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SYSTEMATIC REVIEW

Efficacy and Safety of Dexmedetomidine as an Adjuvant in Epidural Analgesia and Anesthesia: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background and Objective Several clinical trials have examined and indicated the usefulness of epidural dexmedetomidine therapy. However, there has been no systematic analysis of the findings of these trials to date. We undertook this systematic review and meta-analysis to investigate the efficacy and safety of epidural dexmedetomidine adjunctive therapy in different surgical procedures.

Materials and Methods We searched EMBASE, PubMed, the Cochrane Library, and the Clinical Trials.gov database to identify randomized controlled trials investigating the effects of epidural dexmedetomidine adjunctive therapy. The article search was conducted without language or date restrictions. The date of the last search was 27 July 2016. The mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CIs) were calculated for continuous variables, and risk ratios (RRs) were presented for dichotomous outcomes. Heterogeneity was assessed using τ^2, χ^2 and I^2 analyses.

Results Twelve randomized controlled trials were included in the final analysis. Compared with the control treatment, epidural dexmedetomidine administration prolonged the duration of analgesia ($P < 0.0001$), reduced the time to sensory block ($P = 0.002$), decreased the requirement for rescue analgesia ($P < 0.00001$) and achieved a significantly higher sedation score ($P < 0.0001$). Although dexmedetomidine adjunctive therapy did not affect mean arterial pressure ($P = 0.33$), systolic blood pressure ($P = 0.32$) or diastolic blood pressure ($P = 0.28$), it significantly lowered heart rate ($P = 0.0009$). Symptoms indicative of hypotension and bradycardia events were more common in the dexmedetomidine group, but the difference in the overall risk of hypotension and bradycardia was statistically insignificant ($P > 0.05$) in comparison with that reported for the control therapies. Furthermore, dexmedetomidine effectively reduced post-operative pain ($P = 0.03$), whilst the occurrence of other side effects, such as pruritus, dizziness, dry mouth, nausea and vomiting did not differ significantly from that reported for the control therapies, except the risk of shivering was significantly higher with control therapies ($P = 0.03$).

Conclusion This systematic review and meta-analysis demonstrates that dexmedetomidine as an adjuvant in epidural procedures is generally safe and well tolerated. Furthermore, dexmedetomidine acted synergistically and provided an improved sedation and analgesic profile.

Key Points

Dexmedetomidine is an α_2 adrenoreceptor agonist that has highly selective sedative, analgesic, and sympatholytic effects.

The aim of this study was to conduct a systematic review and meta-analysis of randomized controlled trials to determine whether the addition of dexmedetomidine to background epidural anesthesia provides better efficacy and safety results in patients undergoing different surgeries as compared to those with similar background therapy.

A decrease in intra-operative heart rate was associated with addition of epidural dexmedetomidine, but it did not affect the mean arterial, systolic and diastolic blood pressures.

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1 Introduction

Dexmedetomidine is a relatively recent addition to the toolset of anesthesiologists. Initially described in 1993 [1], dexmedetomidine was approved by the US Food and Drug Administration (FDA) in 1999 for short-term sedation in intensive care units (ICUs). However, the usefulness of dexmedetomidine for non-intubated patients led to its approval by several countries for longer-term sedation [2].

Dexmedetomidine, an imidazole, is an α_2 adrenoreceptor agonist [3, 4] that has highly selective sedative, analgesic, and sympatholytic effects [5–7]. Dexmedetomidine-induced sedation mirrors natural sleep [8] and has been used in a variety of settings, including in procedural sedation [9], ICU sedation, pediatric procedures [10], negating the cardiovascular effects of illicit drugs [11, 12], and veterinary medicine [13].

The advantages of dexmedetomidine include reductions in cognitive dysfunction [14], respiratory depression [3, 5], ICU stays [15, 16], and financial costs [17]. Furthermore, it appears that dexmedetomidine can act synergistically when used in conjunction with other analgesic or anesthetic medications and can reduce their side effects [18–20]. However, it has been suggested that dexmedetomidine reduces both heart rate [21] and blood pressure [5].

Given the frequency and advantages of epidural surgical procedures, we present the findings of a systematic review and meta-analysis for the addition of dexmedetomidine to other anesthetic medications during epidural procedures in different surgeries.

2 Materials and Methods

The present systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

2.1 Picots

Our a priori PICOTS was as follows: population—adults undergoing surgery or another procedure using epidural anesthesia; intervention—dexmedetomidine, in addition to background anesthetic medications; comparator—the same background anesthesia without dexmedetomidine; outcomes—the duration of analgesia, time to sensory block, sedation score, requirement for rescue analgesia, heart rate, blood pressure, pain score, side effects; time—intra-operative period or immediate (24 h) post-operative period; setting—an in-patient, surgical, epidural setting.

2.2 Data Sources and Search Criteria

We searched EMBASE, PubMed, the Cochrane Library, and Clinical Trials.gov database using the following search terms (Precedex OR Dexdor OR Dexdomitor OR Sileo OR Dexmedetomidine) AND epidural AND ("randomized controlled trial"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR randomi*ed[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]). We did not apply date or language restrictions. The date of the last search was 27 July 2016.

2.3 Eligibility Criteria for Study Inclusion

We included studies that met the following inclusion criteria: (1) the study was a randomized controlled trial, (2) the study applied dexmedetomidine along with background anesthesia in an epidural setting, where the comparator was the same background anesthesia at the same dose, (3) dexmedetomidine was included in the epidural medication (not administered intravenously or intramuscularly), (4) the study included at least one of the aforementioned outcomes (duration of analgesia, time to sensory block, sedation score, requirement for rescue analgesia, heart rate, blood pressure, and side effects).

2.4 Study Selection and Quality Assessment

The initial search resulted in 118 abstracts (see Fig. 1). The abstracts were loaded into Eppi-Reviewer 4 [23], which removed duplicate articles. Two authors independently coded the remaining 68 abstracts according to the following criteria: Dexmedetomidine as an intervention, epidural setting, human study, appropriate control, clinical trial, and adult study. After the inclusion criteria were applied, 42 abstracts were included in the full-text analysis. Full-text articles were retained in the analysis if they met the following criteria: Dexmedetomidine as an intervention, epidural setting, human study, appropriate control, clinical trial, adult study, dexmedetomidine as an adjunct to an existing therapy, and the inclusion of at least one of the a priori outcomes. After these further inclusion criteria were applied, 12 studies were included in the final analysis.

Study quality was determined according to the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [24]. The criteria analyzed were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome

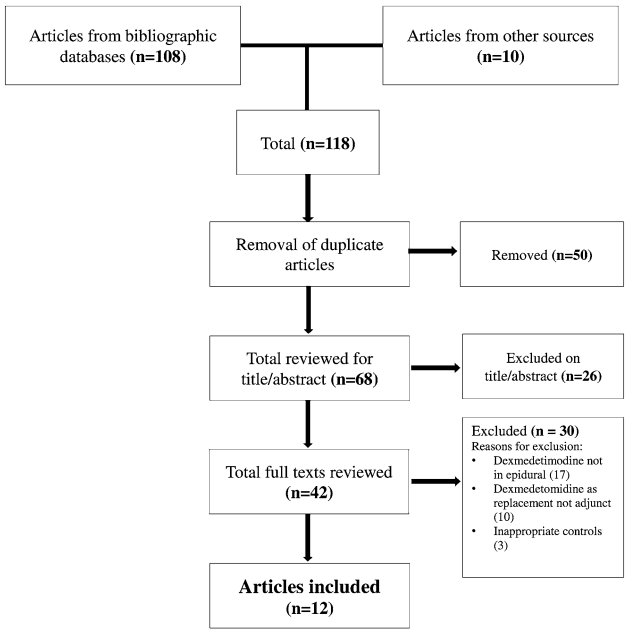

Fig. 1 Flow diagram of included studies

assessment, incomplete outcome data, selective reporting, and other bias.

2.5 Data Extraction

Standardized data extraction was performed using electronic forms. Data extraction was carried out by one author and reviewed by a second author. The extracted data included the study type, time, interventions, number of study participants, and the trial outcomes defined earlier. Means and standard deviations or standard errors were extracted for each outcome. Standard errors were converted to standard deviations.

2.6 Statistical Analysis

The statistical analyses were performed using the Review Manager 5.3 program from the Cochrane Collaboration [25]. MD or SMD with 95% CIs were calculated for continuous variables. It was necessary to use SMD for several outcomes, as the studies frequently differed in the scales used (e.g. sedation score), the definitions of outcomes (e.g. time to sensory block), or the type of intervention (e.g. rescue analgesia) [26]. As such, standardized mean differences are reported without units. The RR and its 95% CI were used for dichotomous outcomes. Meta-analysis was performed using the inverse variance method and a random effects model. Heterogeneity was measured using τ^2, χ^2, and I^2 analyses. Statistical significance for outcomes and heterogeneity was set at $P < 0.05$.

3 Results

3.1 Search Results and Study Characteristics

Twelve studies (comprising 660 patients) were included in the meta-analysis (Table 1). The surgical settings included thoracic [27], caesarean section [28–30], hysterectomy [31], lower limb [32–34], lower limb or lower abdominal [20, 35], lumbosacral spine [19], and nephrectomy [36]. The background anesthesia used in these studies included bupivacaine, bupivacaine plus fentanyl, bupivacaine plus neostigmine, ropivacaine, and levobupivacaine. The studies were small (between 20 and 50 patients per study arm). Eight studies reported the duration of analgesia [20, 28, 29, 31–34, 36]; the time to sensory block was reported in nine studies [20, 28–33, 35, 36]; sedation scores were also presented in nine studies [20, 27–30, 32–34, 36]; the requirement for rescue analgesia was assessed in six studies [27, 30–32, 35, 36]; and heart rate was also documented in seven studies [19, 20, 28, 32–34, 36]. Mean arterial pressure was measured in three studies [19, 20, 28], whereas systolic and diastolic blood pressure were measured in five studies [19, 32–34, 36]. Four studies reported post-operative pain scores [27, 32, 34, 36] and five studies reported side effects [20, 28–30, 32].

3.2 Quality of Included Studies

As stated earlier, the quality of the studies and risk of bias were evaluated using the methods recommended by the Cochrane Collaboration [24]. The quality of the included studies was mixed (Fig. 2). Although most studies had a low risk of attrition or reporting or other bias, most of the reports did not explicitly state whether allocation concealment was undertaken, or whether outcome assessors were blinded. However, given that most of the studies were double blind to participants and personnel, and no attrition took place, we feel that the overall quality of the studies was acceptable.

3.3 Duration of Analgesia

A meta-analysis of eight studies involving 410 participants demonstrated that the addition of dexmedetomidine to existing epidural therapy provided a longer duration of analgesia compared to that reported for the control group (Fig. 3). The standardized mean difference noted between both interventions was 3.50 (95% CI 1.86–5.13, $P < 0.0001$) with a heterogeneity $(I)^2$ of 97%.

3.4 Time to Sensory Block

This analysis included nine studies with a total of 510 study participants. We found that the addition of

Table 1 Studies included in the meta-analysis

References	Surgery	Patients (intervention/control)	Intervention		Control		Study design
			Drug	Dose	Drug	Dose	
Elhakim et al. [27]	Thoracic surgery with one-lung ventilation	25/25	Bupivacaine + dexmedetomidine	Bupivacaine 0.5% 30–l40 mg, Dexmedetomidine 1 μg/kg	Bupivacaine	Bupivacaine 0.5% 30–40 mg	RD, SB (blinded to anesthesiologist), PCS
Han et al. [28]	Caesarean section	20/20	Ropivacaine + dexmedetomidine	Ropivacaine 15 ml 0.75%, Dexmedetomidine 1 μg/kg	Ropivacaine + fentanyl	Ropivacaine 15 ml 0.75%,	RD, PCS, OL
Hanoura et al. [29]	Caesarean section	25/25	Bupivacaine + dexmedetomidine + fentanyl	Bupivacaine 10 ml 0.25%, Fentanyl 100 μg, Dexmedetomidine 1 μg/kg	Bupivacaine + fentanyl	Bupivacaine 10 ml 0.25%, Fentanyl: 100 μg	RD, SB (blinded to surgeons), PCS,
Joy et al. [35]	Lower limb/lower abdominal	30/30	Ropivacaine + dexmedetomidine	Ropivacaine 15 ml 0.5% 75 mg, Dexmedetomidine 1 μg/kg	Ropivacaine	Ropivacaine 15 ml 0.5% 75 mg	RD, DB, PCS
Kalappa et al. [19]	Lumbosacral spine	30/30	Ropivacaine + dexmedetomidine	Ropivacaine 20 ml 0.2%, Dexmedetomidine 1 μg/kg	Ropivacaine	Ropivacaine 20 ml 0.2%	RD, DB, PCS
Karhade et al. [31]	Hysterectomy	30/30	Bupivacaine + dexmedetomidine	Bupivacaine 15–l20 ml 0.5%, Dexmedetomidine 0.5 μg/kg	Bupivacaine	Bupivacaine 15–20 ml 0.5%	RD, NB, PCS
Kaur et al. [32]	Lower limb	50/50	Ropivacaine + dexmedetomidine	Ropivacaine 0.75% 150 mg, Dexmedetomidine 1 μg/kg	Ropivacaine	Ropivacaine 0.75% 150 mg	RD, DB, PCS
Sathyanarayana et al. [33]	Lower limb	20/20	Levobupivacaine + dexmedetomidine	Levobupivacaine 15 ml, Dexmedetomidine 0.5 μg/kg	Levobupivacaine	Levobupivacaine 15 ml	RD, NB, PCS
Sharma et al. [34]	Lower limb	20/20	Bupivacaine + dexmedetomidine + neostigmine	Bupivacaine 6 ml 0.25%, Dexmedetomidine 1 μg/kg	Bupivacaine + neostigmine	Bupivacaine 6 ml 0.25%	RD, DB, PCS
Soni et al. [20]	Lower limb/lower abdominal	20/20	Ropivacaine + dexmedetomidine	Ropivacaine 19 ml 0.75%, Dexmedetomidine 1.5 μg/kg	Ropivacaine	Ropivacaine 19 ml 0.75%	RD, DB, PCS
Yousef et al. [30]	Caesarean section	40/40	Bupivacaine + fentanyl + dexmedetomidine	Bupivacaine 10 ml 0.25%, Fentanyl 50 μg, Dexmedetomidine 0.5 μg/kg	Bupivacaine + fentanyl	Bupivacaine 10 ml 0.25%, Fentanyl 50 μg	RD, DB, PCS
Zeng et al. [36]	Nephrectomy	20/20	Levobupivacaine + dexmedetomidine	Levobupivacaine 12 ml 0.75%, Dexmedetomidine 0.5 μg/kg	Levobupivacaine	Levobupivacaine 12 ml 0.75%	RD, DB, PCS

RD randomized, *SB* single blind, *DB* double blind, *NB* not blinded, *PCS* placebo-controlled study, *OL* open label

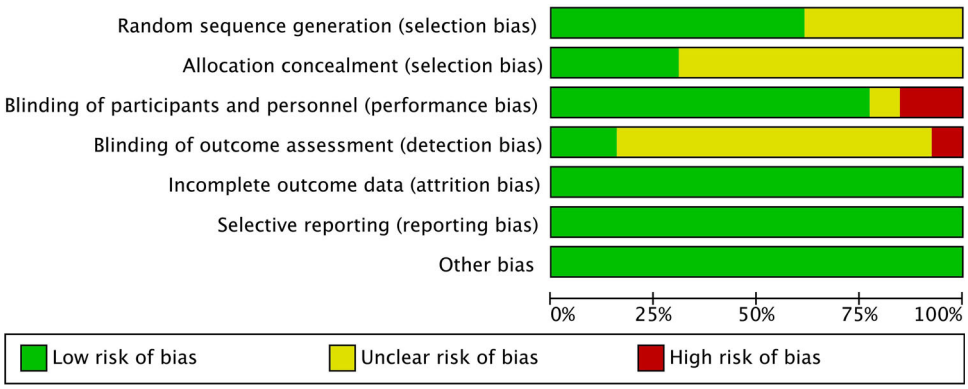

Fig. 2 Risk of bias in included studies. Low risk of bias is represented by *green*, unclear risk by *yellow*, and high risk by *red*

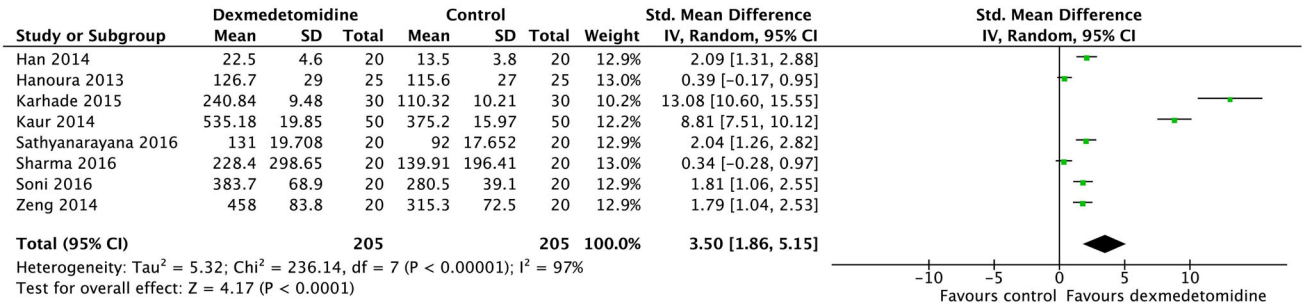

Fig. 3 Meta-analysis of the duration of analgesia (minutes) in studies using epidural dexmedetomidine as an adjunct to background therapy. The standardized mean differences (95% CIs) are presented for each study

dexmedetomidine to background therapy significantly reduced the time to sensory block (Fig. 4). A reduction in time to sensory block was seen in eight of the nine included studies, resulting in an overall difference of −1.13 (95% CI −1.84 to −0.43, $P = 0.002$) with a heterogeneity $(I)^2$ of 92%.

3.5 Sedation Score

A meta-analysis of nine studies involving 480 participants demonstrated that dexmedetomidine added to existing therapy significantly improved the sedation score of patients undergoing procedures with epidural anesthesia (Fig. 5). The resulting difference in sedation score was 1.41 (95% CI 0.74–2.09, $P < 0.0001$). The heterogeneity (I^2 was 90%. Meta-regression of the included studies did not demonstrate a significant correlation between dose and sedation score (co-efficient = 0.16, 95% CI −2.17 to 2.49, $P = 0.89$).

3.6 Rescue Analgesia

The requirement for rescue analgesia, either during a procedure or in the immediate (24-h) post-operative period was meta-analyzed in six studies involving 382 participants. The standardized mean difference in the requirement

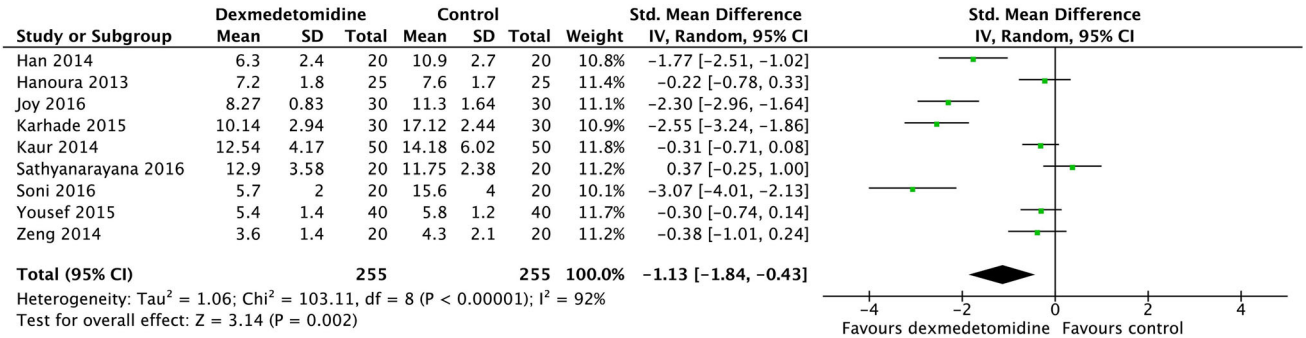

Fig. 4 Meta-analysis of the time to sensory block (minutes) in studies using epidural dexmedetomidine as an adjunct to background therapy. The standardized mean differences (95% CIs) are presented for each study

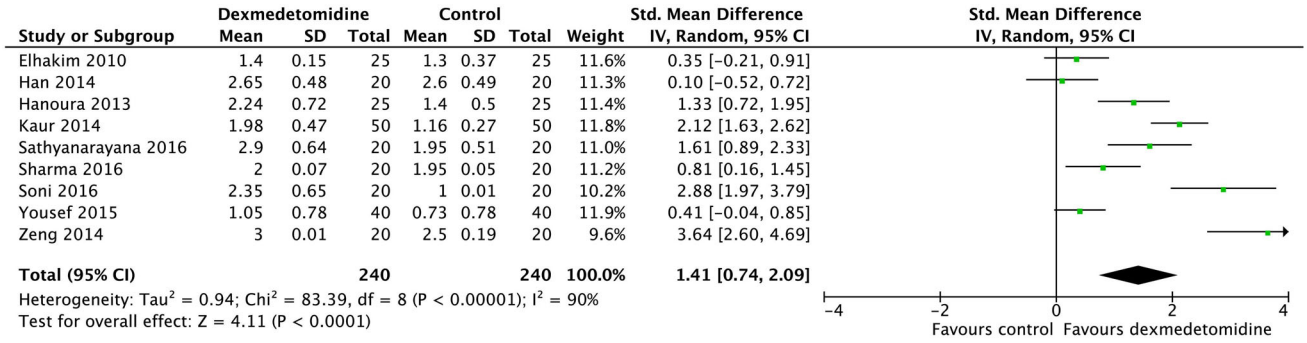

Fig. 5 Meta-analysis of the sedation score in studies using epidural dexmedetomidine as an adjunct to background therapy. The standardized mean differences (95% CIs) are presented for each study

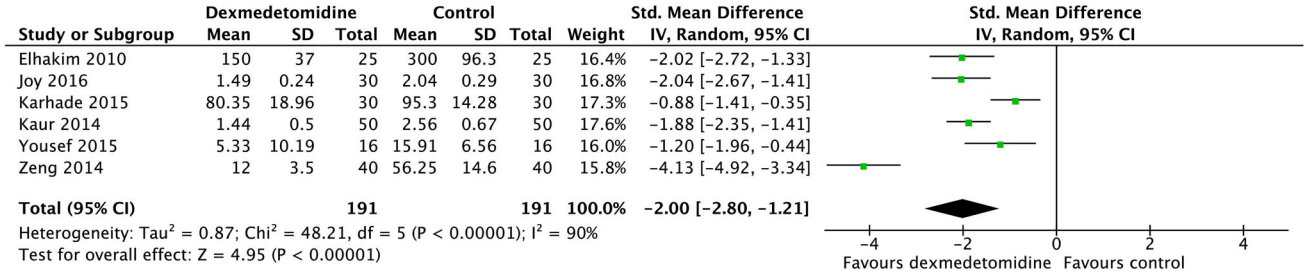

Fig. 6 Meta-analysis of the requirement for rescue analgesia in studies using dexmedetomidine as an adjunct to background therapy. The standardized mean differences (95% CIs) are presented for each study

for rescue analgesia strongly favored the addition of dexmedetomidine (Fig. 6). The SMD was −2.00 (95% CI −2.80 to −1.21, $P < 0.00001$). The heterogeneity $(I)^2$ was 90%.

3.7 Heart Rate

Bradycardia can be an adverse event during anesthesia. To determine if the administration of dexmedetomidine is associated with a lower heart rate, we extracted and meta-analyzed the minimum heart rate in studies that measured this outcome (Fig. 7) in a total of 360 patients. The addition of dexmedetomidine to existing therapy resulted in a mean heart rate reduction of −3.74 beats per minute (bpm) (95% CI −5.95 to −1.53, $P = 0.0009$). The heterogeneity $(I)^2$ was 10%. In order to determine whether low heart rate was correlated with dose, we undertook a random-effects meta-regression of the included studies. There was no significant correlation between dose and minimum heart rate (co-efficient = 0.44, 95% CI −0.31 to 1.18, $P = 0.224$).

3.8 Blood Pressure

Another potential adverse event during epidural procedures is hypotension. We conducted a subgroup meta-analysis of all studies measuring at least one of the following: mean arterial pressure (MAP), systolic blood pressure (SBP), or diastolic blood pressure (DBP). MAP was measured for 140 participants, whereas both SBP and DBP were measured for 280 participants. The lowest blood pressures reported in the studies were recorded for both dexmedetomidine and the control. Although MAP (MD −1.55), SBP (MD −2.15), and DBP (MD −1.13) were slightly lower in the treatment group than in the control group, none of the differences in the variables were statistically significant ($P = 0.33$, 0.32, and 0.28, respectively) (Fig. 8). The heterogeneity (I^2) was 0% for MAP and DBP, and was 39% for SBP.

3.9 Side Effects

Figure 9 shows the risk of side effects for both groups. A meta-analysis of clinical events, such as bradycardia (RR 1.89; 95% CI 0.83–4.28, $P = 0.13$), hypotension (RR 1.75; 95% CI 0.84–3.63, $P = 0.13$), dizziness (RR 0.66; 95% CI 0.09–5.03, $P = 0.69$), pruritus (RR 1.33; 95% CI 0.31–5.75, $P = 0.70$), dry mouth (RR 5.00; 95% CI 0.92–27.13, $P = 0.06$) and nausea and vomiting (RR 1.22; 95% CI 0.57–2.59, $P = 0.63$) showed no statistically significant differences, except that the risk of shivering was significantly associated with control therapies (RR 0.20; 95% CI 0.04–0.86, $P = 0.03$). Furthermore, post-operative pain with adjunct dexmedetomidine therapy was

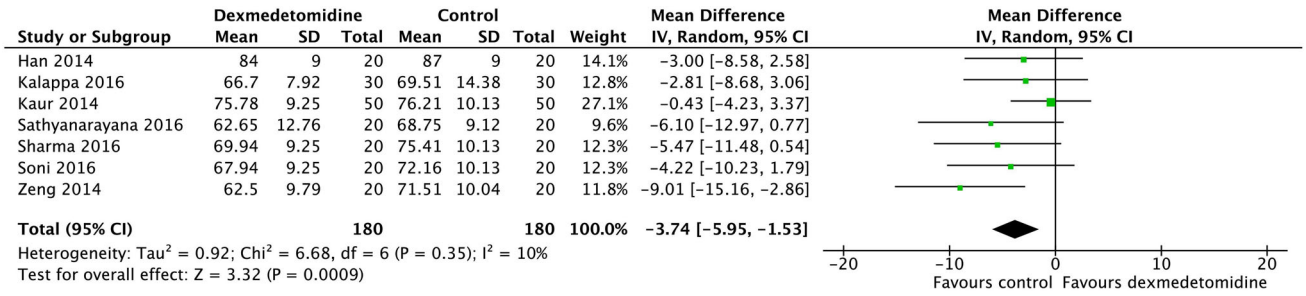

Fig. 7 Meta-analysis of the heart rate (beats/min) in studies using epidural dexmedetomidine as an adjunct to background therapy. The mean differences (95% CIs) are presented for each study

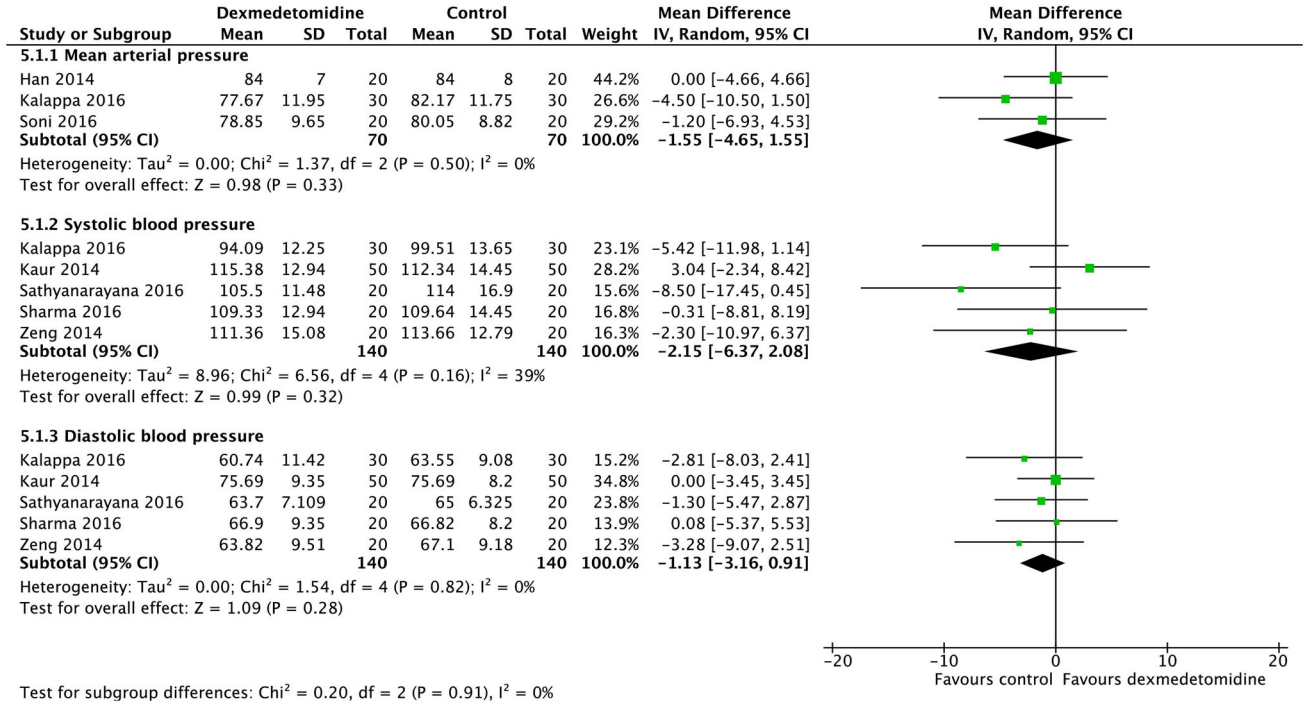

Fig. 8 Subgroup meta-analysis of the mean arterial pressure, systolic blood pressure, and diastolic blood pressure (mmHg) in studies using epidural dexmedetomidine as an adjunct to background therapy. The mean differences (95% CIs) are presented for each study

significantly lower than for the control group (Fig. 10), SMD −0.76 (95% CI −1.46 to −0.06, $P = 0.03$) with heterogeneity (I^2) of 83%.

3.10 Publication Bias

Overall, publication bias was difficult to determine. As the minimum number of studies in a funnel plot should be ten [37], and the use of standardized mean differences limits their usefulness [38], most of our outcomes were not well suited to funnel plots. However, despite a continuing debate about the accuracy of the visual inspection of funnel plots [39], we produced plots for continuous variables that were meta-analyzed as mean differences (Fig. 11). The heart rate plot (Fig. 11a) suggests that there may be a slight bias in favor of dexmedetomidine. Similarly, a visual inspection of the blood pressure plot suggests that some small studies measuring systolic blood pressure may be missing (Fig. 11b). However, these results should be interpreted with caution.

4 Discussion

Dexmedetomidine is a relatively new drug, especially in the epidural and non-ICU settings. As such, the number of appropriately controlled trials was not large. However, the current meta-analysis included 660 patients from 12 trials, which certainly makes it large enough for conclusions to be drawn. This meta-analysis evaluated the sedative and analgesic effects of epidural dexmedetomidine adjunctive therapy in different surgical procedures.

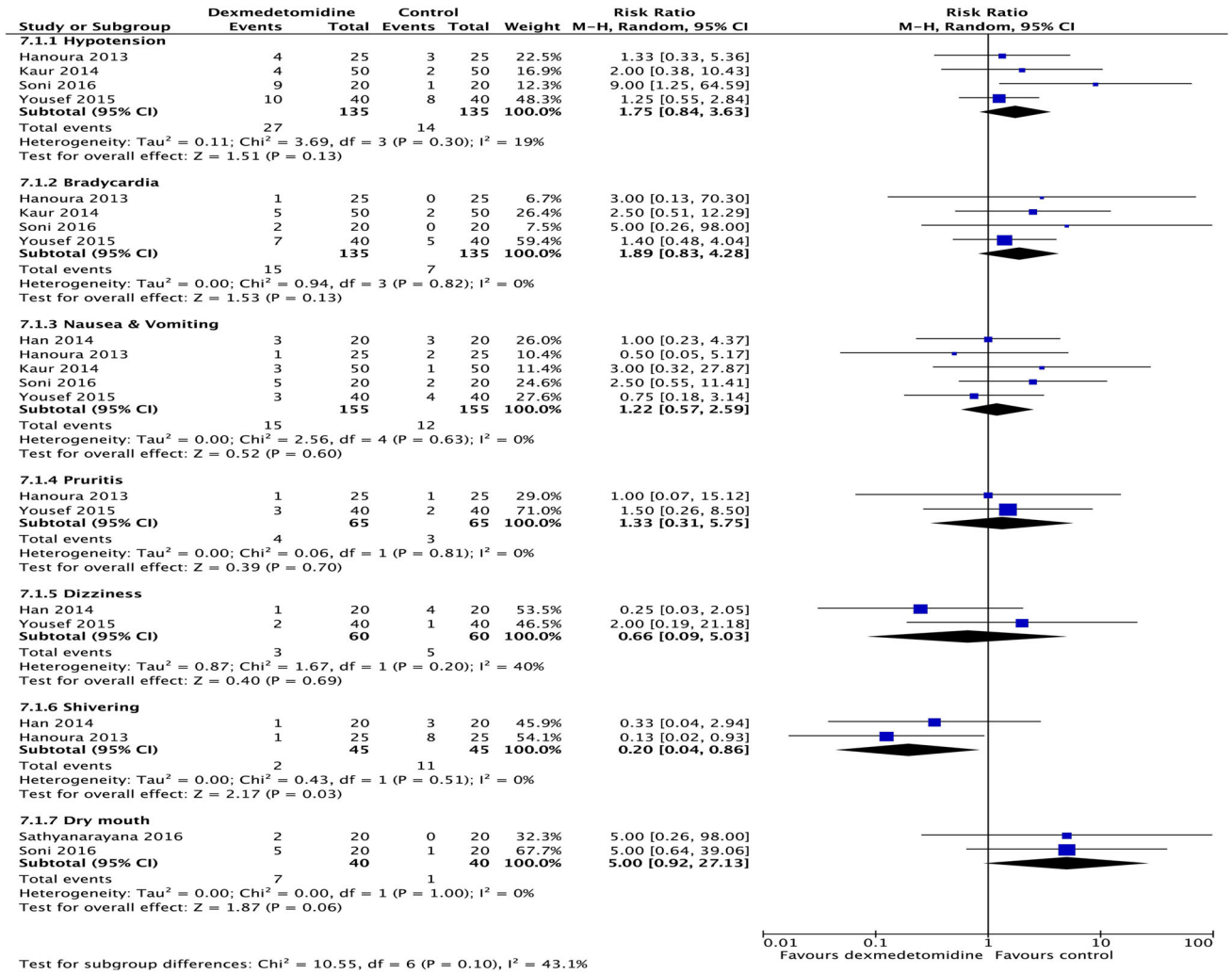

Fig. 9 Meta-analysis of the side effects in the studies using epidural dexmedetomidine as an adjunct to background therapy. The risk ratio (95% CIs) are presented for each study

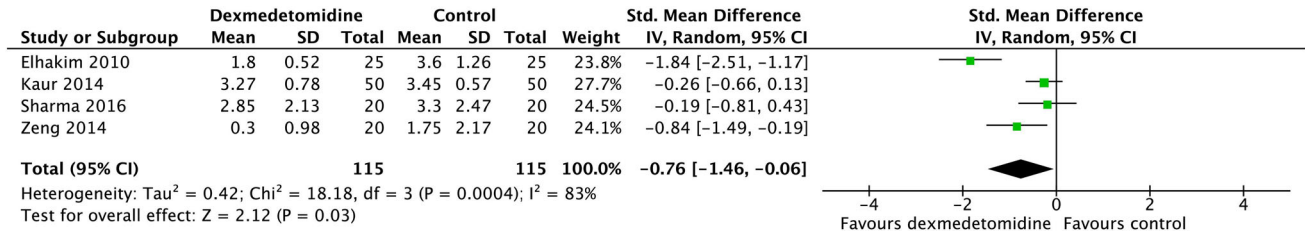

Fig. 10 Meta-analysis of the pain score (post-operative) in studies using epidural dexmedetomidine as an adjunct to background therapy. The standardized mean differences (95% CIs) are presented for each study

The duration of analgesia is a critical parameter while evaluating the efficacy of potential analgesic therapies, and the use of dexmedetomidine was shown to reduce the requirement for additional analgesic and also prevent side effects [40]. This meta-analysis found that the addition of dexmedetomidine resulted in a longer duration of analgesia than in the control treatment. Our analysis validates the individual findings of all of the included trials.

The time taken for a patient to experience sensory block is an important factor in surgery. Depending on the surgery performed and the type of anesthesia used, the time to sensory block in the absence of dexmedetomidine in our included studies was between 4.3 and 17.1 min. Thus, a medication that reduces this time would be a valuable addition to an anesthetic protocol. We found that the addition of dexmedetomidine to other analgesics, such as

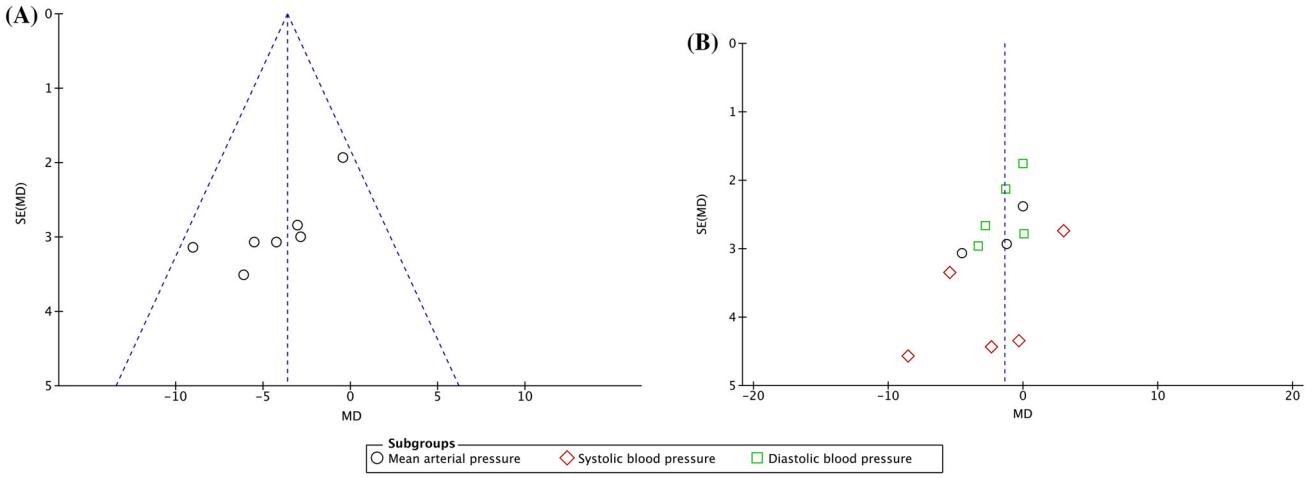

Fig. 11 Funnel plot analysis for the heart rate (**a**) and blood pressure (**b**) outcomes

ropivacaine [20, 28, 32, 35], bupivacaine [29–31], or levobupivacaine [33, 36], significantly reduced the time to sensory block. When compared with other potential adjunct analgesic drugs, dexmedetomidine frequently performs substantially better. Although one study found no significant difference between dexmedetomidine and clonidine in time to sensory block [40], dexmedetomidine was superior to clonidine in four other studies [41–44]. Dexmedetomidine's performance was shown to be similar to that of morphine in one study [45], and when compared with fentanyl, dexmedetomidine was found more efficient in reducing time to sensory block [46, 47].

The addition of dexmedetomidine clearly increased the sedation score, regardless of the type of sedation score used. The advantage of increased sedation is a reduced dependence on agents that are less neuroprotective and that depress respiration. Furthermore, the sedation induced by dexmedetomidine is useful for procedures that require the patient to be roused [48], such as neurosurgery. Even in comparison with other adjuvant analgesic drugs, dexmedetomidine was superior. In studies comparing dexmedetomidine against fentanyl [46, 49] or clonidine [40–42, 44, 50], dexmedetomidine use produced a significantly improved level of sedation. Compared with midazolam, however, no significant differences were seen [51, 52].

A clear and highly significant reduction in the requirement for rescue analgesia was observed (Fig. 6). Although heterogeneity was high ($I^2 = 88\%$), this was mostly driven by a single study by Zeng et al. [36]. Dexmedetomidine is regarded as opioid-sparing [48], and our study demonstrates this convincingly. This highly significant result is consistent with reports of reduced post-operative pain, as measured by the visual analogue scale (VAS) or similar methods [19, 27, 30, 46, 53, 54]. Given that opioids, which are frequently used to relieve intense post-operative pain, cause respiratory depression, the reduction in pain and thus the reduced demand for rescue analgesia are of great value. Indeed, a direct comparison of dexmedetomidine and morphine as adjunct analgesics indicates that they were comparable in terms of preventing the need for rescue analgesia, and that dexmedetomidine caused far fewer side effects [55]. Furthermore, the rescue analgesic requirements were significantly reduced in groups given dexmedetomidine, rather than fentanyl, as an adjunct analgesic agent [47, 49].

A decrease in heart rate has previously been reported to be a consequence of dexmedetomidine use [5, 40, 56–58]. Our meta-analysis confirms that, when used as an adjunct to epidural anesthesia, dexmedetomidine was associated with a reduction in trough intra-operative heart rate of − 3.74 bpm. Although highly significant, it is questionable whether such a reduction is of major clinical concern, especially as it can be so easily controlled with the administration of atropine [59–61]. Indeed, although heart rate was significantly reduced after the addition of dexmedetomidine to background anesthesia, this is also the case for other similar agents. Studies comparing dexmedetomidine with clonidine found no differences in heart rate [41, 42], while one study found it to be better than clonidine [43]. The effect of dexmedetomidine on heart rate was also comparable to that of fentanyl [46, 49]. A study that compared dexmedetomidine with midazolam found no difference in heart rate [52], whereas another study found midazolam to be superior to dexmedetomidine [51].

The use of dexmedetomidine has been associated with a decrease in blood pressure [5, 58, 62–65]. However, at least in the context of its use as an adjunct in epidural anesthesia, dexmedetomidine did not elicit a significant decrease in mean arterial pressure, systolic blood pressure, or diastolic blood pressure when used with other anesthetics.

As for the other outcomes, dexmedetomidine has been compared with other potential adjunct analgesic drugs in terms of its effects on mean arterial pressure, systolic blood pressure, and diastolic blood pressure. In the two included studies that compared dexmedetomidine with midazolam, one found no difference in the effects of dexmedetomidine and midazolam [52] and the other found dexmedetomidine to be better than midazolam [51]. Three studies comparing dexmedetomidine with clonidine [41–43] and two studies comparing dexmedetomidine with fentanyl [46, 49] found the effect of dexmedetomidine on blood pressure to be comparable to that of the other drugs.

Dexmedetomidine therapy had been linked with side effects such as hypotension, bradycardia, dizziness, pruritus, dry mouth, shivering, nausea, and vomiting [20, 28–30, 32]. Our analysis did not find any significant risk of these side effects, with the exception that more patients in the treatment group experienced hypotension than in the control group. Nonetheless, a study comparing the effectiveness of dexmedetomidine and fentanyl in epidural procedures found a significant risk of dryness of the mouth, nausea, and vomiting with dexmedetomidine therapy [47]. However, the same research group also compared dexmedetomidine with clonidine and found no significant risk of these side effects [40].

A major limitation of this meta-analysis was the inadequate reporting of the method of randomization and allocation concealment. Other concerns were the lack of blinding in two studies and the low number of study participants in all of the included trials (20–50 patients in each trial arm).

5 Conclusion

The current meta-analysis found that the addition of dexmedetomidine to other anesthetic agents during epidural procedures provided a longer duration of analgesia, as well as highly significant improvements in the time to sensory block and the sedation score, and decreased the requirement for rescue analgesia. Although patients' intraoperative heart rate significantly reduced, blood pressure was not significantly affected. Additionally, the risk of side effects reported in the trials was shown to be statistically insignificant. More randomized controlled trials are necessary to elucidate the effects of dexmedetomidine on these variables in epidural anesthesia.

Author contributions XZ developed the concept for the systematic review and meta-analysis; he performed all statistical analyses and wrote the manuscript. DW and MS did literature searches, data collection, and extraction. YGL provided guidance and performed the critical revision of the intellectual concept and content of the article. All authors approved the final version of the article.

Compliance with ethical standards

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