META-ANALYSIS

Effects of Intravenous and Intrathecal Dexmedetomidine in Spinal Anesthesia: A Meta-Analysis

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Keywords

Bradycardia; Dexmedetomidine; Duration of sensory and motor block; Hypotension; Postoperative analgesia; Side effects.

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SUMMARY

Purpose: To assess the effects of dexmedetomidine on the duration of sensory and motor block, postoperative analgesia, hypotension, bradycardia, and side effects in patients undergoing spinal anesthesia. **Methods:** Two researchers searched MEDLINE, EMBASE, and the Cochrane controlled trial register independently for randomized controlled trials comparing dexmedetomidine with a placebo without any language restrictions. **Results:** A total of 412 patients from eight trials were included in this study. The results revealed that dexmedetomidine was statistically significant in prolonging the duration of sensory block (mean difference, MD = 73.55; 95% CI, [55.69, 91.40] $P < 0.00001$, $I^2 = 89\%$) and motor block (MD = 59.11; 95% CI, [29.58, 88.65] $P < 0.00001$, $I^2 = 91\%$) and the time to first request for postoperative analgesia (MD = 245.77, 95% CI, [143.53, 348.00] $P < 0.00001$, $I^2 = 98\%$). The occurrence of hypotension (OR = 0.60, 95% CI, [0.3–1.23], $P = 0.40$, $I^2 = 3\%$) and side effects (OR = 0.9, 95% CI, [0.36–2.22], $P = 0.88$, $I^2 = 0\%$) was not significantly different between dexmedetomidine and placebo. However, dexmedetomidine was associated with more frequent bradycardia requiring atropine (OR = 7.55; 95% CI, [2.76–20.63], $P = 0.63$, $I^2 = 0\%$). **Conclusions:** This meta-analysis has shown that dexmedetomidine prolonged the duration of spinal anesthesia and improved postoperative analgesia and did not increase the incidence of hypotension and adverse events, but needs more atropine to reverse bradycardia.

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The first two authors contributed equally to this work.

Introduction

Spinal anesthesia was used widely for patients undergoing urological procedures and lower limb surgery. Different adjuvants such as morphine, fentanyl, and clonidine had been used to prolong spinal anesthesia, providing the possible advantages of the better pain control in the early postoperative period and reduced deep vein thrombosis. For example, the combination of low-dose bupivacaine and opioids provides satisfactory analgesia for spinal anesthesia [1]. Clonidine, an α_2 -agonist, has been used extensively in the intrathecal route [2–5]. It prolongs the duration of spinal blockade as well as postoperative analgesia [6,7]. Clonidine also has been used intravenously within 1 h after the spinal block and found that it prolonged bupivacaine spinal anesthesia for approximately 1 h without adverse effect [8].

Dexmedetomidine, a highly selective α_2 -adrenoreceptor agonist, has been used for premedication and as an adjunct to general anesthesia. Intravenous dexmedetomidine decreases the inhalational anesthesia and opioid requirements during general anesthesia [9]. Also, it has been used safely in patients undergoing surgical procedures under regional anesthesia [10,11], and we

hypothesize that intravenous or intrathecal dexmedetomidine might prolong the duration of spinal analgesia and decrease postoperative analgesia similar to clonidine.

Methods**Searching Strategy**

Two researchers searched the MEDLINE, EMBASE, and the Cochrane library independently. Mesh and key words used for the searches included “dexmedetomidine,” “spinal anesthesia,” “intrathecal,” “intravenous”. References cited in these articles were also obtained to prevent missing of articles. Double blinded, randomized control trials on dexmedetomidine versus placebo, without any language restrictions, were included in this study.

Inclusion Criteria

Intravenous dexmedetomidine and intrathecal dexmedetomidine were all included, and participants of any sex but just adult were

included, selecting low dose of dexmedetomidine ($\leq 5 \mu\text{g}$) when using in intrathecal route. Children and use high dose of dexmedetomidine were excluded.

Data Extraction

Two reviewers (Xiao-Yin Niu and Xi-Bing Ding) selected eligible studies independently, extracted data and recorded the trial characteristics with a standard data collection form. Any conflict was resolved by mutual agreement. The following data were collected: name of first author, publishing date, number of patients, the drugs for spinal anesthesia, the method of dexmedetomidine, the duration of sensory and motor block, post-operative analgesia, hypotension, bradycardia, and side effects (Table 1). All data collected were defined according to the definition chosen by individual trial and the data not standardized. Dexmedetomidine or saline was given by infusion in the trials by Hong [12], Kaya [13], Elcicek [14], Al-Mustafa [15], whereas in the other trials by Solanki [16], Abu-Halaweh [17], Kanazi [18], Gupta [19], intrathecal route was used. The first author of two studies [15,17] was the same person, so we used the second author's name "Abu-Halaweh" to represent [17].

The level of sensory block was assessed with the patients in the supine position using pinpricks or ice cubes in the mid-thoracic line. Motor block was assessed immediately after sensory block assessment using a Modified Bromage Scale [20] (0 = no paralysis; 1 = unable to raise extended leg; 2 = unable to flex knee; 3 = unable to flex ankle).

Assessment of Bias Risk

We used Cochrane Handbook v5.0.2 to assess the risk of bias for all eligible studies [21]. The following information was evaluated: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and each of them was graded as "high risk of bias," "low risk of bias," and "uncertain of bias." Two reviewers (Xiao-Yin Niu and Xi-Bing Ding) evaluated the studies independently, while discrepancies were discussed with the third reviewer (Quan Li) until consensus was achieved.

Statistical Analysis

The main outcomes of this study were the duration of sensory and motor block, hypotension, side effects, and the time to first request for postoperative analgesia and the request for atropine. To assess the duration of sensory and motor block, we performed a subgroup analysis comparing intravenous and intrathecal dexmedetomidine. The duration of sensory and motor block and the time to first request for postoperative analgesia are continuous data, so they are reported as mean difference (MD) with 95% confidence interval (CI), using a random effects model. The occurrence of hypotension, side effects, and the request of atropine are categorical outcomes, so they are reported as relative risk (RR) with 95% confidence interval (CI), using a fixed effects model. Statistical heterogeneity was assessed using the I^2 -test.

Table 1 The design of the included studies

Author	Years	Application	NO.	Blind	Treatment	Operation	Drug for spinal anaesthesia	Primary endpoint	Secondary endpoints
Hong	2012	DM/NS	26 vs. 25	Double	Intravenous	TURP	Bupivacaine	Duration of sensory and motor block	Hypotension, bradycardia, side effects, pain after operation
Kaya	2010	DM/MZ/NS	25 vs. 25 vs. 25	Double	Intravenous	TURP	Bupivacaine	Duration of sensory and motor block	Hypotension, bradycardia, pain after operation
Elcicek	2010	DM/NS	30 vs. 30	Double	Intravenous	Lower limb surgery	Ropivacaine	Duration of sensory and motor block	Bradycardia, side effects
Al-Mustafa	2009	DM/NS	24 vs. 24	Double	Intravenous	TURP	Bupivacaine	Duration of sensory and motor block	Hypotension, bradycardia side effects
Solanki	2013	D/C/B	30 vs. 30 vs. 30	Double	Intrathecal	Lower limb surgery	Bupivacaine	Duration of sensory and motor block	Hypotension, side effects pain after operation
Abu-Halaweh	2009	D5/D10/DN	21 vs. 21 vs. 22	Double	Intrathecal	TURP/TURBT/TVT	Bupivacaine	Duration of sensory and motor block	Hypotension, bradycardia side effects
Kanazi	2006	D/C/B	20 vs. 20 vs. 20	Double	Intrathecal	TURP/TURBT	Bupivacaine	Duration of sensory and motor block	Hypotension, bradycardia side effects
Gupta	2011	DM/NS	30 vs. 30	Double	Intrathecal	Lower limb surgery	Ropivacaine	Duration of sensory and motor block	Hypotension, bradycardia, side effects, pain after operation

DM, D, Dexmedetomidine; NS, B, Saline; D5, 5 μg dexmedetomidine; D10, 10 μg dexmedetomidine; C, Clonidine; TURP, Transurethral resection of the prostate; TURBT, Transurethral resection of bladder tumors; TVT, Placement of tension-free vaginal tape.

Results

Characteristics of Eligible Trials

A total of eight randomized controlled trials involving 412 patients were identified (206 received dexmedetomidine and 206 did not). The process is shown by The QUOROM [22] flowchart in detail in Figure 1. The design of the included studies in the meta-analysis is shown in Table 1. The summary of results from each individual study is shown in Table 2. Six studies [12,13,15–18] used bupivacaine and two studies [14,19] used ropivacaine for spinal anesthesia. Four studies [12–15] used dexmedetomidine in the intravenous route and four studies [16–19] used it in the intrathecal route. In the four studies that used intravenous route, one compared dexmedetomidine with midazolam and saline [13],

whereas the remaining three compared dexmedetomidine with saline. In the four studies that used intrathecal route, two compared low dose of dexmedetomidine ($\leq 5 \mu\text{g}$) with clonidine and saline [16,18], the third study compared low dose of dexmedetomidine ($5 \mu\text{g}$) with high dose of dexmedetomidine ($10 \mu\text{g}$) and saline [17], and the fourth study compared low dose of dexmedetomidine ($5 \mu\text{g}$) with saline [19], and in the first three studies, the dexmedetomidine or the saline was supplemented with bupivacaine, and in the last study, it was supplemented with ropivacaine. This meta-analysis just compared dexmedetomidine with saline, so we ignored clonidine and midazolam. Besides, we selected the low dose of dexmedetomidine. We excluded one study because it compared the high dose of dexmedetomidine ($10 \mu\text{g}$) with saline.

In the four studies that used intravenous dexmedetomidine, two used a loading dose of $1 \mu\text{g/kg}$ dexmedetomidine over 10 min: the maintenance dose in one study was $0.5 \mu\text{g/kg/h}$ [15] and another was $0.4 \mu\text{g/kg/h}$ [14]. In the remaining two studies, one study received dexmedetomidine $0.5 \mu\text{g/kg}$ [13] and another was $1 \mu\text{g/kg}$ [12]. The treatment of bupivacaine was also different: two studies used 12.5 mg, one study used 6 mg, two studies used 15 mg, and one study used 12 mg. One study used 22.5 mg ropivacaine.

Risk of Bias

The risk of bias assessment in the included studies showed that most of the studies had low risk of bias (Table 3). As we could not access each study's original protocol, all studies were considered free from "selective reporting" bias.

The Duration of Sensory and Motor Block

Whatever intravenous route (sensory: MD = 59.25; 95% CI, [33.58, 84.91] $P < 0.0001$, $I^2 = 87\%$, motor: MD = 37.79; 95% CI, [12.53, 63.05] $P = 0.0009$, $I^2 = 82\%$) or intrathecal route (sensory: MD = 89.59; 95% CI, [59.09, 120.10] $P < 0.00001$, $I^2 = 90\%$, motor: MD = 90.18; 95% CI, [66.27, 114.10] $P = 0.1$, $I^2 = 56\%$) or pooled (sensory: MD = 73.55; 95% CI, [55.69, 91.40] $P < 0.00001$, $I^2 = 89\%$, motor: MD = 59.11; 95% CI, [29.58, 88.65] $P < 0.00001$, $I^2 = 91\%$), dexmedetomidine could prolong the duration of sensory and motor block. But there was significant heterogeneity in the duration of sensory ($I^2 = 87\%$) and motor ($I^2 = 82\%$) block when intravenous dexmedetomidine, whereas the heterogeneity was not evident in motor block but still significant in sensory block when intrathecal dexmedetomidine (sensory: $I^2 = 90\%$, motor: $I^2 = 56\%$); however, when pooled, the heterogeneity of both was significant (sensory: $I^2 = 89\%$, motor: $I^2 = 91\%$; Figures 2 and 3).

The Side Effects and the Occurrence of Hypotension

Seven studies recorded the side effects [12,14–19] and seven studies recorded the occurrence of hypotension [12,13,15–19]. But in one study, there were no any adverse events occurring in the dexmedetomidine and saline group. The side effects included nausea, headache, vomiting, shivering. The effects of dexmedetomidine on the side effects (OR = 0.9; 95% CI, [0.36–2.22], $P = 0.88$, $I^2 = 0\%$) and hypotension (OR = 0.60; 95% CI, [0.3–1.23],

Figure 1 Flowchart.

Table 2 The summary of results from individual study

Author	Duration of sensory block (min)	Duration of motor block (min)	The time to first request for post-operative analgesia	The occurrence of hypotension	The side effects	The requirement of atropine
Hong						
DM	78 ± 35	46 ± 42	6.6 ± 2.5 h	1/26	2/26	10/25
NS	39 ± 18	24 ± 33	2.1 ± 1.8 h	2/25	2/25	1/26
Kaya						
DM	145 ± 26	193 ± 27	216 ± 3 min	2/25		2/25
NS	97 ± 27	180 ± 34	122 ± 34 min	4/25		1/25
Elcicek						
DM	249 ± 56	284 ± 63			3/30	9/30
NS	195 ± 53	225 ± 53			2/30	0/30
Al-Mustafa						
DM	262 ± 35	200 ± 43		0/24	0/24	2/24
NS	165 ± 32	138 ± 31		4/24	1/24	0/24
Solanki						
DM	302 ± 68	279 ± 67	824 ± 244 min	7/30	3/30	
NS	224 ± 44	209 ± 45	406 ± 118 min	5/30	2/30	
Abu-Halaweh						
DM	277 ± 23	246 ± 26		0/21	0/21	0/21
NS	166 ± 33	140 ± 32		4/22	1/22	0/22
Kanazi						
DM	303 ± 75	250 ± 76		1/20	0/20	0/20
NS	190 ± 48	163 ± 47		1/20	0/20	0/20
Gupta						
DM	126 ± 17		478 ± 21 min	2/30	0/30	2/30
NS	63 ± 8		242 ± 22 min	1/30	1/30	0/30

Table 3 The risk of bias assessment in the included studies

Author	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Hong	Low	Unclear	Low	Low	Low
Kaya	Low	Unclear	Low	Low	Low
Elcicek	Low	Low	Low	Low	Low
Al-Mustafa	Unclear	Unclear	Low	Low	Low
Solanki	Low	Unclear	Low	Low	Low
Abu-Halaweh	Low	Low	Low	Low	Low
Kanazi	Low	Unclear	Low	Low	Low
Gupta	Low	Unclear	Low	Low	Low

$P = 0.40$, $I^2 = 3\%$) both were not significantly different from saline (Figures 4 and 5). And the heterogeneity of both was not significant. When studying the effects of dexmedetomidine on the side effects and hypotension, we pooled the articles of intravenous and intrathecal dexmedetomidine.

The Time to First Request for Postoperative Analgesia

In the eight studies, there were four studies [12,13,16,19] described the time to first request for postoperative analgesia. Dexmedetomidine could prolong the time to first request for postoperative analgesia

(MD = 245.77; 95% CI, [143.53, 348.00], $P < 0.00001$, $I^2 = 98\%$). There was significant heterogeneity in the time to first request for postoperative analgesia among the four studies (Figure 6).

The Requirement of Atropine

There were seven studies reporting the requirement of atropine [12–15,17–19], and in two studies [17,18], the requirement of atropine was zero in the two groups. However, the analysis still indicated that dexmedetomidine could cause bradycardia in many cases, requiring atropine (MD = 7.55 95% CI [2.76, 20.63], $P = 0.63$, $I^2 = 0\%$; Figure 7).

Figure 2 Forest plot for duration of sensory block in minutes.

Figure 3 Forest plot for duration of motor block in minutes.

Discussion

Dexmedetomidine is a new drug for anesthesia, and more and more anesthesiologists use it to improve the quality of anesthesia. In this meta-analysis, using dexmedetomidine during spinal anaesthesia prolonged the duration of sensory and motor block and the time to first request for post-operative analgesia. The use of dexmedetomidine made more patients need atropine but did not increase the risk of side effects and hypotension.

Our results showed that dexmedetomidine might be able to prolong the duration of sensory and motor block. But there was high level of heterogeneity between the studies in this outcome. The possible explanations could be the following aspects. First, the dose of bupivacaine and dexmedetomidine was different; second, the method of using dexmedetomidine is not unified, including intravenous dexmedetomidine and intrathecal dexmedetomidine; third, the evaluation criteria of the sensory and motor block recovery was different, using the Modified Bromage Scale [20] (0 = no paralysis; 1 = unable to raise extended leg; 2 = unable to

Figure 4 The effect of dexmedetomidine on the side effects.

Figure 5 The effect of dexmedetomidine on the occurrence of hypotension.

Figure 6 Forest plot for the time to first request for postoperative analgesia.

Figure 7 The effect of dexmedetomidine on the requirement of atropine.

flex knee; 3 = unable to flex ankle) to evaluate the motor block recovery. Motor block duration of some studies was the time required to return to Modified Bromage Scale 1, the remaining was Modified Bromage Scale 0; and fourth, the type of surgery was variable.

Our results showed that dexmedetomidine would not increase the risk of side effects, such as nausea, headache, vomiting, shivering, and hypotension. Al-Ghanem [23] had reported intrathecal dexmedetomidine without any adverse neurological consequences, and four articles [12,15,17,18] in this study demonstrated that no patient reported neurological impairment within 2 weeks after surgery. Previous studies reported that dexmedetomidine caused no or minimal respiratory depression [24]. Dexmedetomidine is usually used in general anesthesia, and it could reduce blood pressure and heart rate. Besides, we all know that hypotension occurs easily in spinal anesthesia and it can be treated with either ephedrine or phenylephrine [25]. When used in spinal anesthesia, it did not induce hypotension. However, we found that it increased the risk of bradycardia requiring atropine. The bradycardia could be reversed by atropine, so serious outcome would not happen. The heterogeneity between the studies in these outcomes was not significant.

Patients usually feel so pain that they need analgesia after surgery. The use of dexmedetomidine in spinal anesthesia might prolong the time to first request for postoperative analgesia. But the heterogeneity was significant. Only four articles involved this outcome, and the subjectivity of different patients and the type of surgery may cause the significant heterogeneity. The mechanism of the analgesic effect of dexmedetomidine remains unclear and may be related to the involvement of Protein Kinase B/Akt [26].

There are several limitations in our study. First, there were high levels of heterogeneity when evaluating the duration of sensory and motor block and the time to first request for postoperative analgesia due to different intrathecal drugs (bupivacaine, ropivacaine), patient cohorts, evaluation criteria, type of surgery. Second, the sample sizes of these studies were small which may lead to a small-study effect; thus, we should be cautious of the application of this meta-analysis. Furthermore, the safety of dexmedetomidine that used in intrathecal route in humans has not been

extensively studied. Dexmedetomidine may appear safe in the short term [27,28], but subsequent long-term human neurotoxicity data, including the investigation of potential delayed adverse neurological effects, are lacking [29]. Third, two studies [14,15] used a loading dose of dexmedetomidine and maintained at a certain dose, another two studies [12,13] just maintained at a certain dose. The difference between them may cause the different outcomes, which we did not analyse. Fourth, dexmedetomidine is known to have a sedative effect, providing better conditions for patients [30]. Patients may be easily aroused and remain cooperative, which is different from other sedatives [31]. It is reported that dexmedetomidine may cure the bipolar disorder [32,33]. We did not study the sedative effect because the data in the studies were not uniform. Intravenous and intrathecal dexmedetomidine were both involved in this meta-analysis, but we cannot analyse the difference between them. We will pay close attention to the clinical trials about this.

In summary, we found that the use of dexmedetomidine including intravenous and intrathecal could statistically significantly prolong the duration of sensory and motor block and the time to first request for postoperative analgesia. There was no increased risk of the side effects and the occurrence of hypotension, but the risk of bradycardia increased.

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Conflict of Interest

The authors declare no conflict of interest.

References

- Qiu MT, Lin FQ, Fu SK, et al. Combination of low-dose bupivacaine and opioids provides satisfactory analgesia with less intraoperative hypotension for spinal anesthesia in cesarean section. *CNS Neurosci Ther* 2012;**18**:426–432.
- Racle JP, Benkhadra A, Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesth Analg* 1987;**66**:442–446.
- Dobrydnjov I, Axelsson K, Samarutell J, Holmstrom B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. *Acta Anaesthesiol Scand* 2002;**46**:806–814.
- Fogarty DJ, Carabine UA, Milligan KR. Comparison of the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anaesthesia in patients undergoing total hip replacement. *Br J Anaesth* 1993;**71**:661–664.
- Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. *Acta Anaesthesiol Scand* 1994;**38**:724–728.
- Strebel S, Gutzler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: A dose-response study. *Anesth Analg* 2004;**99**:1231–1238.
- van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: A randomized controlled trial. *Br J Anaesth* 2006;**97**:365–370.
- Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. *Acta Anaesthesiol Scand* 2003;**47**:1001–1005.
- Fragen RJ, Fitzgerald PC. Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55–70 years. *J Clin Anesth* 1999;**11**:466–470.
- Karaaslan D, Peker TT, Alaca A, et al. Comparison of buccal and intramuscular dexmedetomidine premedication for arthroscopic knee surgery. *J Clin Anesth* 2006;**18**:589–593.
- Jaakola ML. Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. *J Clin Anesth* 1994;**6**:204–211.
- Hong JY, Kim WO, Yoon Y, Choi Y, Kim SH, Kil HK. Effects of intravenous dexmedetomidine on low-dose bupivacaine spinal anaesthesia in elderly patients. *Acta Anaesthesiol Scand* 2012;**56**:382–387.
- Kaya FN, Yavasoglu B, Turker G, et al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. *Can J Anaesth* 2010;**57**:39–45.
- Elcicek K, Tekin M, Kati I. The effects of intravenous dexmedetomidine on spinal hyperbaric ropivacaine anesthesia. *J Anesth* 2010;**24**:544–548.
- Al-Mustafa MM, Badran LZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, Al-Ghanem SM. Intravenous dexmedetomidine prolongs bupivacaine spinal anesthesia. *Middle East J Anesthesiol* 2009;**20**:225–231.
- Solanki SL, Bharti N, Batra YK, Jain A, Kumar P, Nikhar SA. The analgesic effect of intrathecal dexmedetomidine or clonidine, with bupivacaine, in trauma patients undergoing lower limb surgery:

- A randomised, double-blind study. *Anaesth Intensive Care* 2013;**41**:51–56.
17. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, et al. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. *Saudi Med J* 2009;**30**:365–370.
 18. Kanazi GE, Aouad MT, Jabbour-Khoury SI, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand* 2006;**50**:222–227.
 19. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. *Indian J Anaesth* 2011;**55**:347–351.
 20. Bromage PR, Burfoot MF, Cromwell DE, Pettigrew RT. Quality of epidural blockade. I. Influence of physical factors. *Br J Anaesth* 1964;**36**:342–352.
 21. Higgins JPT, Altman DG. In: Higgins JPT, Green S, editors. *Assessing risk of bias in included studies: cochrane handbook for systematic reviews of interventions*. England: John Wiley & Sons Ltd, 2008:187–241.
 22. Moher D, Cook DJ, Jadad AR, et al. Assessing the quality of reports of randomised trials: Implications for the conduct of meta-analyses. *Health Technol Assess* 1999;**3**:1–98.
 23. Al-Ghanem SM, Massad IM, Al-Mustafa MM, et al. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double blind controlled study. *Am J Appl Sci* 2009;**6**:882–887.
 24. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000;**90**:699–705.
 25. Lin FQ, Qiu MT, Ding XX, Fu SK, Li Q. Ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean section: An updated meta-analysis. *CNS Neurosci Ther* 2012;**18**:591–597.
 26. Li SS, Zhang WS, Yang JL, Xiong YC, Zhang YQ, Xu H. Involvement of Protein Kinase B/Akt in analgesic effect of dexmedetomidine on neuropathic pain. *CNS Neurosci Ther* 2013;**19**:364–366.
 27. Brummett C, Norat M, Palmisano J, Lydic R. Perineural administration of dexmedetomidine in combination with bupivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity in rat. *Anesthesiology* 2008;**109**:502–511.
 28. Brummett CM, Padda A, Amodeo F, Welch K, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. *Anesthesiology* 2009;**111**:1111–1119.
 29. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). *Anesth Analg* 1999;**88**:797–809.
 30. Povey HM, Jacobsen J, Westergaard-Nielsen J. Subarachnoid analgesia with hyperbaric 0.5% bupivacaine. *Acta Anaesthesiol Scand* 1989;**33**:295–297.
 31. Ustun Y, Gunduz M, Erdogan O, Benlidayi ME. Dexmedetomidine versus midazolam in outpatient third molar surgery. *J Oral Maxillofac Surg* 2006;**64**:1353–1358.
 32. Severus E, Schaaff N, Möller HJ. State of the art: Treatment of bipolar disorders. *CNS Neurosci Ther* 2012;**18**:214–218.
 33. Bowden CL, Perlis RH, Thase ME, et al. Aims and results of the NIMH systematic treatment enhancement program for bipolar disorder (STEP-BD). *CNS Neurosci Ther* 2012;**18**:243–249.