

INTRATHECAL DEXMEDETOMIDINE USE IN SHIVERING PREVENTION: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS

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ABSTRACT

Shivering is a common postoperative complication and can lead to important interferences in monitorization, in addition to causing discomfort to the patient and increased oxygen consumption. Although frequently related to hypothermia, it can occur in normothermic patients, a fact that raises the importance of using pharmacological strategies for its prophylaxis and treatment. The effectiveness of alpha-2 agonists in preventing this entity has been extensively studied, mainly dexmedetomidine due to its greater selectivity to alpha-2 receptors. Many studies have shown that its intravenous infusion is capable of preventing post-anesthetic shivering, however its use has been questioned due to its possible side effects. Intrathecal administration, on the other hand, has been evaluated as an effective adjuvant drug to local anesthetics. Therefore, this study aims to review the evidence of the intrathecal use of dexmedetomidine as an adjuvant drug in spinal anesthesia to prevent shivering. A search was performed in the MEDLINE database accessed through PubMed and Biblioteca Virtual em Saúde (BVS), which resulted in seven randomized clinical trials presented in this work. They show a significant reduction in the incidence and intensity of shivering after spinal block with the use of five micrograms of intrathecal dexmedetomidine, in addition to promoting an increase in the duration of motor and sensory blocks. However, further studies are still needed to ensure that the hemodynamic repercussions are not significant.

Keywords: intrathecal dexmedetomidine; intrathecal adjuvant; shivering; spinal anesthesia.

INTRODUCTION

Shivering is an oscillatory and involuntary muscle activity caused when the hypothalamus's preoptic region is cooled. The mechanisms that lead to central hypothermia during anesthesia are the result of the redistribution of central heat to the periphery¹. The risk factors include male gender, young age, prolonged fasting, American Society of Anesthesiology risk score (ASA) greater than I, compromised nutritional status and extent of induced sympathetic block².

When it comes to spinal anesthesia, it is estimated that its incidence is around the significant number of 55%³. Patients submitted to neuraxial blocks have difficulty in reestablishing the temperature balance, since the vasoconstrictor mechanism is impaired by the sympathetic block. In addition, shivering in these patients does not effectively produce heat, once it is restricted to a small number of muscle groups cephalic to the block¹.

The prevention of this anesthetic complication is mainly due to its adverse effects. Shivering can increase oxygen consumption by 600%, which leads to hypoxemia, increased production of carbon dioxide, lactic acidosis and increased circulation of catecholamines. These changes are even more deleterious in patients with previous impairment of cardiac and pulmonary function, and may worsen their postoperative outcome. Other consequences are increased intraocular and intracranial pressure, worsening of pain at the surgical site, tachycardia and hypertension. It can also lead to interference in the monitoring of blood pressure, oximetry, heart rate and electrocardiogram, also interfering in post-anesthetic care²⁻⁶.

The effectiveness of alpha-2 agonists in preventing this entity has been extensively studied, mainly dexmedetomidine due to its greater selectivity to alpha-2 receptors compared to clonidine². Many studies have shown that its intravenous administration is able to prevent shivering after anesthesia, however it is not considered optimal due to its potential side effects. Intrathecal use, on the other hand, has been evaluated as an effective adjunct to local anesthetics, prolonging the duration of motor and sensory block, in addition to maintaining hemodynamic stability⁷.

OBJECTIVES

The present study aims to review the evidence related to the intrathecal use of dexmedetomidine as an adjunctive drug in spinal anesthesia to prevent shivering, in addition to evaluating other effects commonly associated with alpha-2 agonists such as prolonging motor and sensory block and increasing incidence of hypotension and bradycardia.

METHODOLOGY

This work consists of a descriptive review of randomized clinical trials that evaluated the intrathecal use of dexmedetomidine to prevent shivering in the MEDLINE database (Medical Literature Analysis and Retrieval System online) accessed through PubMed and VHL (Virtual Health Library) published in 2016 to 2021. The PubMed search was performed with the following descriptors: “intrathecal dexmedetomidine AND shivering” last accessed on January 5, 2021. The “randomized clinical trial”, “last 5 years” and “humans” filters were applied, obtaining 7 articles. In the VHL, the same descriptors were used with the filters "controlled clinical trial" and "last 5 years" resulting in 8 articles. 7 duplicate articles were excluded and, therefore, 8 articles remained to be analyzed.

After reading titles and abstracts, another article was excluded from the analysis as it studied the intravenous use of dexmedetomidine. At the end of the evaluation, 7 articles relevant to the proposed theme remained. Figure 1 summarizes the search results.

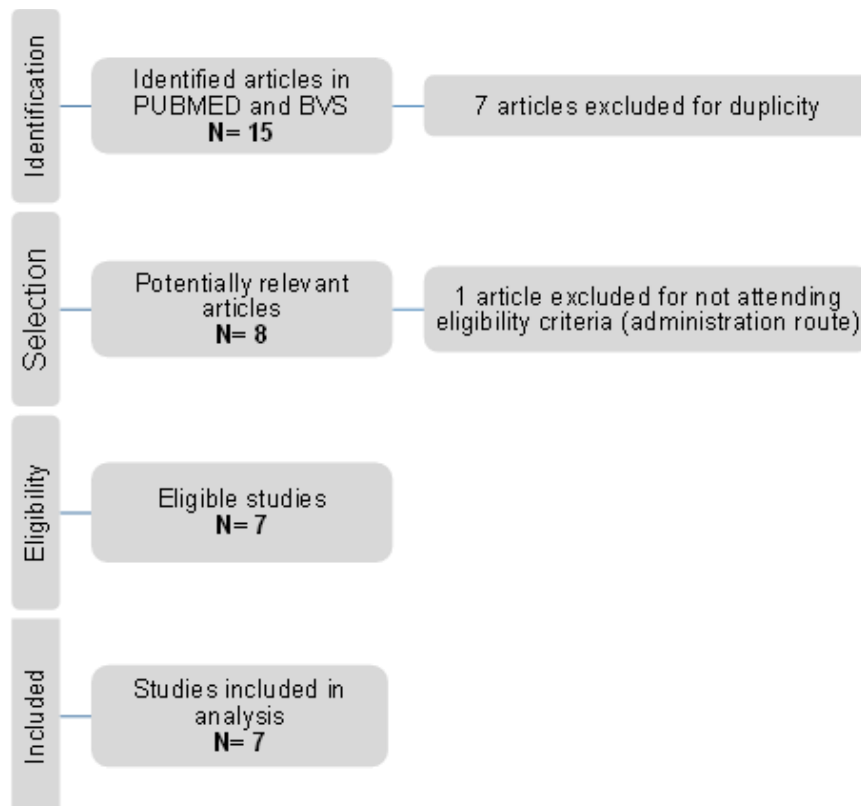


Figure 1 – Flowchart of included articles.

RESULTS AND DISCUSSION

Despite being frequently related to hypothermia, shivering may also occur in normothermic patients, which increases the importance of using pharmacological drugs for prophylaxis and treatment. Many drugs are being studied for their anti-shivering effects, but none are considered the gold standard in the management of this condition⁴. A popular drug is meperidine, but its side effects such as sedation and respiratory depression are important disadvantages⁸. Despite being an opioid, meperidine has a potent alpha-2 adrenoreceptor agonist effect, from which some of its properties, including anti-tremor action, are believed to be derived⁹.

Recent studies have investigated the action of alpha-2 agonists in preventing postoperative shivering. Dexmedetomidine (DEX), due to its very selective alpha-2 agonist action, about 8 times more alpha-2 selective than clonidine, has been preferred^{2,4}. Its anti-shivering mechanism is not yet clear, but it is believed to act centrally, inhibiting thermoregulatory control, in order to reduce the trigger temperature to shivering and vasoconstriction¹⁰.

Most studies have analyzed the intravenous use of this drug and, hence, its intrathecal effects are not well known. Therefore, Nasser et al.¹¹ conducted a study published in 2017, with 50 patients classified as ASA I or II and aged between 18 and 45 years, undergoing elective cesarean section under spinal anesthesia, in order to examine the intrathecal effect of dexmedetomidine shivering prevention. The patients were divided into two groups: 12.5 mg of 0.5% heavy bupivacaine + 5 µg of DEX and 12.5 mg of 0.5% heavy bupivacaine + 0.5 ml of saline, equaling volumes of 3 ml in both solutions. The difference in the incidence of shivering between the groups was significant and smaller in the DEX group (24%) than in the saline group (52%) ($p = 0.04$). In addition, the shivering intensity, classified by the Tsai and Chu method (table 1), was significantly higher in the saline group in which 4 cases presented shivering of intensity ≥ 2 (cut-off point adopted for treatment with meperidine) occurred, while in the DEX group, there was only 1 case with this intensity ($p = 0.03$).

Two other studies surveyed the incidence of shivering as primary objectives. He et al.⁷ conducted a study, also published in 2017, with 90 obstetric patients classified as ASA I or II, aged between 28 and 40 years, gestational age ≥ 37 weeks, undergoing elective cesarean section under spinal anesthesia. The patients were divided into three groups that received volumes equal to 3 ml of solution. All patients received 2.5 ml of 0.5% hyperbaric bupivacaine. In addition, one of the groups received 2.5 µg of dexmedetomidine, another received 5 µg and the control received an equivalent volume of saline. The incidence of shivering was significantly lower in the group that received 5 µg of DEX (6.7%) compared to the group that received saline (36.7%) ($p = 0.005$) and the group that received the lowest dose (33.3 %) ($p = 0.01$). As in the previous work, tremor intensity was also significantly lower than in the other two groups: 9 patients had

moderate to severe shivering in the saline group, 8 in the lowest dose of DEX group and none in the highest dose group ($p = 0.000$). The intensity of shivering was graded using a 4-point scale (table 2).

Table 1 – Tsai and Chu method.

Classification of shivering intensity by Tsai and Chu method
0 = no shivering
1 = piloerection or peripheral vasoconstriction, with no apparent shivering
2 = muscular contraction limited to only one group
3 = muscular contraction in more than one group, but not generalized
4 = full body shivering

Table 2 – Four points scale.

Shivering intensity classification by 4 points scale
None = absence of noticeable muscular tension
Mild = mild masseter muscle tone
Moderate = proximal muscles shivering
Severe = full body generalized shivering

Omar et al.¹⁰ carried out a study published in 2019, with 105 patients who underwent uroscopic surgery, aged between 20 and 60 years and classified ASA I or II in order to compare intrathecal dexmedetomidine and magnesium sulfate in shivering prevention after spinal anesthesia. Magnesium sulfate, a non-competitive antagonist of N-methyl-aspartate (NMDA) receptors, has also been shown to be effective in preventing shivering. Its exact mechanism is still unclear, but a possible theory is that blocking NMDA receptors causes reduction in the levels of norepinephrine and serotonin, which plays a role in thermoregulatory control¹². The patients were divided into 3 groups. All received 2.5 ml of 0.5% hyperbaric bupivacaine (12.5 mg) + 0.5 ml of saline. However, in one of the groups the saline solution contained 25 mg of magnesium sulfate, in the second it contained 5 µg of DEX and in the third group the saline solution was pure. They demonstrated that both magnesium sulfate and DEX significantly reduced the incidence of shivering ($p < 0.001$). Five patients (14.3%) in the DEX group, 8 patients (22.8%) in the magnesium sulfate group and 21 patients (60%) in the control group had shivering. Among these, 5 (14.3%), 6 (17.4%) and 21 (60%), respectively, presented grade ≥ 3 shivering by the Tsai and Chu method (table 1), a statistically significant result ($p < 0.001$).

Other studies have been able to observe a reduction in shivering with the use of intrathecal dexmedetomidine, even though this was not the main outcome. Gautam et al.¹³ conducted a study published in 2017 to assess the effects of intrathecal DEX as an adjunct to hyperbaric bupivacaine in spinal anesthesia. The study included 71 adult participants, ASA I and II, aged between 18 and 75 years, who underwent inguinal hernia repair or vaginal hysterectomy with or without pelvic floor repair, divided into two groups. 12.5 mg of 0.5% hyperbaric bupivacaine was used in both and in one of them 0.5 ml of saline was added and in the other 0.5 ml of saline containing 5 µg of DEX. There was a significant reduction in the incidence of this complication in the dexmedetomidine group (11.1% versus 31.4% in the control, $p = 0.043$). A year later, this same author published a new study¹⁴ with women undergoing abdominal hysterectomy for benign indications, ASA I or II, aged 30-65 years, comparing fentanyl and dexmedetomidine as intrathecal adjuvants. Both groups received a solution with 3.5 ml containing 15 mg of hyperbaric bupivacaine, however in one of them the solution had 25 µg of fentanyl and 10 µg of DEX in the other. The occurrence of shivering was significantly lower in the DEX group (10.3% versus 37.9% in the fentanyl group, $p = 0.029$).

In this context of comparing the intrathecal effects of dexmedetomidine with other drugs commonly used by this route, Qi et al.¹⁵ conducted a study published in 2016 with 118 pregnant women at term, ASA I and II, submitted to elective cesarean sections comparing the effects of intrathecal dexmedetomidine and morphine as adjuvant drugs in spinal anesthesia. The patients were divided into three groups: one group received a solution of 2 ml of 0.5% isobaric bupivacaine containing 5 µg of DEX, another received a solution of 2 ml of 0.5% isobaric bupivacaine containing 100 µg of morphine, and the control received only 2 ml of 0.5% isobaric bupivacaine. The primary objective was to assess the block quality and the effects of analgesia and sedation, but the results showed, in terms of adverse effects, that shivering was significantly reduced in the DEX group (7.7%) compared to the other groups (30 % in the morphine group and 35.9% in the control group) ($p = 0.009$).

Minagar et al.¹⁶ investigated, in a study published in 2019, carried out with 100 patients aged between 18 and 65 years, ASA I and II, who underwent elective lower abdominal surgery, the effect of intrathecal dexmedetomidine associated with local anesthetic on the duration of analgesia. The case group received 12.5 mg of bupivacaine and 0.5 ml of solution containing 5 µg of DEX, while the control group received 12.5 mg of bupivacaine and 0.5 ml of saline. This was the only study in which the incidence of shivering was slightly higher (86%) in the case group than in the control group (72%), but this finding was not statistically relevant ($p = 0.14$). The intensity of shivering, graduated using the Tsai and Chu method (table 1), was higher in the control group, which obtained an average of 1.4 than in the DEX group, which had an average of 0.9. However, this result was also not statistically significant ($p = 0.377$).

Table 3 summarizes the interventions performed, the size of the samples and the incidence of shivering in each group studied.

Table 3 – Obtained results by randomized clinical trials about shivering incidence.

Study	Country	Type of Surgery	Local anesthetic	Intervention	Sample size	Shivering incidence
Qi <i>et al.</i> (2016)	China	Elective cesarean	Isobaric bupivacaine 10 mg	Dexmedetomidine 5 µg versus morphine 100 µg versus saline solution	39/40/39	3/12/14
Gautam <i>et al.</i> (2017)	Nepal	Inguinal hernia repair or vaginal hysterectomy	Hyperbaric bupivacaine 12,5 mg	Saline solution versus dexmedetomidine 5 µg	35/36	11/4
Nasseri <i>et al.</i> (2017)	Iran	Elective cesarean	Hyperbaric bupivacaine 12,5 mg	Saline solution versus dexmedetomidine 5 µg	25/25	13/6
He <i>et al.</i> (2017)	China	Cesarean	Hyperbaric bupivacaine 12,5 mg	Saline solution versus dexmedetomidine 2.5 µg versus dexmedetomidine 5 µg	30/30/30	11/10/2
Gautam <i>et al.</i> (2018)	Nepal	Abdominal hysterectomy	Hyperbaric bupivacaine 15 mg	Fentanil 25µg versus dexmedetomidine 10 µg	29/29	11/3
Omar <i>et al.</i> (2019)	Egypt	Uroscópica	Hyperbaric bupivacaine 12,5 mg	Saline solution versus MgSO ₄ 25 mg versus dexmedetomidine 5 µg	35/35/35	21/11/5

Since there is a strong association between the incidence of shivering and hypothermia², it is important to highlight the strategies used to prevent it. Only three studies^{10,11,7} described the methods used between maintaining the room temperature between 22 and 28 °C, heating the fluids injected intravenously and covering the patient with a surgical field or sheet. Nasseri *et al.*¹¹ performed the measurement of tympanic and forehead temperature before the block, then every 15 minutes, and showed that the temperature trends in the two groups had no significant difference. Omar *et al.*¹⁰ reported that the temperature of all patients remained above 36 °C without the need for active heating. The other studies did not mention the use of measures against hypothermia, which may have occurred, since their primary objectives were to assess the duration of the blockade and analgesia, so that the observation of a reduction in the incidence of shivering was a secondary outcome.

Another well-known effect of alpha-2 agonists is to prolong the duration of motor and sensory block. It is believed that this effect may be caused by direct impairment in the release of excitatory amino acids from spinal interneurons or from binding to motor neurons in the dorsal horn of the spinal cord¹³. Three of the studies observed this outcome and showed that intrathecal dexmedetomidine prolongs the duration of motor and sensory block ($p < 0.05$)^{10,13,15}. Motor block evaluation was performed using the modified Bromage scale. Sensitive block was accessed by the pinprick test in two of the studies^{10,15} and in one¹³ by the loss of thermal sensitivity.

Omar et al.¹⁰ observed that in the dexmedetomidine group the average duration of motor block was $206, 57 \pm 22.06$ minutes, while in the control this average was 157 ± 13.07 min ($p < 0.001$). Sensory block had an average duration of 301.57 ± 39.44 minutes in the DEX group versus 198.14 ± 18.67 minutes in the control group ($p < 0.001$). Gautam et al.¹³ found that the motor blockade had an average duration of 433.06 ± 121.51 minutes against 334.29 ± 97.92 in the control ($p = 0.001$), while the sensitive blockade lasted 497.33 ± 121.51 minutes in the DEX group against $378, 86 \pm 106.7$ in the control ($p = 0.0001$). Qi et al.¹⁵ showed that the regression time of the sensory block 253.21 ± 42.79 minutes and the motor 226.15 ± 40.51 minutes was longer than in the control group (188.33 ± 37.62 and 162.18 ± 25.31 minutes respectively) ($p < 0.001$).

The most significant adverse effects reported with the intrathecal use of dexmedetomidine are hypotension and bradycardia, resulting from postsynaptic activation of alpha-2 adrenoceptors in the central nervous system, which inhibits sympathetic activity¹⁷. Therefore, it is important to assess whether the hemodynamic consequences would not be an important disadvantage.

The evaluated studies used three different doses ($2.5 \mu\text{g}$, $5 \mu\text{g}$ and $10 \mu\text{g}$) of dexmedetomidine. Most of them studied the dose of $5 \mu\text{g}$ and reported a decrease in the incidence of shivering without significant hemodynamic repercussions, but none of them obtained statistical significance for the outcomes of hypotension and bradycardia ($p > 0.05$). Only Gautam et al.¹⁴, who used a higher dose of DEX ($10 \mu\text{g}$) showed a significantly higher incidence of hypotension (51.7% in the DEX group versus 20.7% in the fentanyl group) ($p = 0.028$). In addition, there was a higher incidence of bradycardia (17.2%) than the group that received fentanyl (3.4%), however, without statistical significance ($p = 0.19$). Furthermore, this study did not have a control group, which the author justified by the high incidence of visceral pain in uterine surgeries performed under spinal anesthesia containing only local anesthetic. The $2.5 \mu\text{g}$ dose tested by He et al.⁷ also did not appear to have hemodynamic effects, a result also without statistical relevance, but did not show a reduction in the incidence of shivering. Thus, it is possible to observe a dose-dependence of dexmedetomidine effects.

CONCLUSION

It was found that the addition of 5 µg of dexmedetomidine as an adjunct drug to intrathecal bupivacaine was effective in reducing the incidence and intensity of shivering in a dose-dependent manner after spinal block, in addition to prolonging the duration of sensory and motor blocks without significant hemodynamic effect in patients with risk stratification ASA I and II. Smaller doses (2.5 µg) were not able to reduce the incidence of shivering, while larger doses (10 µg) had significant hemodynamic repercussions.

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