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Intraoperative epidural analgesia for pain relief after lumbar decompressive spine surgery: A systematic review and meta-analysis

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ABSTRACT

Introduction: During lumbar decompressive spine surgery, the epidural space is easily accessible. This intraoperative situation allows surgeons to apply an epidural bolus of analgesia at the end of the surgical procedure. In literature, several papers about the methods and effectiveness of delivering local analgesia during lumbar decompressive spine surgery have been published.

Research question: This systematic review and meta-analysis aims to summaries the current literature on the effectiveness and safety of intraoperative epidural analgesia in lumbar decompressive surgery, delivered as a bolus.

Material and method: A systematic search was conducted according to the PRISMA guidelines. Inclusion criteria were randomized controlled trials or comparative cohort studies of patients aged 18 years or older who underwent decompressive lumbar spine surgery. Nonsteroidal epidural analgesia had to be administered as a bolus, intraoperatively, as an adjunct to standard analgesia therapy. Primary outcome measures were reduction in postoperative pain scores, analgesics consumption and length of hospital stay. Secondary outcomes were adverse events.

Results: Eight studies evaluating the effectiveness of intraoperative epidural analgesia were included. Seven studies reported statistically significant reductions in postoperative VAS-pain scores. Six studies reported a statistically significant decrease in postoperative analgesics consumption. Four studies reported on the length of hospital stay, with no statistically significant difference between study groups.

Discussion and conclusion: This systematic review and meta-analysis suggests that additional intraoperative epidural nonsteroidal analgesia, delivered as a bolus, can reduce postoperative pain and postoperative analgesics consumption in patients undergoing decompressive spinal surgery. Further well-powered research is needed to bolster the evidence.

1. Introduction

In lumbar spine surgery, laminectomy and interlaminar decompression belong to the procedures most often performed. The goal of these procedures is alleviating symptoms, such as pain, numbness and weakness of legs and buttocks, caused by compression of the cauda equina due to narrowing of the spinal canal in the degenerating spine (Overdevest et al., 2015). There is a rise in the incidence of degenerative spinal disorders with the current aging population, possibly leading to an increase of lumbar decompressive surgery (O'Lynnger et al., 2015).

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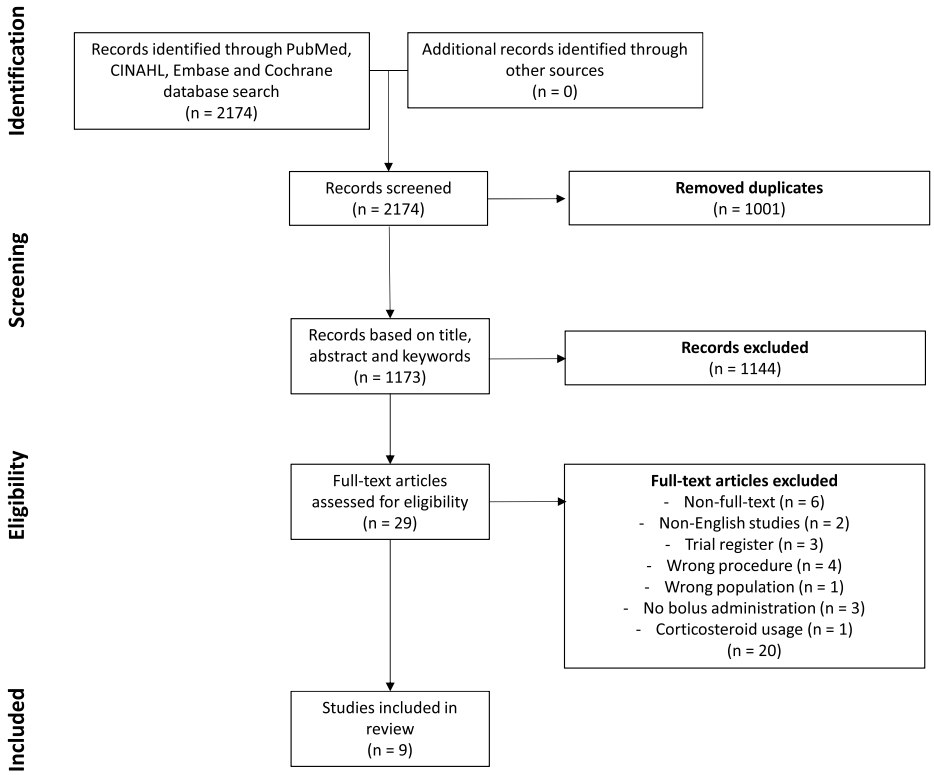

Fig. 1. PRISMA flowchart.

Table 1
Study characteristics.

Study characteristics						Quality	
Author/year	Study design	Total patients	Epidural analgesia	Control	Follow-up	Risk of bias	Level of evidence
Guilfoyle et al. (2012)	Randomized prospective comparative study	60	Catheter, fentanyl	None	48 h	Some concerns	2
McNeill et al. (1995)	Randomized prospective comparative study	28	Catheter, morphine	Placebo	48 h	Some concerns	2
Bourke et al. (1992)	Randomized double blind study	20	Topical, morphine	Placebo with IM morphine	24 h	Some concerns	2
Giri et al. (2018)	Prospective randomized comparative study	40	Gelfoam, nalbuphine	Placebo	48 h	Some concerns	2
Hassanein et al. (2016)	Prospective, randomized, double-blinded trial	50	Gelfoam, morphine	Directly instilled, morphine	48 h	Some concerns	2
Kundra et al. (2014)	Prospective, randomized, double-blinded study	150	Gelfoam, morphine	Directly instilled, morphine	48 h	Low	2
Mishra et al. (2004)	Prospective, randomized and double-blinded study	60	Sponge, morphine	Placebo	24 h	Low	2
McNeill et al. (1995)	Double blind, randomized, controlled trial	50	Gefloam, bupivacaine	Placebo	24 h	Low	2

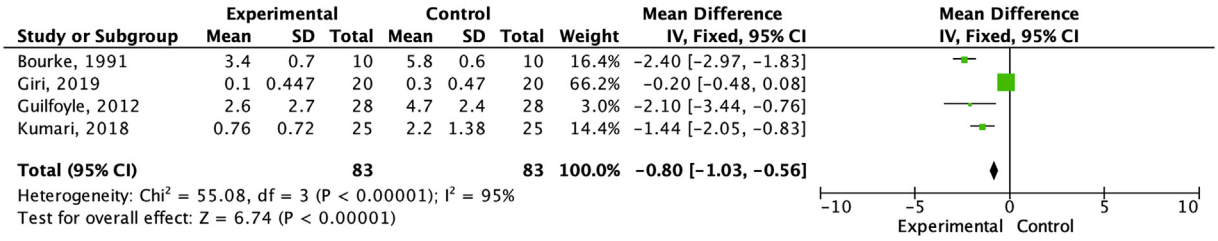

Fig. 2. Forest plot comparison between experimental and control for the outcome of VAS-pain score at recovery CI: confidence interval.

Following decompressive surgery, patients receive oral or intravenous analgesia, frequently opioids. Often, consumption of opioids is accompanied with side effects, that potentially impact length of hospital stay (Kurteva et al., 2021). Moreover, patients tend to continue the use of

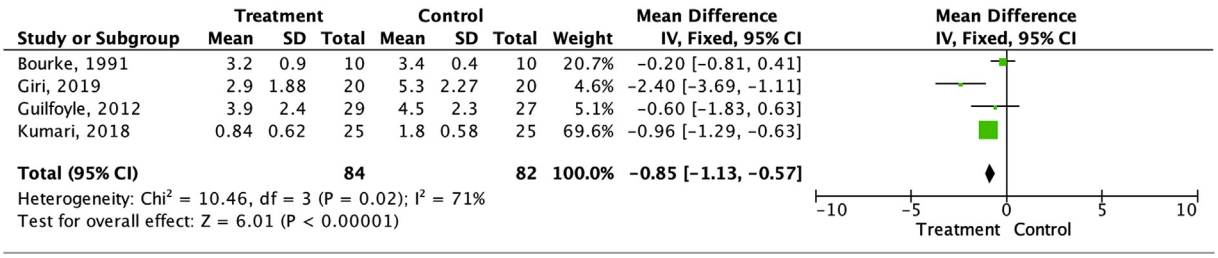

Fig. 3. Forest plot comparison between experimental and control for the outcome of VAS-pain score at 24 h postoperatively CI: confidence interval.

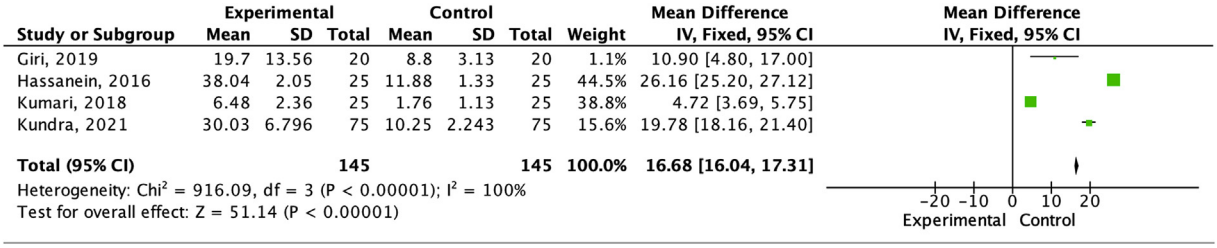

Fig. 4. Forest plot comparison between experimental and control for the outcome of first analgesic requirement CI: confidence interval.

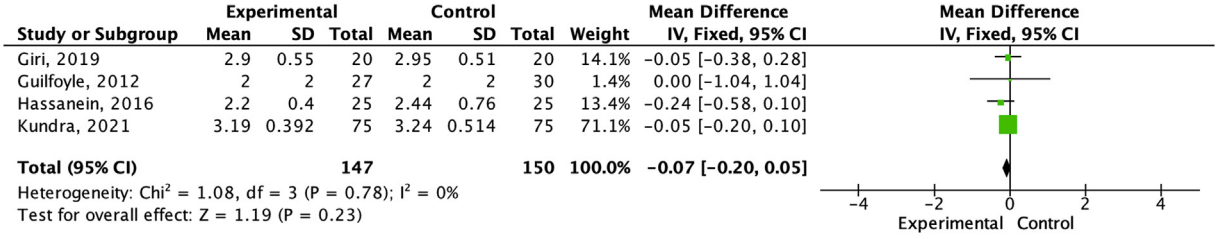

Fig. 5. Forest plot comparison between experimental and control for the outcome of duration of hospital stay CI: confidence interval.

postoperative prescribed analgesics, including opioids, because of their addictive nature (Connolly et al., 2017; Hah et al., 2017). This may increase risk of societal problems related to chronic opioid use (Lipman and Webster, 2015; Dasgupta et al., 2018). Therefore, safe and (cost-)effective alternatives in postoperative pain management in lumbar decompressive surgery are needed.

When completing decompressive surgery, the epidural space becomes easily accessible, this situation allows surgeons to apply an epidural bolus of analgesia, thus can be a safe and effective method for pain relief. In literature, multiple analgesics for administration in the epidural space, including anaesthetics, opioids or steroids are employed (Wilson-Smith et al., 2018; Ranguis et al., 2010; Waqas et al., 2017). Also, various administering methods for local epidural analgesics are available, including catheters, sponges and pastes (Lumbar discectomy, 1995; Jamjoom and Jamjoom, 2014). Recently, a systematic review and meta-analysis suggests that intraoperative epidural administration of steroids could reduce postoperative pain and the use of postoperative opioid analgesics in patients undergoing lumbar spine surgery (Wilson-Smith et al., 2018; Ranguis et al., 2010; Akinduro et al., 2015). However, there are a number of concerns regarding steroid use, most importantly the increased risk of surgical site infection, including epidural abscesses (Lowell et al., 2000; Aljabi et al., 2015). Non-steroidal analgesics may have the potential to be effective in reducing postoperative pain, without the increased risk of infections.

Presently, there is no consensus regarding the effectiveness and safety of intraoperative epidural application of analgesics. The aim of this systematic review and meta-analysis is to summarise the current literature on effectiveness and safety of intraoperative epidural nonsteroidal analgesia in lumbar decompressive surgery, delivered as a bolus.

2. Methods

This systematic review and meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Shamseer et al., 2015). The study protocol has been registered in the PROSPERO-database (registration number: CRD42021236964) prior to the start of the study.

2.1. Eligibility criteria

The review was limited to studies published in the English language and all selected studies had to be published as full text articles. The last search was run in January 2021. Inclusion criteria were randomized controlled trials (RCT's) or comparative cohort studies of patients aged 18 years or older who underwent decompressive lumbar spine surgery (laminectomy or interlaminar decompression). Epidural analgesia had to be administered as a bolus, intraoperatively in addition to standard pain control. Studies that used steroids as comedication were excluded. The included studies needed to provide sufficient data relating to all or part of the following outcome criteria: assessment scores for pain at defined time points in the postoperative period, extent of additional postoperative analgesics consumption, duration of hospital stay and adverse events.

2.2. Search

Potentially eligible studies were identified by searching the databases PubMed, CINAHL, EMBASE and Cochrane, using a combination or part combination of the following terms: spinal stenosis, laminectomy, interlaminar decompression, lumbar vertebrae, epidural analgesia,

Table 2
Summary of results of included studies.

Treatment group						Control group					
Author/year	VAS at recovery	VAS 24 h postoperatively	Hospital stay (days)	Time to first analgesic requirement(hours)	Total postoperative analgesic consumption	VAS at recovery	VAS 24 h postoperatively	Hospital stay (days)	Time to first analgesic requirement(hours)	Total postoperative analgesic consumption	**P-value**
Guilfoyle et al. (2012)	2.6	3.9	2	–	–	4.7	4.5	2	–	–	**p1: 0.003** p2: 0.362 p3: 0.763 p4: p5:
McNeill et al. (1995)	–	–	–	–	18.5 ml morphine	–	–	–	–	34.4 ml morphine	p1: p2: p3: p4: **p5: < 0.05**
Bourke et al. (1992)	3.4	3.2	–	–	14.0 mg morphine	5.8	3.4	–	–	39.4 mg morphine	**p1: ≤ 0.05** **p2: ≥ 0.05** p3: p4: **p5: < 0.05**
Giri et al. (2018)	0.1	2.9	2.9	19.7	150 mg IV diclofenac	0.3	5.3	2.95	8.8	277.5 mg IV diclofenac	p1: 0.088 **p2: 0.00041** p3: 0.383 **p4: 0.0006** **p5: < 0.00001**
Hassanein et al. (2016)	–	–	2.2	38.04	57 mg IV diclofenac	–	–	2.44	11.88	192 mg IV diclofenac	p1: p2: p3: 0.32 **p4: 0.0001** **p5: 0.0001**
Kundra et al. (2014)	–	–	3.19	30.03	–	–	–	3.24	10.25	–	p1: p2: p3: 0.205 **p4: 0.000** p5:
Mishra et al. (2004)	–	–	–	–	–	–	–	–	–	–	p1: p2: p3: p4: p5:
Kumari et al. (2018)	0.76	0.84	–	6.84	120 mg tramadol	2.2	1.8	–	1.76	280 mg tramadol	**p1: < 0.001** **p2: < 0.001** p3: **p4: < 0.001** **p5: < 0.001**

p1: Difference between VAS-pain score at recovery between treatment group versus control group.
p2: Difference between VAS-pain score at 24 h postoperatively between treatment group versus control group.
p3: Difference between duration of hospital stay between treatment group versus control group.
p4: Difference between time to first analgesic requirement in hours between treatment group versus control group.
p5: Difference between total postoperative analgesic consumption between treatment group versus control group.

epidural injection, epidural anaesthesia, sponge, paste, opioid analgesia, opioids, pain, postoperative, pain management, length of stay, hospital stay. A detailed search description is included as additional file 1 in the appendix. After the initial search, all duplicates were removed and articles were analysed by screening the title and abstract by two researchers (SH and AL), independently using 'Rayyan' – a web and mobile application (Ouzzani et al., 2016). Full text screening of the potential eligible studies was performed by the same authors independently. Potential inter-reviewer disagreements were resolved by consensus.

2.3. Quality assessment

With regard to quality assessment, the bias assessment tool Risk of Bias 2 (revised) of the Cochrane Handbook for Systematic Reviews of Interventions was consulted (Sterne et al., 2019). Two researchers (SH and AL) independently evaluated selected studies based on five different domains and scored the criteria with "low", "some concerns", or "high" risk of bias. Levels of evidence were determined with the Oxford Centre for Evidence-based Medicine Levels of Evidence tool (2011). (OCEBM Levels of Evidence Working GroupDurieux et al., 2011).

2.4. Statistical analysis

Statistical analyses of study data were performed using Review Manager (RevMan v5.3, Cochrane Collaboration, Oxford, UK) (Review Manager (RevMan) [Computer program], 2014). Calculations were performed using both random effects model and fixed effect model, and expressed as mean difference and a 95% confidence interval. The I^2-statistic was computed to assess between-study heterogeneity. Heterogeneity was regarded as low with an $I^2 \leq 50\%$, moderate with an $50\% < I^2 < 75\%$ and high with an $I^2 \geq 75\%$. P-values ≤ 0.05 were regarded as statistically significant.

3. Results

3.1. Study selection

The initial systematic search (January 2021) in the databases yielded 2174 articles, of which 1175 remained after removal of duplicates. A total of 29 studies were selected for full text reading. Twenty-one studies were rejected for final analysis because of various reasons; six studies were not available for full text reading (Joughin and Dupuis, 1988; Shah, 1997; Rechtine and Love, 1986; Perez Diaz et al., 2013; Grichnik et al., 1994; Rechtine and Reinert, 1984); two were non-English (Lee et al., 2009; S, 1996); three were trial registered protocols (NL8030, 2019; Isrctn, 2007; NCT01847339, 2013); four studies performed discectomies or spinal fusion surgery (Wilartratsami et al., 2014; Rainov et al., 1996; Chong et al., 1994; Diaz et al., 2012); one performed microscopic decompression (Alican et al., 2020); one study was performed on dogs (Barker et al., 2013); three studies did not administer an epidural bolus of analgesia, but continuing infusion postoperatively (Ibrahim et al., 1986; Jellish et al., 2003; Niyogi et al., 2011); and one study used corticosteroids as part of their analgesic paste (Hurlbert et al., 1999). Finally, eight studies were included in this systematic review (Bourke et al., 1992; Guilfoyle et al., 2012; Hassanein et al., 2016; Kumari et al., 2018; Kundra et al., 2014; McNeill et al., 1995; Mishra et al., 2004). PRISMA flowchart detailing the search is shown in Fig. 1.

3.2. Study characteristics

Study characteristics of the eight included papers are outlined in Table 1. All included studies were randomized controlled trials. Four were placebo-controlled trials (Kumari et al., 2018; McNeill et al., 1995; Mishra et al., 2004). The other studies used different control groups. Bourke et al. (1992) compared an epidural application of 3 mg morphine + 3 ml saline intramuscular in the intervention group with epidural application of 6 ml saline + 3 mg morphine intramuscularly in the control group (Bourke et al., 1992). Hassanein et al. (2016) and Kundra et al. (2014) compared effectiveness of a gelfoam soaked in 5 mg of morphine with morphine directly instilled over the intact epidural space. Guilfoyle et al. (2012) applied their opioids to the epidural space using an epidural catheter, and compared this intervention to a control group that received standard care.

Four studies added additional epidural medication: corticosteroids (Kumari et al., 2018; McNeill et al., 1995), ketamine (Giri et al., 2018) and hydroxyetyl starch (volume expander) 6% (Hassanein et al., 2016). McNeill et al. (1995) used two subgroups; one group underwent decompressive spine surgery for spinal stenosis while the other group underwent discectomy. For the purpose of this review and to maintain homogeneity across included studies, we solely focused on the effectiveness of opioids as an adjunct in decompressive spine surgery.

Publication years ranged from 1992 to 2021. Studies were conducted in the USA, United Kingdom, India and Egypt.

3.3. Quality assessment

Results of the qualitative analysis of included studies are outlined in Table 1. Complete methodological quality assessment can be found in additional file 2 in the appendix. Risk of bias was graded 'low' for three studies (Kundra et al. (2014), Mishra et al. (2004) and Kumari et al. (2018) and 'some concerns' for the other five (Bourke et al., 1992; Guilfoyle et al., 2012; Hassanein et al., 2016; McNeill et al., 1995). Level of evidence was 2 for all studies.

3.4. Results of studies

A table summarising the results of the included studies regarding postoperative pain, postoperative analgesics consumption and duration of hospital stay is presented in Table 2. A narrative summary on pain, analgesics consumption, duration of hospital stay and adverse events follows here.

3.5. Postoperative pain scores

Seven studies reported on postoperative pain measured using the Visual Analogue Scale (VAS) with a total of 430 subjects (Bourke et al., 1992; Guilfoyle et al., 2012; Hassanein et al., 2016; Kumari et al., 2018; Kundra et al., 2014; Mishra et al., 2004). All studies reported on early and late VAS-pain score ranging from recovery score to 24 h postoperatively. VAS-pain score at recovery ranged from 0.1 to 3.4 in the treatment group versus 0.3 to 5.8 in controls; in five studies this difference was statistically significant. VAS-pain score at 4 h postoperatively was reported in four studies and ranged from 0.1 to 0.25 in the treatment group versus 0.25 to 1.85 in controls (Hassanein et al., 2016; Kumari et al., 2018; Kundra et al., 2014). VAS-pain score at 6 h postoperatively was reported in three studies and ranged from 0.1 to 0.25 in the treatment group versus 0.1 to 3.2 in controls (Kumari et al., 2018; Kundra et al., 2014). VAS-pain score at 24 h postoperatively was reported in four studies and ranged from 2.9 to 3.9 in the treatment group and from 3.4 to 5.3 in the control group. (Bourke et al., 1992; Guilfoyle et al., 2012; Kumari et al., 2018). Meta-analysis revealed statistically significant differences between VAS-pain score at recovery and 24 h postoperatively, in favour of the treatment groups. The mean difference of VAS-pain score at recovery was −0.80 points (95% CI [−1.03, −0.56], $p < 0.00001$) and at 24 h postoperatively −0.85 points (95% CI [−1.13, −0.57], $p < 0.00001$). Heterogeneity was high and moderate with an I^2 of 95% and 71%, respectively. Both forest plots are included as Figs. 2 and 3 in the figure legend. Two of the seven studies had a low risk of bias (Kumari et al., 2018; Kundra et al., 2014).

3.6. Use of postoperative analgesics

Six studies reported on consumption of postoperative analgesics with a total population of 338 (Bourke et al., 1992; Hassanein et al., 2016; Kumari et al., 2018; Kundra et al., 2014; McNeill et al., 1995). Five reported 'total postoperative analgesics consumption' which was statistically significantly lower in the treatment groups (Bourke et al., 1992; Hassanein et al., 2016; Kumari et al., 2018; McNeill et al., 1995). McNeill et al. (1995)Kundra et al. (2014) and Bourke et al. (1992) administrated additional morphine when needed. Giri et al. (2018) and Hassanein et al. (2016) administrated additional diclofenac intravenous (IV) and Kumari et al. (2018) used tramadol for additional pain control. McNeill et al. (1995) and Bourke et al. (1992) reported a difference of 15.9 ml and 25.4 mg of morphine, respectively, Hassanein et al. (2016) and Giri et al. (2018) reported a difference of 135 mg and 127 mg of diclofenac IV, respectively and Kumari et al. (2018) reported a difference of 160 mg of tramadol, all in favour of the treatment groups.

Four studies reported on time to first analgesic requirement after surgery, which was significantly longer in the treatment groups (6.84–38.04 h) than in the control groups (1.76–11.88 h) (Hassanein et al., 2016; Kumari et al., 2018; Kundra et al., 2014). Meta-analysis revealed a statistically significant difference between first analgesic requirement, in favour of the treatment groups. The mean difference in first analgesic requirement was 16.68 h (95% CI [16.04, 17.31], $p < 0.00001$). Heterogeneity was high with an I^2 of 100%. Forest plot is included as Fig. 4 in the figure legend. Two of the seven studies had a low risk of bias (Kumari et al., 2018; Kundra et al., 2014).

3.7. Duration of hospital stay

Four studies reported on the duration of hospital stay with a total study population of 300 (Guilfoyle et al., 2012; Hassanein et al., 2016; Kundra et al., 2014). The mean hospital stay in days ranged from 2.00 to 3.19 in the treatment group and from 2.00 to 3.24 in the control group. This difference in favour of the treatment group reached no level of statistical significance in any of the included studies. Meta-analysis revealed no statistically significant difference in duration of hospital stay between study groups. Heterogeneity was low with an I^2 of 0%. Forest plot is included as Fig. 5 in the figure legend. One of the five studies had a low risk of bias (Kundra et al., 2014).

3.8. Adverse effects

Detailed results of adverse events are outlined in additional file 3 in the appendix. Adverse events were reported in all nine studies. Data from the study by McNeill et al. (1995) was not implemented in the qualitative analysis, as it did not differentiate between decompressive spine surgery or discectomy surgery in their report of adverse events. The most frequently reported adverse events were pruritis, nausea/vomiting, urinary retention and respiratory depression. Pruritis occurred in 0%–30.66% in the treatment group and in 0%–38.66% in the control group. It occurred significantly more frequent in the treatment group in one paper that used nalbuphine as epidural analgesia (2018). It is unclear if pruritis was localized or generalized. Nausea/vomiting occurred in 0%–45% in the treatment group and in 0%–44% in the control group, and occurred significantly more frequent in the treatment group in one paper that used bupivacaine as epidural analgesia (Kumari et al., 2018). Urinary retention occurred 0%–40% in the treatment group and in 0%–28% in the control group, and occurred significantly more frequent in the treatment group in two studies (Kundra et al., 2014). Both studies used opioids as epidural analgesia; morphine and nalbuphine.

4. Discussion

The aim of this systematic review and meta-analysis was to summaries the current literature on the effectiveness and safety of additional intraoperative epidural nonsteroidal analgesia in lumbar decompressive surgery, delivered as a bolus. Eight papers were selected. The methodological quality was assessed and details on level of postoperative pain, consumption of analgesics, duration of hospital stay and adverse events were extracted from these papers. The most important finding of this review is that additional epidural analgesia is effective in decreasing postoperative pain and postoperative analgesics consumption.

4.1. Postoperative pain

Statistically significantly lower VAS-pain scores were observed in the treatment groups compared to the control groups at recovery, 4 and 6 h after the procedure. In some studies, significant differences were still measurable at 24 h postoperatively (Hassanein et al., 2016; Kumari et al., 2018). The mean difference in VAS-pain score between treatment and control groups at recovery is 1.6 (1.7 vs 3.3) and at 24 h postoperatively 1.1 (2.7 vs 3.8). The question is how to interpret these differences; literature on minimal clinically important difference (MCID) in VAS-pain score is inconclusive. Most studies on postoperative pain control suggest that a difference of 3 points can be considered as clinically important(-Myles et al., 2017; Martin et al., 2013; Tashjian et al., 2009). However, it is recommended that MCID's should be considered context-specific and take into account the level of baseline pain (Olsen et al., 2017). Level of postoperative VAS-pain is relatively low in both groups, hence the VAS-pain reduction seems minimal. Nonetheless, the difference between treatment and control group is almost 50% at recovery and almost 33% at 24 h postoperatively. Furthermore, in most of the included studies, patients in the treatment groups consumed less postoperative analgesics, including morphine. When both groups consumed the same number of analgesics, the differences between VAS-pain scores would potentially be larger, in favour of the treatment group. Mean VAS-pain scores in the treatment group remain below 3 (1.7 at 2 h and 2.7 at 24 h postoperatively) which reflects as acceptable postoperative pain control (Myles et al., 2017). The increase in pain score from 2 to 24 h postoperatively can be explained by the fact that the analgesic effect of the bolus has worn off. Three studies found no significant difference in VAS-pain score between treatment and control groups at recovery. This may has been caused as a consequence of general anaesthesia on overall pain perception (Hassanein et al., 2016; Kundra et al., 2014). Details regarding induction of general anaesthesia was not available in sufficient studies to explore potential differences. In two of these studies, statistically significant differences in favour of the treatment group became apparent 2 h later (Hassanein et al., 2016). Kundra et al. (2014) was the only study that reported no statically significant differences in VAS-pain score between the study groups in the first 24 h postoperatively. Meta-analysis of included studies also revealed statistically significant difference in VAS-pain scores at recovery and 24 h postoperatively. However, these differences did not reach MCID and the heterogeneity of VAS-pain difference at recovery was high and moderate at 24 h postoperatively.

4.2. Postoperative analgesics consumption

In terms of postoperative analgesics consumption, total consumption and time to first analgesic requirement was observed. All studies that reported on total analgesics consumption reported that statistically significantly less additional analgesics were administered to patients in the treatment groups. In three of these studies this concerned opioids, with significant differences in total consumption between treatment and control group; 15.9 ml and 25.4 mg of morphine and 160 mg of tramadol. Because of the variety of analgesics employed as additional pain control, quantitative analysis on total postoperative analgesics consumption was not possible.

Time to first analgesic requirement after surgery was also significantly longer in the treatment groups and meta-analysis revealed a statistically significant difference between first analgesic requirement in

hours. Although heterogeneity was high in this analysis, a trend can be observed in favour of the treatment groups. The above mentioned findings are important, as morphine consumption should be limited as much as possible after surgery, given its known side effects and growing societal problems related to chronic opioid use, especially in surgical patients (Lipman and Webster, 2015; Dasgupta et al., 2018). It remains a challenge for clinicians to manage acute pain and still minimize the risks of persistent opioid use following surgery (Hah et al., 2017).

4.3. Duration of hospital stay

In terms of duration of hospital stay, no study reported a statistically significant difference between study groups. The mean duration of hospital stay ranged from 2.0 to 3.24 days, comparable to current literature (Basques et al., 1976). Meta-analysis also revealed no statistically significant difference in duration of hospital stay between study groups with a low heterogeneity. To consistently match the other outcome measurements in this systematic review, we would expect a shorter hospital stay in the treatment groups. Perhaps, larger sample sizes are needed to demonstrate statistically significant differences.

4.4. Adverse events

Adverse events were reported in all papers. Quantitative analysis was not implemented to summaries adverse events across included studies, as insufficient data was provided and the methods to collect these events were not detailed. The rate of adverse events reported in the study groups were reasonably consistent among the included studies. A statistically significant difference in occurrence of urinary retention in the treatment group was mentioned in two studies (Kundra et al., 2014). Both studies used a gelfoam soaked in opioids as additional analgesics agent. Epidural opioids are known to increase the risk for urinary retention (Baldini et al., 2009). Nonetheless, the other six included studies in this systematic review reported no statistical significantly higher incidence of urinary retention in the treatment groups, including the studies that used a catheter to deliver the bolus of analgesia (Guilfoyle et al., 2012; McNeill et al., 1995). Kumari et al. (2018) used levobupivacaine as additional analgesic agent and reported no cases of urinary retention. Potentially, non-opioid analgetic agents such as bupivacaine are the key to bypass adverse events linked to epidural opioid administration. No severe adverse events, such as respiratory depression, were reported in the included studies. Morphine consumption can contribute to several side effects, including constipation, nausea and sedation (Glare et al., 2006). Although several studies reported a statistically significant difference in morphine consumption postoperatively between treatment and control groups, none of these studies reported statistically significantly more adverse events, like these, in the control groups (Bourke et al., 1992; Kumari et al., 2018; McNeill et al., 1995). Finally, surgical site infection, an adverse event occasionally reported when steroids are administered epidurally, was not reported in the included studies.

4.5. Techniques of epidural drug delivery

As mentioned before, several methods of delivering local or regional analgesia during decompressive spine surgery have been described in literature. In this systematic review and meta-analysis, four different methods are described (catheter, sponge, gelfoam and direct application). A catheter and a sponge/gelfoam have their own advantages and disadvantages. Using a catheter creates the possibility to deliver the analgesia more rostrally in the spinal canal resulting in a potentially immediate and more effective pain reduction (Loo et al., 2009; Panyakhamlerd, 2012). Indeed, the one study that used a catheter and reported on VAS-pain score at recovery reported a statistically significant difference, while not all studies that used a sponge/gelfoam to deliver the analgesia reported this difference to be statistically significant (Giri et al., 2018; Guilfoyle et al., 2012). The advantage of using a sponge/gelfoam lies in their slow-release properties, with the possibility to deliver analgesia for a longer period (Lumbar discectomy, 1995). These expectations are confirmed in this systematic review, as three studies using a sponge/gelfoam reported statistically significantly lower VAS-pain scores up until 24 h postoperatively and the catheter study by Guilfoyle et al. (2012) did not (Hassanein et al., 2016; Kumari et al., 2018). Further research is needed to make undisputed conclusions on differences between these routes of administration. According to the results outlined in this review both routes of administration seem effective in reducing postoperative pain. However, the statistically significant differences in adverse events between study groups were reported only in studies that used a gelfoam. Noteworthy, all gelfoam studies used opioids as additional analgesia, potentially explaining this occurrence. Finally, a slow-releasing analgesic sponge is more expensive than a catheter and not universally available (Hassanein et al., 2016; Offley et al., 2013).

4.6. Other spinal procedures

Studies on intraoperative epidural analgesia for other spinal procedures, like discectomies and microscopic decompressive spine surgery suggest similar levels of effectiveness and also report reduction of VAS-pain scores and analgesics consumption (Alican et al., 2020; Bourke et al., 1992; Waikakul and Chumniprasas, 1992). Instrumented spinal surgery and spinal fusion surgery are procedures associated with more postoperative pain, compared to laminectomies and discectomies (Reynolds et al., 2013; Mino et al., 2017). Therefore these procedures also seem eligible for intraoperative epidural analgesia as an adjunct to standard pain control. However, currently there is no literature available that describes the use of intraoperative epidural analgesia in the form of a bolus for this type of surgery. Only three studies describe the effectiveness of continuous epidural analgesia for postoperative pain control in patients undergoing spinal fusion surgery, with moderate effect on pain scores (Sucato et al., 2005; Kranke et al., 2015; Blumenthal et al., 2006). Milbrandt et al. (2009) have shown that the administration of a single preoperative intrathecal morphine injection is as effective in reducing pain until 24 h postoperative as continuous infusion through an epidural catheter in spinal fusion surgery.

4.7. Limitations

This systematic review and meta-analysis is bound by several important limitations. First, literature is heterogeneous regarding outcome measurements, surgical technique, timing and method of pain assessment and type and dosage of the analgesia used. We aimed to limit the heterogeneity by maintaining strict inclusion criteria, such as nonsteroidal analgesics, but heterogeneity remained high. Partially, this was expected as we included several ways of analgesics administration during surgery. Quantitative analysis revealed moderate to high heterogeneity in most outcome measures; making it more difficult to draw solid conclusions.

In addition, the number of studies included was small, primarily because of the scarcity of comparative studies that met our inclusion criteria. Due to this, the number of patients within each group was small, potentially limiting the level of evidence. One of the reasons limited data were available is because significantly more research is conducted on the effectiveness of steroidal analgesics than nonsteroidal analgesics. Nonetheless, the effectiveness, and moreover, the safety of epidural steroids in lumbar spine surgery is still limited (Ranguis et al., 2010; Akinduro et al., 2015). There are still a number of concerns regarding steroid use, most importantly the increased risk of surgical site infection and delayed healing of the wound (Lowell et al., 2000; Aljabi et al., 2015). Currently, epidural steroids application is still considered a matter of debate in decompressive spine surgery.

Overall study quality was reasonable. Most of the included studies were labelled as “some concerns” regarding to confounding, as reported in the risk of bias analysis. This was expected as most studies were well-

designed randomized comparative cohort studies. Finally, two of the included studies were performed in 1991 and 1995. Making assumptions based on old data, like these, represents a strong limitation. The study by Mishra et al. (2004) was performed in 2004 and the remaining included studies in 2012 or later. As a result of the above-mentioned limitations, the outcomes of this review and meta-analysis should be interpreted with caution.

5. Conclusions

This is the first systematic review and meta-analysis to evaluate effectiveness of intraoperative epidural nonsteroidal analgesia, as an adjunct to standard postoperative pain control, on reduction of postoperative pain, analgesics consumption, length of hospital stay and adverse events. The existing literature provided limited and heterogenous data. However, based on the assessment of included studies, differences were demonstrated regarding pain reduction and postoperative analgesics consumption in favour of the treatment groups.

Although it seems that there is place for epidural intraoperative analgesia as an adjunct in decompressive lumbar spine surgery, significantly more data are required from well-powered RCT's with validated outcome measures. In this perspective, a RCT is planned at our institute to determine whether intraoperative epidural analgesia is superior to placebo in reducing postoperative pain in patients undergoing decompressive lumbar spine surgery, and to determine whether opioid use is significantly lower in the treatment group during the first 48 h after surgery.

Authors' contribution

SH: concept & design, drafting protocol, AL: concept & design, drafting protocol, KR: concept & design, critical revision of protocol, supervision, HvS: concept & design, critical revision of protocol, supervision, WvH: critical revision of protocol, supervision, MR: critical revision of protocol, supervision, DH: critical revision of protocol, supervision, SK: critical revision of protocol, supervision, IC: concept & design, critical revision of protocol, supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2021.100306.

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