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ORIGINAL RESEARCH **REGIONAL ANESTHESIA**

Neuraxial block quality of dexmedetomidine-containing regimens in orthopedic surgeries: a meta-analysis

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Abstract

Background: Dexmedetomidine is used as an adjuvant to local anesthetic agents in spinal anesthesia and is believed to increase quality of sensory and motor blocks. Our aim was to assess the effects of dexmedetomidine as an adjunct on block quality of spinal anesthesia in orthopedic procedures.

Methodology: A systematic review of randomized control trials was conducted to assess the effect of intrathecal dexmedetomidine added to local anesthetic agents on the block quality of spinal anesthesia in orthopedic surgeries. PubMed, Google scholar, and Medline databases were searched for randomized controlled clinical trials. Studies met our inclusion criteria, if they used intrathecal 5 µg dexmedetomidine as an additive to 2.5−3 ml (12.5−15 mg) bupivacaine or ropivacaine, and these were included in our meta-analysis.

Results: Eight trials comprising 510 patients matched our inclusion criteria. Time to one sensory segment block regression (mean difference 139.72 min; 95% confidence interval (CI) 35.18−244.26; P = 0.009), two sensory segments block regression (mean difference 54.8 min; 95% CI [31.36−78.24]; P < 0.001), and Bromage score of zero (mean difference 93.66 min; 95%CI [30.20−157.12]; P = 0.004) were significantly prolonged in dexmedetomidine group. There were no significant differences between dexmedetomidine group and control group in duration of surgery (P = 0.33) or time till block reaches T10 dermatomal level (P = 0.30). Finally, time to reach Bromage score of III following injection was significantly shorter in dexmedetomidine group (mean difference 2.62 min; 95%CI [−5.12−−0.13]; P = 0.04).

Conclusion: Dexmedetomidine was found to achieve extended motor and sensory block when needed, bearing in mind higher cost and potential side effects.

Key words: Dexmedetomidine, Spinal Anesthesia, Orthopedic surgery, Meta-analysis.

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1. Introduction

Spinal anesthesia is commonly used for orthopedic procedures. The technique utilizes a small dose of local anesthetic solution introduced into the intrathecal space. This is followed by variable degrees of autonomic, sensory and motor blocks to the nerves arising around the area of injection[1]. Due to lower complications rate and better perioperative outcomes, spinal anesthesia has become a tempting choice for surgeries involving the lower part of the body.[2,3] Now-a-days, spinal anesthesia is considered a standard of care for many major orthopedic surgeries like lower limb and low back surgeries.[4–7] A number of local anesthetic solutions were utilized in spinal anesthesia, including bupivacaine, lidocaine, 2-chloroprocaine and ropivacaine.[9–11] With extensive usage, studying the effects of additive agents like opioids, benzodiazepines and sympathomimetics became important.[11,12] Agents like neostigmine and dexmedetomidine have been evaluated in many trials that confirmed relative safety and beneficial outcomes.[13,14]

Dexmedetomidine, the drug of interest in our study, is a highly selective alpha 2-agonist and has combined analgesic as well as sedative properties.[15,16] Due to its minor depressant effects on cardiovascular and respiratory systems, and a tendency to mimic physiological sleep, dexmedetomidine has been widely used in the intensive care settings as an intravascular (IV) sedative agent.[17,18] Although dexmedetomidine showed some beneficial effects in multiple randomized clinical trials, hypotension, hypertension and bradycardia were commonly reported following its long term IV use.[19] Trials testing its implementation in neuraxial anesthesia were promising.[20] As neuraxial anesthesia is widely used in orthopedic surgeries, the question remains whether it is effective and safe to add dexmedetomidine to the spinal anesthesia solution for these surgeries.

In this systematic review and meta-analysis, we aim to compare the outcomes of spinal anesthesia after adding dexmedetomidine to bupivacaine versus a sole bupivacaine or ropivacaine-based saline regimen. We conducted a meta-analytic score to evaluate outcomes such as time to sensory segments regression as well as block and duration of block. The significance of this study is to provide a guidance for the use of dexmedetomidine for spinal anesthesia in orthopedic surgeries depending on block quality.

2. Methodology

This systematic review of controlled trials assessed the effect of intrathecal dexmedetomidine added to local anesthetic agents on the block quality of spinal anesthesia in orthopedic surgeries. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to conduct the present meta-analysis.21 The study protocol was registered in the PROSPERO database under number: CRD42021234462

We searched the databases PubMed, Google Scholar, and Medline using the keywords ‘dexmedetomidine’, ‘spinal anesthesia’, ‘orthopedic surgery’ and ‘intrathecal’, without any language restriction, updated until November 10, 2020. References were reviewed to make sure all potential data were collected.

Inclusion criteria included:- (1) randomized controlled clinical trials (RCT); (2) treatment group received intrathecal 5 µg dexmedetomidine in addition to 2.5−3 ml (12.5−15 mg) ropivacaine or 2.5−3 ml (12.5−15 mg) bupivacaine, while the control group received 0.5 ml of 0.9% normal saline as additive; and (3) the outcomes included at least one of the following: duration of surgery, time for reaching T10 dermatome sensory block, time to one sensory segment block regression, time to two sensory segments block regression, time to reach Bromage score 0, and time to reach Bromage score of 3. Exclusion criteria contained: (1) systematic reviews, case reports and retrospective studies; (2) non-intrathecal administration of dexmedetomidine; and (3)

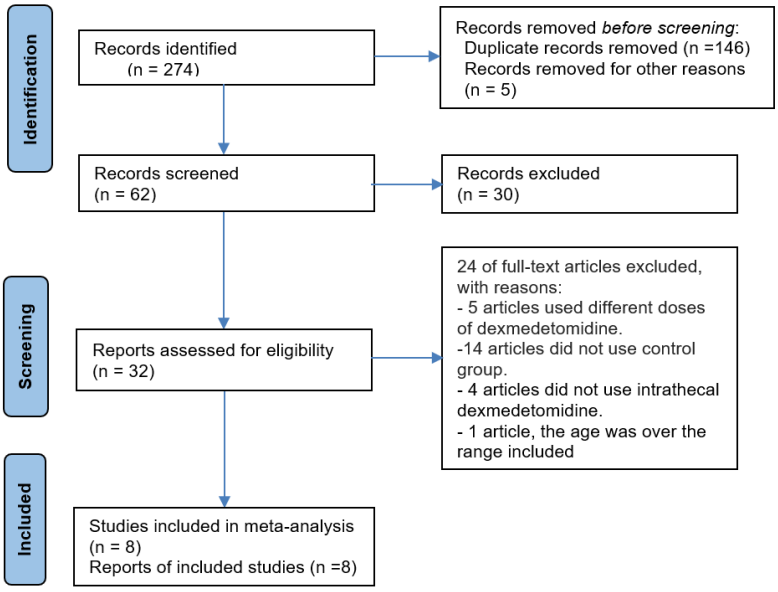

Figure 1-a: Study flow diagram

using an additional drug to the local anesthetic rather than dexmedetomidine.

Data extraction

Two authors independently extracted the data from the included studies based on standardized datasheet, and for any disagreement, a third author was counselled to solve the disagreement. The following data were extracted; the year of publication, the number of samples in the experimental group and control group, the type of intervention, the follow-up period of the study, the length of one and two segments block, the time for fading of motor block and the time of complete motor block.

Quality assessment

Each study was evaluated by two authors. The quality of the trials has been evaluated according to Cochrane-risk-of-bias tool.[22] Categories that were evaluated: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other bias. Categories were allocated to three levels according to risk of bias; low risk, unclear risk, and high risk.

Statistical analysis

We used Review Manager (version 5.3 for MacOS; The Nordic Cochrane Center, The Cochrane Collaboration) to conduct the meta-analysis of the extracted data. The I2 statistic was used to assess heterogeneity. The criteria and solutions for heterogeneity in the trials included in this meta-analysis are as follows; we used the fixed-effect model for the meta-analysis when I2 < 50%, otherwise we used the random-effects model for the meta-analysis. The results of the continuous outcomes are described by the mean difference and 95% confidence interval (CI).

Bromage score was calculated during the time interval between injection of the drug into the subarachnoid space, and the patient's inability to lift the straight extended leg (Bromage 3). Measurements were calculated as follows: Bromage score 0: free movement of legs/feet; Bromage score 1: just able to flex knees with free movement of foot; Bromage score 2: unable to flex knees, but with free movement of foot; and Bromage score 3: unable to move their legs/feet

3. Results

3.1. Study selection and characteristics

We identified 274 papers through database search and after removal of the duplicate data we got 151. Following scanning of these papers, 62 trials were identified. Thirty were removed after reading abstracts because of irrelevance, and the remaining 32 articles were retrieved in full text. After thorough reading, 5 articles were removed because they used different doses than our inclusion criteria, 14 articles were removed because there were no control groups, 4 articles were removed because they did not use dexmedetomidine intrathecally, and one was removed because mean age was over the range included. Hence, we finally got 8 articles,[23–30] for quality evidence synthesis in this meta-analysis with number of participants n = 510 (Figure 1-a).

All studies included used 5 µg dose of dexmedetomidine added to bupivacaine or ropivacaine in treatment groups (Table 1), and none had high risk of bias when employing Begg's test [Risk of bias, (Figure 1)].

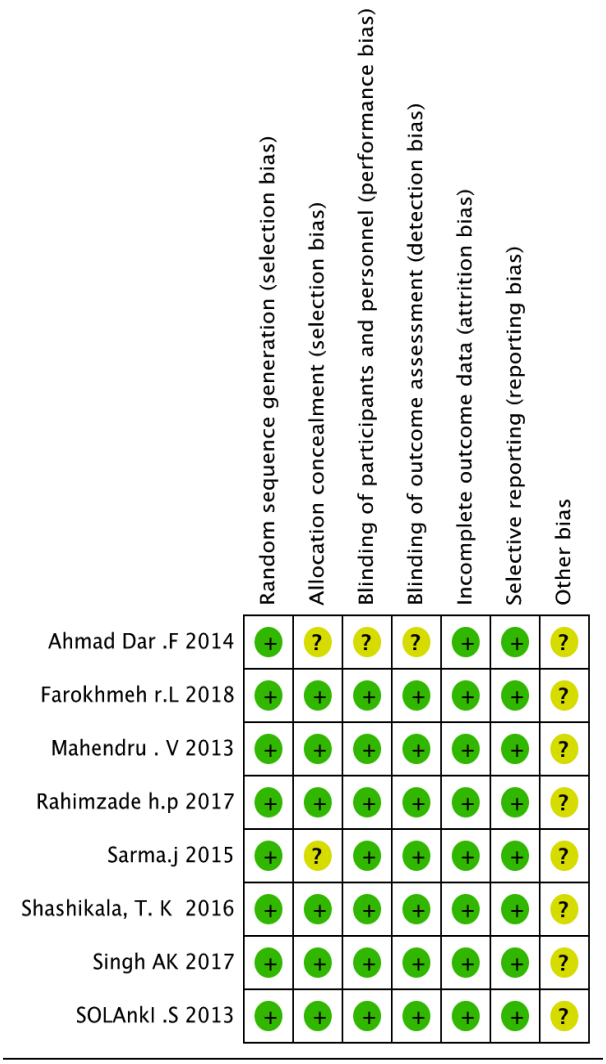

Figure 1: Risk of bias assessment

3.2. Duration of the surgery

Four studies showed no significant differences in the duration of surgery between dexmedetomidine and control groups as shown in Figure 2.

Mean difference = 6.58 min; 95%CI [−6.57–19.73]

Heterogeneity: $Tau^2 = 123.67$; $Chi^2 = 10.17$; df = 3 (P = 0.02); $I^2 = 71\%$

Test for overall effect: Z = 0.98 (P = 0.33).

3.3. Time to reach T10 dermatomal level:

Four studies showed no significant differences in time to reach T10 dermatomal level block between Dexmedetomidine and control groups as shown in Figure 3.

Mean difference = −1.69 min; 95% CI [−4.91−1.53]

Heterogeneity: $Tau^2 = 10.25$; $Chi^2 = 83.38$; df = 3 (P < 0.00001); $I^2 = 96\%$

Test for overall effect: Z = 1.03 (P = 0.30).

3.4. Time to one sensory segment block regression:

Four studies showed significant prolongation of time to one sensory segment block regression in dexmedetomidine group as shown in Figure 4.

Mean difference = 139.72 min; 95%CI [35.18−244.26]

Heterogeneity: $Tau^2 = 11285.09$; $Chi^2 = 666.95$; df = 3 (P < 0.00001); $I^2 = 100\%$

Test for overall effect: Z = 2.62 (P = 0.009).

3.5. Time to two sensory segments block regression:

Five studies showed significant prolongation of time to two sensory segments block regression in the dexmedetomidine group as shown in Figure 5.

Mean difference= 54.8 min; 95%CI [31.36−78.24]

Heterogeneity: $Tau^2 = 690.03$; $Chi^2 = 140.25$; df = 4 (P < 0.00001); $I^2 = 97\%$

Test for overall effect: Z = 4.58 (P < 0.00001).

The analysis showed heterogeneity between the results due to unknown reason:

For the first subgroup:

Table 1: Summary of the included studies

Authors	Country	Year	Number of patients		Treatment	
			Control	Dexmed	Control	Dexmedetomidine
Solanki .S	India	2013	30	30	Bupivacaine 15 mg	Bupivacaine 5 mg + dexmedetomidine 5 µg
Mahendru . V	India	2013	30		Hyperbaric bupivacaine 12.5 mg, 2.5 ml, with normal saline 0.5 ml	Bupivacaine 12.5 mg (2.5 ml) plus dexmedetomidine 5 µg (0.5 ml)
Farokhmehr. L	Iranian	2019	30	30	Ropivacaine 0.5% 3 ml (15 mg)	Ropivacaine 0.5% 3 ml (15 mg) with 5 µg of dexmedetomidine intrathecally,
Rahimzadeh. P	Iranian	2018	30	30	Hyperbaric bupivacaine 0.5% 2.5 ml	Hyperbaric bupivacaine 0.5% 2.5 ml plus dexmedetomidine 5 µg
Ahmad Dar. F	Kashmir	2014	30	30	Bupivacaine 0.5% 3 ml (15 mg) + 0.5 ml normal saline	Bupivacaine 0.5% 3 ml (15 mg) + 0.5 ml (5 µg) dexmedetomidine
Singh Ak	India	2017	25	25	Ropivacaine 0.5%	Dexmedetomidine 5 µg + Ropivacaine 0.5%
Sarma J	India	2015	50	50	Bupivacaine 0.5% 15 mg + 0.5 ml normal saline	Bupivacaine 0.5% 15 mg + 5 µg dexmedetomidine
Shashikala	India	2016	30	30	Bupivacaine 12.5 mg (2.5 ml)	Bupivacaine 12.5 mg (2.5 ml) plus 5 µg dexmedetomidine (0.5 ml)

Mean difference = 82.96 min; 95%CI [78.54−87.39]

Heterogeneity: Tau² = 0.00; Chi² =0.76; df = 2 (P = 0.38); I² = 0%

Test for overall effect: Z = 36.74 (P < 0.00001)

For the second subgroup:

Mean different =36.10 min; 95%CI [29.68−42.52]

Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 2 (P = 0.68); I² = 0%

Test for overall effect: Z = 11.02 (P < 0.00001)

Test for subgroup differences:

Chi² = 137.81; df = 1 (P < 0.00001), I² = 99.3%

Although the cause of heterogeneity is unknown, results still show significant prolongation of time to two segment block regression.

3.6. Time to reach Bromage score 0:

Five studies showed significant prolongation of time to reach Bromage score of 0 in the dexmedetomidine group as shown in Figure 6.

Mean difference= 93.66 min; 95%CI [30.20−157.12]

Heterogeneity: Tau² = 5133.17; Chi² = 414.23; df = 4 (P < 0.00001); I² = 99%

Test for overall effect: Z = 2.89 (P = 0.004).

3.7. Time to reach Bromage score 3:

Four studies showed significant decrease in time to reach Bromage score of 3 in the dexmedetomidine group as shown in Figure 7.

Mean difference = −2.62 min; 95%CI [−5.12−−0.13]

Heterogeneity: Tau² = 6.07; Chi² = 78.96; df = 3 (P < 0.00001); I² = 96%

Test for overall effect: Z = 2.06 (P = 0.04)

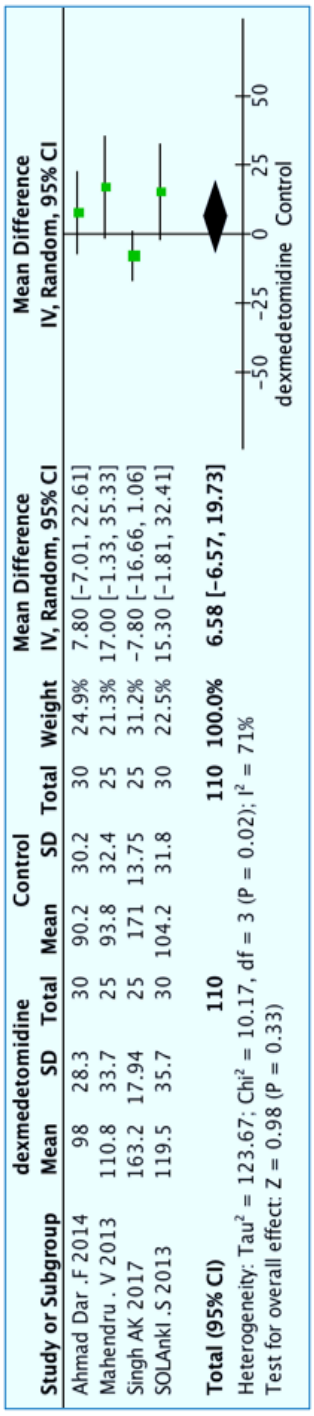

Figure 2: Duration of surgery

Figure 3: Time to reach T10

4. Discussion

This meta-analysis was performed to evaluate the effect of using dexmedetomidine as an additive in the blocking quality of spinal anesthesia. Spinal anesthesia has become the standard mode of anesthesia for many orthopedic surgeries in the lower limbs.[1–3] Orthopedic surgeries are performed in many different approaches, and have different durations; hence need different anesthetic techniques. In the view of inherent risks

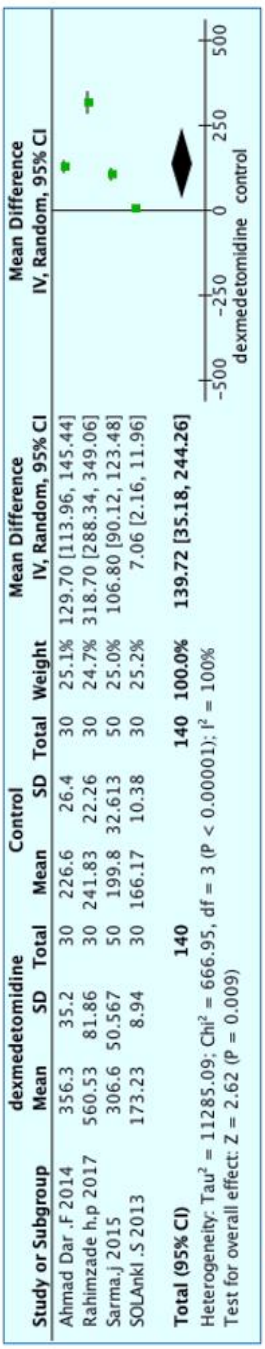

Figure 4: Time to one sensory segment block

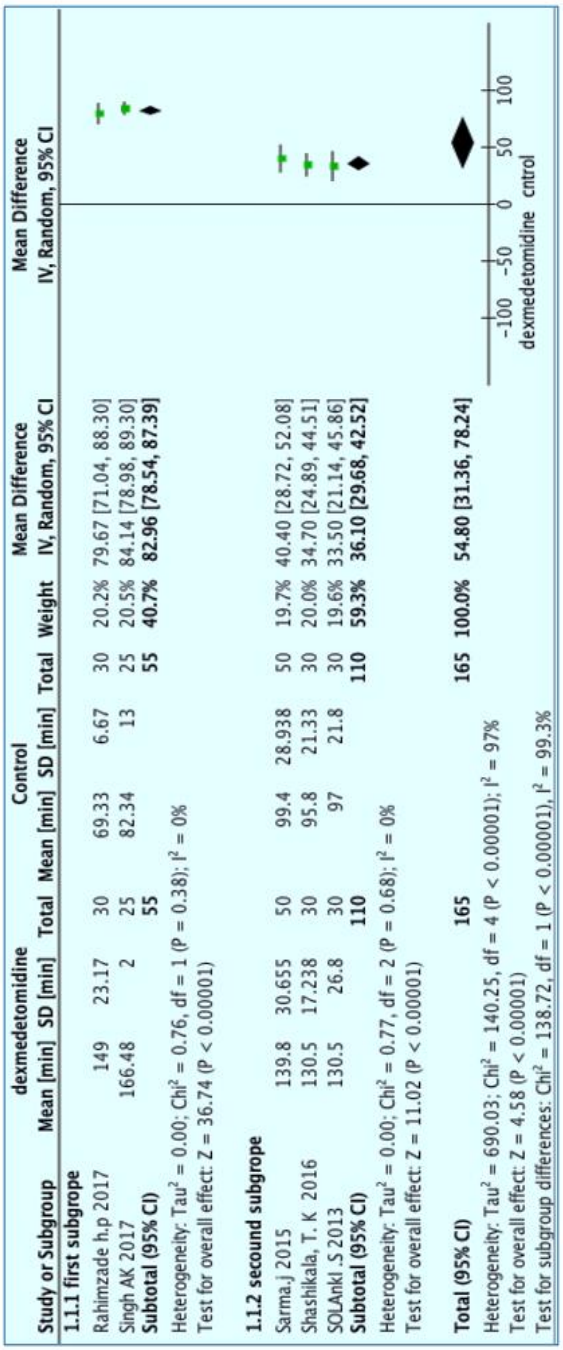

Figure 5: Time to two sensor block regression

involved in implementing high doses of bupivacaine to achieve longer duration of neuraxial anesthesia,[31,32] a scoping review of other safe additives is essential. In this systematic review, dexmedetomidine appears to achieve extended motor and sensory block.

Intravenous dexmedetomidine is a centrally-acting sedative with a relatively wide therapeutic index.[33,34] When used as an IV sedative, dexmedetomidine group has significantly higher values of mean arterial pressure and O_2 saturation compared to propofol group.[35] Furthermore, when dexmedetomidine was infused intravenously during spinal anesthesia, it enhanced sensory and motor blockade quality and induced a state similar to physiological sleep with a fair degree of amnesia.[36] Some studies on animal models suggested further benefits regarding ischemia preconditioning and airway irritation.[37,38] As for spinal dexmedetomidine, a previous meta-analysis including 639 patients compared dexmedetomidine and fentanyl as additives to local anesthetics in spinal anesthesia and showed there was no significant difference in the incidence of bradycardia, hypotension, nausea, vomiting, shivering and respiratory depression, while dexmedetomidine patients showed a significantly longer duration of sensory block with reduced pruritus.[39]

This meta-analysis was performed to evaluate the quality of block with addition of dexmedetomidine to spinal anesthesia. The main findings were as follows: (1) times to one and two sensory segments block regression are longer with dexmedetomidine groups over control groups, (2) Time for fading of motor block is longer with dexmedetomidine groups, (3) Time to reach complete motor block is shorter with dexmedetomidine, (4) Anesthesiologists should be vigilant about the dexmedetomidine side effects when used in spinal anesthesia.

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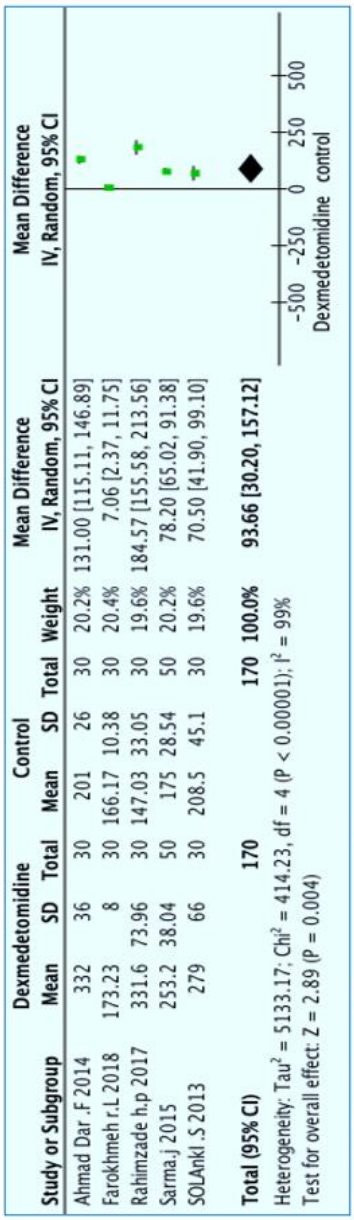

Figure 6: Time to reach Bromage score 0

Figure 7: Time to reach Bromage score 3

to one and two sensory segments block regression are longer with dexmedetomidine groups over control groups, (2) Time for fading of motor block is longer with dexmedetomidine groups, (3) Time to reach complete motor block is shorter with dexmedetomidine, (4) Anesthesiologists should be vigilant about the dexmedetomidine side effects when used in spinal anesthesia.

Dexmedetomidine has an established safety in animal and human trials.[40–43] It produces analgesia through inhibiting the release of C-fibers and hyperpolarization of dorsal horn neurons.[44] These antinociceptive effects might explain the prolongation of sensory block following intrathecal injection. The drug also binds to α2 adrenergic receptors on motor neurons of dorsal horn, which explains the prolongation of motor block.[45] Dexmedetomidine previously has been utilized in the peripheral nerve blocks. The quality of peripheral nerve block has been evaluated in a study on the effect of dexmedetomidine which showed that the sensory block onset was faster and the duration of block was longer in the group receiving dexmedetomidine as an additive to ropivacaine.[46]

Zhang et al.[47] have investigated the different ranges of doses of intrathecal dexmedetomidine and found that a dose between 5−15 μg/kg is considered a high dose, while 2−5 μg/kg is a low dose. Although using higher doses of dexmedetomidine prolongs sensory and motor block, it increases the risk of bradycardia. When added to epidural anesthesia, dexmedetomidine improves the quality of analgesia and intra-operative conditions in cesarean section.[48] Some practical and physiological aspects could limit the implementation of dexmedetomidine. Somnolence has been reported with dosing errors.[49] Moreover, dexmedetomidine cannot be used as a sole agent and its price is much higher than the average price of other anesthetic drugs.

This meta-analysis is novel regarding the efficiency of using dexmedetomidine as an additive in spinal anesthesia in orthopedic surgeries. Trials included were having low risk of bias and well-designed. Studies with a high risk of bias were excluded to enhance the reliability of our conclusion. Other meta-analysis investigated the differences between dexmedetomidine and opioids in spinal anesthesia claimed dexmedetomidine had no effect on nausea and vomiting, bradycardia or hypotension during cesarean section.[50]

5. Limitations

We acknowledge our study has limitations, including the lack of incorporating physiological aspects and cardiovascular effects of dexmedetomidine in our

analysis. The number of studies included was small due to tight inclusion criteria.

6. Conclusion

In conclusion, our meta-analysis indicated that adding dexmedetomidine to the spinal solution increase the duration of sensory and motor block of spinal anesthesia. Our results support use of dexmedetomidine to increase block quality of spinal anesthesia in orthopedic surgeries.

7. Trial registration

The study protocol has been registered in PROSPERO (CRD42021234462).

8. Competing interests

No conflict of interest was declared by the authors.

9. Funding

No internal or external funding was involved in the conduct of this study.

10. Availability of data

The numerical data generated in this study is available with the authors.

11. Authors contribution

Abdulrahman: Data collection, data analysis, manuscript writing and supervision

Aiman Data collection, data analysis, manuscript writing

Hamza: Manuscript writing and data collection

Tala: Manuscript writing

Anas: Data collection

Mahmoud: Supervision

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