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Effect of Intrathecal Dexmedtomidine as an Adjuvant for Cesarean Section: A Review

Radhika Bajaj [a*#] and Amol Singam [a‡]

[a] Department of Anaesthesiology, JNMC, AVBRH, Datta Meghe Institute of Medical Sciences, Sawangi, Wardha, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Intrathecal dexmedetomidine has been used in spinal anesthesia during caesarean sections. The purpose of this review article was to investigate the effect of intrathecal dexmedetomidine on the adverse reactions of spinal anesthesia during cesarean section.
Objective: To evaluate the efficacy and safety of dexmedetomidine as a neuraxial adjuvant for elective caesarean section.
Methods: We did a literature search assessing the effect of intrathecal dexmedetomidine as an adjuvant in elective caesarean section in PubMed, EMbase, Web of science, EBSCO and GOOGLE library databases.
Results: 11 Randomized control trials were included. Overall, compared with control intervention in patients with elective cesarean section, dexmedetomidine intervention could significantly improve the characteristics of the block, including onset of sensory block, duration of the sensory block and duration of the motor block. Additionally, when compared with control group dexmedetomidine could prolong time to rescue analgesiaThe incidence of shivering in the dexmedetomidine group was significantly lower than that in the control group. The incidences of nausea and vomiting, bradycardia, hypotension and pruritus were not different between the two groups.
Conclusion: *Intrathecal* Dexmedetomidine can effectively improve the characteristics of the block, prolong time to rescue analgesia, and reduce the occurrence of shivering during cesarean section, but it does not affect the occurrence of nausea and vomiting, bradycardia or hypotension.

[#] *Junior Resident*
[‡] *Professor*
**Corresponding author: E-mail: radhikabajaj16@ymail.com;*

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1. INTRODUCTION

Spinal anesthesia is widely popular method for elective cesarean section as it has been associated with several benefits such as fewer number of adverse neonatal outcomes, allows the mother to experience the childbirth as she is fully conscious throughout the procedure, shorter hospital stays following cesarean section in comparison to general anesthesia [1–3]. Regardless, spinal anesthetic has numerous downsides, which includes poor pain relief, shivering intraoperatively and not extended post surgical analgesia . To improve neuraxial anesthesia and analgesia quality during both intra and post operation, aid early recovery from motor block, reduce the incidence of associated side effects, combined local anesthetics with adjuvant drugs such as opioids was well accepted currently to be usedin clinical neuraxial anesthesia practice [4–6]. The adjuvants most typically used in combination are opioids and clonidine.

Dexmedetomidine is a novel and highly selective α2-A receptor with sedative, anxiolytic, analgesic, anti-hypertensive and sympatholytic effects. Pre-clinic evidence showed that dexmedetomidine, used as an adjuvants to local anesthetic for neuraxial anesthesia, can shorten the onset time of the block [7], decrease postoperative pain intensity [8], prolong the duration of the block [9], reduce the requirement of the analgesics [10] and lower the incidence of adverse effect [11]. Hence, we have performed a meta-analysis to explore the effects of dexmedetomidine as a neuraxial adjuvant on features of the anesthesia, analgesia and side effects during elective cesarean section.

2. METHOD

This systematic review was performed in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [12] and the Cochrane Handbook for Systematic Reviews of Interventions. All data were collected from previous published studies, and thus, no ethical approval and patient consent were required.

3. SEARCH STRATEGY

We systematically searched for articles, case reports in PubMed, EMbase, Web of science and GOOGLE. We also cross- checked the reference lists and relevant reviews to include additional eligible studies. The search strategy was done using a combination of free text words and Medical Subject Headings (MeSH) terms. We have included international and national articles and publications related to the use of dexmedetomidine in pregnant females for caesarean section.

Inclusion criteria:

The inclusion criteria were as follows:

(1) Original and independent studies;
(2) RCTs;
(3) Neuraxial dexmedetomidine was delivered via any intravertebral routes, such as epidural, intrathecal, and caudal route in women undergoing elective cesarean sections.

Exclusion criteria:

Any study with one of the following conditions was excluded:

(1) Non-RCTs
(2) Abstracts from conferences, letters to the editor, or animal studies;
(3) Systematic reviews.

3.1 Data Extraction

The following information was extracted from each article: first author, the published year, the number of cases, baseline characteristics of patients, dexmedetomidine, control, study design, the onset of sensory block, the onset of motor block, the duration of the sensory block, the duration of motor block, the time to rescue analgesia, fentanyl consumption, nausea/ vomiting, pruritus, hypotension, bradycardia, shivering.

4. MAIN CONTENT

Information about the effects of intrathecal dexmedetomidine on shivering is sparse.

Hala E A Eid et al. [13] aimed to study dose related prolongation \sof hyperbaric bupivacaine (15 mg) spinal anaesthesia by dexmedetomidine in two different doses (10 µg and 15 µg) with respect to duration of sensory and motor block

and postoperative analgesic requirements produced by spinal bupivacaine (15 mg) (15 mg). 48 adult patients scheduled for ortho procedures. Each patient was administered 3.5 ml spinal injectate that consisted of 3 ml 0.5 percent hyperbaric bupivacaine and 0.5 ml containing either 10 µg dexmedetomidine (Group D1), 15 µg dexmedetomidine (D2) or normal saline (Group B) (Group B). Heart rate, arterial blood pressure, sensory level, motor block, discomfort and degree of sedation were measured intraoperatively and up to 24 hours following spinal anaesthesia. They discovered that Dexmedetomidine \ssignificantly lengthened time to two segment regression, sensory regression \sto S1, regression of motor block to modified Bromage 0 and time to first rescue analgesic. In addition, it considerably lowered postoperative painscores. In addition, group D2 patients showed greater sedation ratings and lower postoperative analgesic needs than Group D1 or B. Hemodynamic stability was maintained in the three groups. They determined that intrathecal dexmedetomidine in dosages of 10 µg and 15 µg substantially extended the anaesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose-dependent manner for extended complicated lower limb surgical techniques.

Al-Ghanem SM et al. [14] did a research of adding dexmedetomidine (5 µg) or fentanyl (25 µg) to intrathecal isobaric bupivacaine (10 mg) in gynecological procedures to evaluate the start and length of sensory and motor block as well as surgical analgesia and harmful consequences. 76 Patients were randomly randomised to receive intrathecally either 10 mg isobaric bupivacaine with 5 µg dexmedetomidine (group D n = 38) or 10 mg isobaric bupivacaine with 25 µg fentanyl (group F n = 38). They noticed that individuals in group D had considerably longer sensory and motor block times than individuals in group F. The onset times to reach T10 dermatome and to attain maximal sensory intensity as well as onset time to reach modified Bromage 3 motor block were not substantially different between the two groups. The mean period of sensory regression to S1 was longer ingroup D than group F (274 ± 73 vs 179 ± 47). The regression time of motor block to reach modified Bromage 0 was longer in group D than group F (240 ± 60 versus 155 ± 46). They concluded that among women undergoing gynecological surgery with spinal analgesia, 10 mg simple bupivacaine supplemented with 5 µg dexmedetomidine caused extended motor and sensory block compared to 10 mg standard bupivacaine with 25 µg fentanyl.

Shushruth WR et al. [15] examined the impact of adding dexmedetomidine (Dxm) (5 µg) vs fentanyl (25 µg) to intrathecal bupivacaine (10 mg) on spinal block features and neonatal prognosis in caesarean delivery. 60 ladies were placed into three groups: Control group (n = 30) received intrathecal placebo, with bupivacaine 10 mg in 2.5 ml, Dxm group (n = 30) received intrathecal dexmedetomidine 5 µg with bupivacaine 10 mg in 2.5 ml. and Fentanyl group (n = 30) got intrathecal fentanyl 25µg + bupivacaine 10 mg. in 2.5 ml. They observed the onset time to attain peak sensory and motor level were shorter in DXM and Fentanyl groups compared with the control group with no significant difference between DXM and Fentanyl groups. Also DXM group had substantially longer sensory and motor block durations than individuals in control and Fentanyl group. No harmful effects on mothers or newborns were detected among three groupings. They determined that DXM looked to be a desirable adjuvant to spinal bupivacaine in caesarean section delivering high quality of spinal anaesthesia with minimum side effects and no detrimental effects on the babies.

Rajni Gupta et al. [16] with an intention to examine the onset and duration of sensory and motor inhibition, hemodynamic impact, postoperative analgesia, and side effects of dexmedetomidine or fentanyl administered intrathecally as adjuvant with hyperbaric 0.5 percent bupivacaine performed a research on 60 patients categorized as ASA class I and II scheduled for lower abdominal surgeries. Patients were randomly randomised to receive either 12.5mg hyperbaric bupivacaine with 5µg dexmedetomidine (group D, n=30) or 12.5 mg hyperbaric bupivacaine with 25 µg fentanyl (group F, n=30) intrathecal. The mean period of sensory regression to S1 was 476±23 min in group D and 187±12 min in group F($P<0.001$). The regression time of motor block to reach modified Bromage 0 was 421±21 min in group D and 149±18 minutes in group F ($P<0.001$).

They determined that intrathecal dexmedetomidine was related with persistent motor and sensory block, hemodynamic stability, and lower requirement for rescue analgesics in 24 h as compared to fentanyl.

Hala E A Eid et al. [13] sought to evaluate dosage related prolongation of hyperbaric

bupivacaine (15 mg) spinal anaesthesia by dexmedetomidine With two distinct dosages (10 µg and 15 µg) with regard to duration of sensory and motor block and postoperative analgesic needs generated by spinal bupivacaine (15 mg) (15 mg). 48 adult patients scheduled for ortho procedures. Each subject was given 3.5 ml spinal injectate that consisted of 3 ml 0.5 percent hyperbaric bupivacaine and 0.5 ml containing either 10 µg dexmedetomidine (Group D1), 15 µg dexmedetomidine (D2) or normal saline (Group B) (Group B). Heart rate, arterial blood pressure, sensory level, motor block, discomfort and level of sedation were measured intraoperatively and up to 24 hours after spinal anaesthesia. They discovered that Dexmedetomidine considerably delayed duration to two segment regression, sensory regression At S1, regression of motor block to modified Bromage 0 and time to first rescue analgesic. In addition, it considerably lowered postoperative pain 44 scores. In addition, group D2 patients showed greater sedation ratings and lower postoperative analgesic needs than Group D1 or B. Hemodynamic stability was maintained in the three groups. They determined that intrathecal dexmedetomidine in dosages of 10 µg and 15 µg substantially extended the anaesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose-dependent manner for extended complicated lower limb surgical techniques.

S Fyneface-Ogan et al. [17] intentionally undertook a research to assess the impact of adding dexmedetomidine to hyperbaric bupivacaine for neuraxial analgesia for labor. Ninety laboring multiparous women were assigned to undergo single shot intrathecal bupivacaine alone (B), bupivacaine with fentanyl (BF), or bupivacaine with dexmedetomidine (BD) (BD). Sensory and motor block properties; duration from injection to two dermatome sensory regression, sensory regression to S1 dermatome, and motor block regression to Bromage 1 were detected. Labor pain was measured using a 10 cm verbal pain scale. Peak sensory block levels were not significant. The time for sensory and motor blocks to reach T10 dermatome and Bromage 1, respectively, was quicker in group BD than in the other groups (P = 0.0001). The period for sensory regression to S1 was greatly delayed in the group BD (P = 0.0001). Motor block regression time to Bromage 1 was also extended in the group BD (P = 0.0001). Neonatal outcome (APGAR) was normal in all groups. They proposed that single shot intrathecal bupivacaine 45 oral dexmedetomidine dramatically extended sensory block in labour women.

Vidhi Mahendru et al. [18], with a goal to know the dexmedtomine effectiveness as an adjuvant to hyperbaric bupivacaine, performed a prospective randomized double blinded research in 120 people of either sex of ASA I and II scheduled for lower limb procedures. With bupivacaine 12.5mg, group BS was added normal saline, group BF 25µgm fentanyl, group BD with 5 µgm dexmedetomidine and group BC with 30 µgm clonidine. The initial time to attain maximal sensory and motor level, the regression time of sensory and motor block, hemodynamic abnormalities, and side effects were recorded. Patients in Group BD showed considerably longer sensory and motor block times than patients in Groups BC, BF, and. The mean time of two segment sensory block regression was 147 ± 21 min in Group BD, 117 ± 22 in Group BC, 119 ± 23 in Group BF, and 102 ± 17 in Group BS (P <0.0001). The regression time of motor block to attain modified Bromage zero (0) was 275 ± 25, 199 ± 26, 196 ± 27, 161 ± 20 in Group BD, BC, BF, and BS, respectively (P < 0.0001). The onset periods to achieve T8 dermatome and modified Bromage 3 motor block were not substantially different between the groupings. They noticed that BD group showed considerably delayed necessity of rescue analgesic. They have found that the usage of intrathecal dexmedetomidine as adjuvant to bupivacaine for extended duration 46 surgical operations causes severe intra operative anaesthesia and after surgical analgesia with minimal side effects.

Hem Anand Nayagam et al. [19] did a prospective randomized double blind trial of intrathecal fentanyl & dexmedetomidine added to low dosage bupivacaine for spinal anaesthesia for lower abdomen operations in 150 patients. Group F (n = 75) got bupivacaine 0.5 percent heavy (0.8 ml) + fentanyl 25 µg (0.5 ml) + normal saline 0.3 ml and Group D (n = 75) got bupivacaine 0.5 percent heavy (0.8 ml) + dexmedetomidine 5µg (0.05 ml) + normal saline 0.75 ml, aiming for a final concentration of 0.25 percent of bupivacaine (1.6 ml), injected intrathecally. Time to reach T10 block level, peak sensory block level (PSBL), time to achieve peak block level, time to two segment regression (TTSR), the degree of motor block (MBS), side-effects and the time to first analgesic request (TFAR) were recorded. PSBL (P = 0.000) and TFAR (P = 0.000) were extremely significant.

Mean time to PSBL (<0.05) and MBS (P = 0.035) were significant. They found that the clinical advantage of dexmedetomidine versus fentanyl was that it encouraged the propagation of the block and gave longer post surgical analgesia compared to fentanyl.

Veena Chatrath et al. [20] examined the analgesic effectiveness and negative effects of adding dexmedetomidine to bupivacaine in spinal anaesthesia for infraumbilical operations. Spinal anaesthesia was obtained with 12.5 mg With 0.5 percent hyperbaric bupivacaine in group B (n = 50) and with 12.5 mg of 47 0.5 percent hyperbaric bupivacaine + 10 µg of dexmedetomidine in group D (n = 50). The two groups were compared in regard to hemodynamic characteristics, onset of sensory block to T10 and regression to S1, time to attain Bromage 3 and regression to Bromage 0, duration of analgesia, number of doses of rescue analgesia necessary, and problems arising in 24hr. They have concluded that addition of dexmedetomidine to bupivacaine leads to early onset of sensory and motor inhibition with sustained duration, and patients stayed pain free for a longer period with lower requirement for rescue analgesia in the postoperative period as compared with simple bupivacaine.

Elkanky et al. [21] that intrathecal dexmedetomidine at a dose of 5 µg provided a beneficial antishivering effect without major adverse effects in parturients undergoing CSs under SA. In this study, factors such as core body temperature, ambient temperature and temperature of intrathecal drugs were comparable in the two groups. However, factors such as sensory block levels, which may also increase shivering5 were not mentioned.

Gupta et al. [6] on intrathecal dexmedetomidine, parturients were allocated to three groups. Dexmedetomidine 2.5 µg and 5 µg were administered respectively. Dexmedetomidine (5 µg) added to bupivacaine for SA significantly reduced the incidence and intensity of shivering during CSs. However, dexmedetomidine at a dosage of 2.5 µg appeared to be ineffective. A dose - response experiment for dexmedetomidine is needed to determine the optimal dose required for prevention of shivering without significant side effects. The mechanism of dexmedetomidine in inhibiting shivering is complex. It is possible that dexmedetomidine reduces central thermosensitivity through stimulation of central α2-adrenergic receptors, thereby decreasing the central thermoregulatory threshold for shivering.30 In addition, intrathecal dexmedetomidine may prolong the motor and sensory blockade and provide an analgesic effect in CS.

5. DISCUSSION

Using sedatives and opioids in a parturient have long been contentious since these medicines tend to pass the uteroplacental barrier and can have detrimental effects on the kid. But newer medications as remifentanil and dexmedetomidine due to their diff erent and unique pharmacokinetics do not cross placenta significantly. Dexmedetomidine has a significant placental retention (0.77 maternal/fetal index). Also, it is extremely lipophilic as a result of which it is preserved in placental tissue [8]. Because of these qualities, it doesn't penetrate the uteroplacental barrier, and even if it does cross, it is minimal. Also, it enhances the frequency and amplitude of uterine contraction directly. But one must be able to explain the use of dexmedetomidine in a parturient, since it is still an off-label usage, if used for labor analgesia or as an adjuvant to general anesthetic for cesarean section. However, in maternal conditions like Pulmonary Hypertension (primary/acquired), PIH Rheumatic Heart Disease (especiallmitral Stenosis), Th yrotoxicosis, and Coronary artery disease were hemodynamic fl uctuations during labor or cesarean section can be disastrous, dexmedetomidine can be used in recommended doses due to its desirable properties of analgesia, sedation, sympatholysis, and ability to reduce anesthetic requirement. But dexmedetomidine must be utilized by an expert Anesthesiologist in a well-equipped set up with rigorous hemodynamic monitoring. Most of the case studies that reported the use of dexmedetomidine in parturients have indicated that infants born were with normal Apgar scores which demonstrates that even if there is any uteroplacental transfer, it doesn't aff ect the fetal well-being [3]. However caution needs to be exercised while taking dexmedetomidine in presence of bradyarrhythmias, severe left ventricular or biventricular dysfunction and in volume deprived individuals. Also, administration of dexmedetomidine necessitates dosage modification in case of hepatic or renal impairment.

Our meta-analysis clearly suggested that dexmedetomidine as a neuraxial adjuvant could

improve the characteristics of the block, such as shortening the onset time of the block, prolonging the duration of the block, prolonging rescue analgesia time, increasing dose of fentanyl consumption, decreasing the incidence of shivering, but had no effect on nausea and vomiting, bradycardia, hypotension and pruritus.

6. CONCLUSION

With diligent monitoring of hemodynamics and correct selection of patient, dexmedetomidine may be utilized in a parturient with medical problems in which tachycardia and hypertension is not acceptable. We systematically searched for articles, case reports in PubMed, EMbase, Web of science and GOOGLE. We also cross-checked the reference lists and relevant reviews to include additional eligible studies. The search strategy was done using a combination of free text words and Medical Subject Headings (MeSH) terms. We have included international and national articles and publications related to the use of dexmedetomidine in pregnant females for caesarean section Literature suggests that dexmedetomidine doesn't cross uteroplacental barrier due to its high placental extraction but as its use in labor analgesia/ as an adjunct to general anesthesia still remains off label, the concerned Anesthesiologist must select the patient carefully and should be able to justify its use. One should strive to avoid the administration of dexmedetomidine in presence of bradyarrhythmias, severe left ventricular/biventricular dysfunction and hypovolemic conditions. Dose modification is necessary as advised in presence of hepatic and renal impairment.

Currently, there is no gold standard treatment for shivering during CSs under NA. In this review, intrathecal dexmedetomidine, intrathecal fentanyl, intrathecal sufentanil and intravenous tramadol seem to be effective interventions. Intravenous ketamine and intrathecal meperidine are associated with increased side effects as the doses increase. Therefore, they may be not suitable for parturients.

7. LIMITATION

Some limitations of this systematic review need to be mentioned. Firstly, in most of the studies, a single sort of medicine is explored and the comparison across other drugs is scant. More research comparing the antishivering impact of various medicines are needed. Secondly, doseresponse tests are not undertaken to identify the dosage necessary for adequate suppression of shivering without generating serious adverse effects. Future trials in this sector should focus on the appropriate dose of the beneficial medicine utilizing a bigger sample size.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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