than 10%, and not clinically relevant according to the Prospect methodology. Thus, lidocaine infusion is not recommended due to conflicting evidence.

Intrathecal opioid administration is not recommended due to limited evidence.[38] Although intrathecal treatments may be a promising therapeutic option, further studies are needed in adult populations to make proper recommendations.[73] Wound infiltration has been shown to reduce postoperative pain after laminectomy and microdisectomy, but not for complex spine surgery in adults.[74] Also, data were insufficient to recommend the use of lateral thoracolumbar interfascial plane blocks bilaterally, or a bilateral erector spinae plane block although results from recent publications are promising.[75]

Various multimodal analgesic approaches have been proposed. Kim *et al.*[28] found lower pain scores and less opioid consumption. There was no significant superiority of multimodal analgesia in the RCT by Maheshwari *et al.*[29] But there are some biases, as patients received epidural analgesia or local wound infiltration and, in some cases, acetaminophen was continued postoperatively and gabapentin was continued at the discretion of the surgery team.

There are currently no studies in the literature that directly assess the effectiveness of muscle relaxants and nonbenzodiazepines.[76] We did not find evidence to promote one surgical technique over another.[77]

The limitations of this review are related to those of the included studies. There was considerable heterogeneity across the studies, such as the type of surgery. The

Table 2 Overall recommendations for peri-operative pain management in patients undergoing complex spine surgery

Pre-operative and intra-operative recommendations
Oral or i.v. paracetamol (Grade D)
Oral or i.v. NSAIDs / COX-2 specific inhibitors (Grade A)
i.v. Ketamine infusion (Grade A)
Postoperative recommendations
Epidural analgesia with local anaesthetics and with or without opioids (Grade B)
Oral or i.v. paracetamol (Grade D)
Oral or i.v. NSAIDs/COX-2 specific inhibitors (Grade A)
Opioids as rescue medication (Grade D)

COX, cyclooxygenase; i.v., intravenous.

Table 3 Analgesic interventions that are not recommended for pain management in patients undergoing complex spine surgery

Intervention	Reason for not recommending
Oral gabapentinoids	Significant risk of adverse effects
i.v. methadone	Significant risk of adverse effects
Erector spinae plane block	Limited procedure-specific evidence
Thoracolumbar interfascial plane block	Limited procedure-specific evidence
i.v. lidocaine	Limited procedure-specific evidence
i.v. glucocorticoid	Lack of procedure-specific evidence
i.v. dexmedetomidine	Limited procedure-specific evidence
Epidural opioids	Limited procedure-specific evidence
Intrathecal opioids	Limited procedure-specific evidence
Local anaesthetic wound infusion	Limited and inconsistent procedure-specific evidence
i.v. magnesium	Limited procedure-specific evidence
Surgical interventions	Limited procedure-specific evidence

i.v., intravenous.

number of vertebrae involved differed between studies and also differed in some populations within a single RCT. There was also heterogeneity in the drug doses administered, the methods of drug administration and the sample sizes. Not all drugs in the RCTs were compared with a multimodal analgesic regimen. One of the major gaps in the literature is the lack of studies assessing analgesic interventions for different types of pain (e.g. neuropathic or radicular pain), or specific patient populations (e.g. opioid-dependent patients or those with major psychiatric disorders).

In summary, major spine surgery with multilevel instrumentation is painful, requiring significant opioid use. This review has identified the analgesic regimen for optimal pain management after complex spine surgery (Table 2). We also identified analgesic interventions that are not recommended (Table 3). We recommend multimodal pain management including pre- or intra-operative paracetamol and NSAIDs or COX-2 specific inhibitors and continued in the postoperative period. Intra-operatively, we recommend the use of a low-dose ketamine infusion. Further, we suggest the use of an epidural catheter, placed under direct visualisation by the surgeon, and postoperative infusion with local anaesthetic alone or combined with opioids. As rescue analgesia postoperatively, we recommend the use of opioids. Well designed procedure-specific studies are necessary to assess the clinical benefits of the recommendations.

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Assistance with the study: EA and PW* equally contributed to this manuscript, and therefore share first authorship. PW and EA conducted the literature search and analysed the retrieved articles with AS, JG and HB. PW and EA wrote the manuscript, which was reviewed and edited by all the other authors who have also participated in the PROSPECT Working Group meetings using the Delphi method and in defining the methodology of the PROSPECT group.

Appendix: PROSPECT working group**: E. Albrecht, H. Beloeil, F. Bonnet, A. Delbos, S. Freys, G. P. Joshi, H. Kehlet, P. Lavand'homme, P. Lirk, D. Lobo, E. Pogatzki-Zahn, N. Rawal, J. Raeder, A. Sauter, S. Schug, M. van de Velde

Search terms: complex spine surgery OR scoliosis surgery OR thoracolumbar instrumentation OR thoracolumbar spine surgery OR spinal fusion AND pain OR pains OR pain management OR postoperative pain OR postoperative pain OR analgesia OR anaesthesia OR VAS OR visual analogue OR VRS OR verbal rating scale OR NRS OR numerical rating scale OR pain rating OR epidural OR neuraxial OR intrathecal OR paravertebral OR spinal OR infiltration OR nerve block OR neural block OR paravertebral block OR field block OR ilioinguinal block OR transversus abdominis plane block OR TAP block OR NSAID OR nonsteroidal anti-inflammatory OR nonsteroidal anti-inflammatory OR cyclo-oxygenase (COX)-2 OR paracetamol OR acetaminophen OR clonidine OR opioid OR ketamine OR corticosteroid OR gabapentin OR pregabalin.

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Conflicts of interest: Philipp Lirk has no conflicts of interest to declare. Girish P. Joshi has received honoraria from Baxter and Pacira Pharmaceuticals. Francis Bonnet has received honoraria from Pfizer, The Medicine Company, Abbott France and Nordic Pharma France. Henrik Kehlet has received honoraria from Pfizer and Grunenthal. The Anaesthesiology Unit of the University of Western Australia, but not Stephan Schug privately, has received research and travel funding and speaking and consulting honoraria from bioCSL, Eli Lilly, Indivior, iX Biopharma and Pfizer. Narinder Rawal has received honoraria from Baxter and Sintetica. Marc Van de Velde received honoraria from Sintetica, Grunenthal, Vifor Pharma, MSD, Nordic Pharma, Janssen Pharmaceuticals, Heron Therapeutics and Aquettant. Hélène Beloeil has received honoraria from Orion, Abbvie and Aspen.

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