Evaluating the Effect of Dexmedetomidine Intravenous Infusion on Labor Pain Management in Primipar Term Pregnant Women

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Abstract

Background: The pain of labor is very severe. Most women prefer painless labor to routine labor if they are aware of the methods of analgesia. The aim of this study was to evaluate the effect of Dexmedetomidine intravenous infusion on labor pain management in primipar term pregnant women.

Methods: In this Non-randomized clinical trial with control group, all primipar term pregnant women were enrolled in the study. In the intervention group, after the active phase of labor, Dexmedetomidine was given according to the protocol and continued until phase two of labor. The control group received no intervention to reduce pain. Patients in both groups were evaluated for, fetal heart rate, Apgar scores, vital signs, pain intensity and sedation score.

Results: There were no significant difference in primary fetal heart rate, primary maternal hemodynamics, and mean Apgar scores of 1 and 5 minutes, between the two groups (p>0.05). There was no significant difference in the mean of fetal heart rate in different stages between two groups. Intra-group analysis in the intervention group showed that mean systolic and diastolic blood pressure were significantly decreased after drug administration but were in normal range. The active phase of labor in the intervention group was significantly shorter than the control group (p = 0.002). The mean VAS score after Dexmedetomidine administration decreased significantly from 9.25 at baseline to 4.61 after drug administration, 3.88 during labor and 1.88 after placental expulsion. The mean RSS score after Dexmedetomidine administration increased significantly from 1 at baseline to 2.05 after drug administration, 2.22 during labor and 2.05 after placental expulsion.

Conclusion: Based on results, it seems that administration of Dexmedetomidine to manage labor pain with careful monitoring of mother and fetus is recommended. Due to limited studies, further larger and multicenter studies are needed to be performed.

Trial registration: This study was registered on Iranian registry of clinical trials, identification number IRCT20161022030421N5, registered on February 2, 2019, https://irct.ir/trial/40134.

Background

The labor pain is very severe. Even the use of distraction techniques, such as music or video games, does not delay the time to seek analgesia (1). Failure to communicate between a gynecologist and the patient leads to obstacles in the patient's knowledge of the painless delivery method and therefore the tendency of pregnant women to have cesarean Sect. (2). Based on previous investigation, it is reported that most women prefer these methods instead of routine labor if they are aware of these analgesic methods (3). Using analgesia for delivery reduces the incidence of elective cesarean Sect. (4). Most painless delivery methods accelerate labor by reducing the duration of active phase (5–8). In addition, pain relief is associated with a decreased prevalence of postpartum depression (9, 10).
Although, most studies on painless delivery currently focused on the epidural method and this method has been recognized as a safe and uncomplicated procedure for the mother and infant (11–15), this procedure may sometimes fails, or it may be contraindicated for any reason, or the mother may refuses to use the neuroaxial method (16, 17).

Dexmedetomidine is a specific α2 agonist, with sedative and analgesic effects, and the least probable respiratory depression (18). It has been used successfully to control shivering due to spinal cesarean section, and has had no significant hemodynamic complications; and the sedation was appropriate (19).

As there is limited studies in this issue and in previous case reports, intravenous Dexmedetomidine was used in labor and no complication was observed in the mother and infant (16, 17, 20–23), we aimed to evaluate the effect of Dexmedetomidine intravenous infusion on labor pain management in primipar term pregnant women who are contraindicated or refused for epidural procedure.

**Methods**

In this Non-randomized clinical trial with control group, all primipar term pregnant women, American Society of Anesthesiologists I and II, who referred to Baqiyatallah Hospital in Tehran from August 2019 to March 2020 were enrolled. Patients with fetal distress, latent phase of labor, prolong premature rupture of membrane, liver failure, renal failure, 2 or 3-degree heart block, neuropsychiatric diseases, and drug abusers were excluded. Mothers who were candidates for pain relief through intravenous drugs, after obtaining written consent were included in the intervention group, and mothers who were not candidates for pain relief and who decided to experience labor pain entered the control group after accepting the project.

In active phase of labor (diagnosed by a gynecologist), the patients were monitored for systolic blood pressure(SBP), diastolic blood pressure(DBP), pulse rate(PR), respiratory rate(RR) and percent of saturated hemoglobin(SPO2), and their vital signs were recorded in the questionnaire every five minutes to 15 minutes after placental expulsion. Fetal heart rate (FHR) monitoring was performed continuously and recorded every 5 minutes. FHR1, FHR2, and FHR3 were recorded at baseline, during administering bolus dose of Dexmedetomidine, and during labor, respectively. It was explained to patients on how to assess pain. Then, in the intervention group, after recording the initial effacement and dilatation, Dexmedetomidine (manufactured by Exir Pharmaceuticals) was infused intravenously for 10 minutes at a dose of 1 µg / kg (0.4% solution), followed by infusion of 0.2–1 µg / kg /hr. The dose of continuous infusion was based on the rate of analgesia by verbal analogue scale score (VAS ≤ 3) or sedation by ramsay sedation scale score (RSS < 5). The infusion continued until stage II of labor and this period was recorded as stage I. In the event of hemodynamic complications (SBP < 100 or PR < 60 or FHR < 100), the drug was temporarily discontinued and intravenous atropine at a dose of 0.01 mg / kg, and intravenous ephedrine at an initial dose of 10 mg were administered.

The control group received no intervention to reduce pain. Routine care was performed in these patients.
From the beginning of stage II until the birth of the infant it was recorded as stage II and stage III was indicated from the birth of the infant until the placental expulsion.

Patients in both groups were evaluated for pain intensity by VAS score and sedation by RSS score up to 15 minutes after placental expulsion. After birth, neonatal Apgar scores of 1 and 5 minutes were recorded. 15 minutes after placental expulsion, satisfaction of midwives was assessed in intervention group with the 5-point Likert index (strongly satisfied = 5, satisfied = 4, no comment = 3, dissatisfied = 2 and highly dissatisfied = 1).

**Ethical Considerations:**

This research project was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (number: IR.BMSU.REC.1397.250 date: 2019-02-15) and it was registered in the Iranian registry of clinical trials (IRCT20161022030421N5 date: 2019-07-20). Consent letters were obtained from participants.

**Data analysis**

The data were analyzed by SPSS software (version 22). Quantitative data were analyzed using descriptive software and displayed as Mean ± SD. Crosstabs software and Chi-Square test were used to compare percentages or frequencies. The normality of quantitative data was assessed by Kolmogorov-Smirnov test. Independent sample t-test was used to compare parametric data between two groups. Paired t-test was used to compare quantitative parameters before and after the intervention. Charts and figures were drawn in Excel and SPSS software. In this study, p value less than 0.05 was considered statistically significant.

**Results**

A total of 46 patients were studied in this study including 20 patients in the intervention group and 26 patients in the control group. No patient was excluded in the two groups. Two patients in control group and three in intervention group underwent cesarean section for different reasons. There was no significant difference in mean age (p = 0.79), height (p = 0.94), and weight (p = 0.2) between the intervention and control groups. Comparison of mean cervical dilatation and effacement between the two groups showed no significant difference in mean dilatation (p = 0.89) and effacement (p = 0.87). The comparison of demographic characteristics between the two groups is shown in (Table 1).
Results showed a significant difference in mean duration of first stage of labor between intervention and control groups (\(p = 0.002\)). There was no significant difference in the mean duration of second (\(p = 0.95\)) and third (\(p = 0.47\)) stages of delivery between groups (Table 2).

Two patients (8.33\%) in intervention and no patients in control group needed assisted delivery device and no significant difference was noted between groups (\(p = 0.22\)). Need of oxytocin in control and intervention groups was 10 out of 26 patients (38.46\%) and 8 out of 20 patients (40\%), respectively. There
was no significant difference in the frequency of patients who were in need for oxytocin administration between the two groups (p = 0.91).

Furthermore, there was no significant difference in FHR1 between groups (p = 0.98). Mean FHR1 was 132.55 ± 9.11 in the intervention group and 132.50 ± 9.88 in the control group. The mean FHR1, FHR2 and FHR3 in the intervention group were 132.55 ± 9.11 and 134.38 ± 8.40 and 133.44 ± 8.02, respectively. There was no significant difference in mean of FHR1 and FHR2 (p = 0.31), mean of FHR1 and FHR3 (p = 0.42) and mean of FHR2 and FHR3 (p = 0.51) in intervention group. Mean FHR1 and FHR3 in the control group were 132.50 ± 9.88 and 135.08 ± 8.84, respectively. There was no significant difference in the mean of FHR1 and FHR3 in the control group (p = 0.51).

Mean baseline DBP in the intervention and control groups were 81.88 ± 6.39 and 81.00 ± 8.82, respectively. There was no significant difference in mean baseline DBP between the two groups (p = 0.72), indicating the homogeneity of samples before the study.

The mean of first, second, third and fourth DBP in the intervention group were 81.88 ± 6.39, 79.11 ± 12.8, 77.50 ± 10.47 and 73.0 ± 8.01, respectively (Fig. 1).

There was no significant difference in the mean of first and second DBP (p = 0.16). But there was a significant difference between the mean of first and third DBP (p = 0.039) and the mean of first and fourth DBP (p = 0.023). There was no significant difference in the mean of second and third DBP (p = 0.31), second and fourth DBP (p = 0.11) and mean third and fourth DBP (p = 0.09) (Fig. 1).

The mean of first, third and fourth DBP in the control group was 81.00 ± 8.82, 83.22 ± 6.07 and 80.81 ± 6.27, respectively. There was no significant difference between the mean of first to third DBP in the control group (p > 0.05) (Fig. 2).

Mean baseline SBP in the intervention group was 134.70 ± 10.68 and in the control group 132.88 ± 10.77. There was no significant difference in mean baseline SBP between the two groups (p = 0.34), indicating that the samples were homogeneous before drug intervention.

Mean baseline, second, third and fourth SBP in the intervention group were 134.70 ± 10.68 and 128.0 ± 16.32 and 126.05 ± 10.66 and 121.44 ± 9.90 mmHg, respectively. Significant differences were observed in mean of first and second SBP (p = 0.034), mean of first and third SBP (p = 0.028) and mean of first and fourth SBP (p = 0.019). There was no significant difference in the mean of the second and third SBP (p = 0.42), but there was a significant difference in the mean of the second and fourth SBP (p = 0.043) and mean third and fourth SBP (p = 0.047) (Fig. 1).

The mean of first, third and fourth SBP in control group were 132.88 ± 10.77, 135.00 ± 7.63 and 132.68 ± 7.42, respectively. There was no significant difference between the mean of first and third SBP (p > 0.05) (Fig. 2).
Mean baseline PR in the intervention group was 98.05 ± 20.12 minutes and in the control group was 92.53 ± 17.41 minutes. There was no significant difference in mean baseline PR between the two groups (p = 0.32), indicating that the samples were homogeneous before drug use.

Mean first, second, third and fourth PR in the intervention group were 98.05 ± 20.12 and 93.44 ± 19.43, 92.66 ± 16.74 and 93.11 ± 13.86, respectively. There was no significant difference in mean PR during the different stages. Mean first, third and fourth PR in control group were 92.53 ± 17.41, 93.33 ± 12.82 and 92.70 ± 12.16, respectively. There was no significant difference in mean PR at different stages (p > 0.05).

No patient in both groups needed treatment with atropine or ephedrine.

Mean baseline RR was 14.55 ± 1.23 in the intervention group and 14.34 ± 1.29 in the control group. There was no significant difference in mean baseline RR between the two groups (p = 0.59), indicating that the samples were homogeneous prior to drug intervention.

Mean baseline, second, third, and fourth RRs in the intervention group were 14.55 ± 1.23 and 13.88 ± 1.18, and 13.44 ± 1.09 and 13.27 ± 0.89, respectively. Although Mean first, third and fourth RR in control group were 14.34 ± 1.29, 13.75 ± 0 3.02 and 13.58 ± 3.02, respectively. There was no significant difference between the mean of first to third RR (p > 0.05). Also, no patient in the two groups had percent of saturated hemoglobin less than 94.

Mean baseline VAS score was 9.25 ± 1.37 in the intervention group and 9.46 ± 1.14 in the control group. There was no significant difference in the mean baseline VAS score between the two groups (p = 0.57), indicating that the samples were homogeneous before drug intervention.

Mean baseline, second, third, and fourth VAS scores in the intervention group were 9.25 ± 1.37, 4.61 ± 1.75, 3.88 ± 1.45, and 1.88 ± 0.47, respectively. Significant differences in mean of first and second VAS (p < 0.01), mean of first and third VAS (p < 0.01), mean of first and fourth VAS (p < 0.001) and mean of second and fourth VAS (p < 0.05) and the mean of the third and fourth VAS scores (p < 0.05), but the mean of the second and third VAS scores were not significant (p = 0.38) (Fig. 3).

Mean first and third VAS scores in control group were 9.46 ± 1.14 and 9.45 ± 1.17, respectively. But the fourth VAS score was 3.12 ± 2.25 significantly lower than the first and third VAS score (p < 0.001).

Mean baseline RSS score was 1.00 ± 0.00 in intervention group and 1.11 ± 0.32 in control group. There was no significant difference in the mean baseline RSS score between the two groups (p = 0.12), indicating that the samples were homogeneous before drug intervention.

Mean baseline, second, third and fourth RSS scores in the intervention group were 1.0 ± 0.00, 2.05 ± 0.63 and 2.22 ± 0.54, and 2.05 ± 0.23, respectively. There was a significant difference between the mean of the first and second RSS scores (p < 0.001), the mean of the first and third RSS scores (p < 0.001), and the mean of the first and fourth RSS scores (p < 0.001), but there was no significant difference in the mean
scores of second and third RSS and mean second and fourth RSS and mean third and fourth RSS scores (p > 0.05).

The mean of first, third and fourth RSS scores in the control group were 1.11 ± 0.32 and 1.12 ± 0.33, and 1.12 ± 0.33, respectively. There was no significant difference in the mean of the first, third and fourth RSS scores (p > 0.05).

Comparing the mean Apgar scores of 1 and 5 minutes in the two groups showed no significant difference in the mean Apgar scores of 1 minute (p = 0.09) and 5 (p = 0.34) between the intervention and control groups. Mean Apgar scores at 1 and 5 minutes in the intervention group were 9.06 ± 0.25 and 9.87 ± 0.34, respectively. Mean Apgar scores at 1 and 5 minutes in the control group were 8.84 ± 0.47 and 9.32 ± 0.68, respectively.

The mean score of midwifery satisfaction of the patients in the intervention group was 4 ± 0.91 based on the five-point Likert scale.

Discussion

In this study, investigators assessed the effect of intravenous Dexmedetomidine infusion on pain score and neonatal Apgar score in primipar term pregnant women in two groups, intervention and control groups. Intra-group analysis in the intervention group showed that mean SBP and DBP were significantly decreased after drug administration but were in normal range and no patient needed treatment.

There was no significant difference in pulse rate and respiratory rate of mothers in both groups during the study.

The first stage of labor in the intervention group was significantly shorter than the control group. The mean duration of the first stage of labor in the two intervention and control groups was 81.23 ± 75.83 minutes and 192.75 ± 120.76 minutes, respectively. There was no significant difference between the mean duration of second and third stages of labor between the two groups.

There was no significant difference in mean baseline VAS score between the two groups, but intra-group studies showed that the mean pain score after Dexmedetomidine administration decreased significantly from 9.25 at baseline to 4.61 after drug administration, 3.88 during labor and 1.88 after placental expulsion. There was no change in mean pain score in the control group until delivery. The Ramsay sedation scale score increased significantly from 1 at baseline to 2.05 after drug administration, 2.22 during labor and 2.05 after placental expulsion.

Results showed that administration of Dexmedetomidine without any complications in mother and neonate significantly reduced labor pain and accelerated the first stage of labor.

In review of the articles, there were no clinical studies regarding the use of Dexmedetomidine to manage labor pain and there were only a few case studies that reported the use of Dexmedetomidine in pregnant
women for a variety of reasons (16, 17, 20–23). In these case studies, Dexmedetomidine was proven safe for the fetus and newborn.

This study was consistent with studies by Palanisami (16), Mendoza (17), Souza (20), Abu-Halaweh (21), El Tahan (22), and Newman (23); and showed that maternal Dexmedetomidine infusion had no complication on the fetus or neonate.

In reviewing articles related to labor pain management, there are many findings related to different epidural methods that consider this method as a suitable method for labor pain management. Including in a study by Deshmukh on pregnant women, investigators compared the effect of epidural analgesia with control group and concluded that epidural analgesia had no effect on labor duration, but with excellent analgesia, along with improved neonatal APGAR score. They suggested that the epidural method was suitable for painless delivery (24). Karn et al. also considered the epidural method as the most effective method of analgesia for labor (2).

However, this procedure had some complications, as Uemura et al reported prolonged sensory dysfunction in a perineal area following epidural analgesia in a 36-year-old pregnant mother, due to ropivacaine neurotoxicity (25). In recent researches, simpler methods comparable to the epidural method of pain control have been recommended. Faied et al, in 2019 conducted a study comparing intradermal injection of distilled water with epidural bupivacaine in the first phase of labor. The analgesia in both epidural and sterile water groups was good compared to normal saline. The analgesia was comparable in the epidural and sterile water groups. Complications were more common in the epidural group than in normal saline and distilled water. they suggested that distilled water injection was a safe and effective method for reducing first-stage labor pain similar to that of bupivacaine (26). There was another factor more important than pain reduction, and that was patient satisfaction. In this regard, Richardson et al, performed a study on pregnant mothers who underwent epidural analgesia, nitrous oxide, or nitrous oxide initiation followed by epidural analgesia. While 92% of neuroaxial group reported good analgesic effect of this method but only 52% of Nitrous Oxide group reported good analgesic effect, Overall satisfaction of Nitrous Oxide group was 93% and in neuroaxial group was 97%. That is, despite the great difference in the analgesic rate of the Nitrous Oxide method, the rate of satisfaction was close to that of the neuroaxial method. They stated that factors other than the extent of pain relief, such as maintaining a sense of childbirth, mobility and force, seems to influence mothers' satisfaction with analgesia (27).

In a study by the Sia et al, the efficacy of clonidine and Dexmedetomidine on human pregnant myometrial stripes was obtained from 6 patients during elective cesarean section. Their results showed that Dexmedetomidine increased uterine contractility at plasma concentrations of $1 \times 10^{-9}$ gr / ml (28). Another study by Sia found that if Dexmedetomidine was used correctly during labor, it could cause hemodynamic relaxation and stability with minimal risk of respiratory depression in the pregnant mother. (29), and similar to Sia studies, the current study showed that administering Dexmedetomidine led to a significant change in the first stage of labor, and hemodynamics changes were in the normal range; no maternal respiratory depression was observed as well.
In 2018, Jia et al. compared 3 groups of 40 women candidates for painless labor. PCIV analgesia with remifentanil, patient controlled epidural analgesia, and routine labor. The active phase was shorter in the two intervention groups than the control group. Stage two and three did not differ in the three groups. (5).

In 2019, Garg et al. compared intravenous tramadol with intravenous paracetamol in labor analgesia. Paracetamol group showed better analgesia with less labor duration. (6).

In a study Zutshi et al, studied 200 pregnant women in two groups to control labor pain. 100 women received acetaminophen and 100 women received normal saline. Duration of labor was shortened in both groups without any complications on mother and fetus. (7). It seems that analgesia for labor, either epidural or intravenous (remifentanil, paracetamol, acetaminophen, normal saline) was associated with a decrease in the active phase of labor, which was consistent with the current study.

Nguyen et al. used PCIV analgesia with fentanyl in patients with relative contraindication for epidural analgesia. In the control group, nabalophen bolus was administered in alternate doses. They concluded that drug-related complications were very uncommon on infants and mothers; and intravenous fentanyl was a good option for mothers who have epidural contraindication. Patients’ pain score was reduced by this method (reached about eight at two and three hours) but returned to baseline after three hours(30). In this method, the same as current study, maternal and neonatal complications were uncommon, but decreased pain with fentanyl was not as good as this study, and the pain score reached to at least eight and was not persistent. While in the current study, mean pain score was less than five, and analgesia continued until delivery.

In a nationwide survey of obstetricians, anesthesiologists, and midwives, Logtenberg investigated the incidence of serious complications associated with remifentanil infusion for painless delivery, at 60 hospitals in the Netherlands, over a ten-year period. Cases of insufficient pain control, maternal apnea, and even maternal cardiac arrest and neonatal respiratory depression were reported, however, all complications were treated. They therefore suggested that remifentanil should be used under the supervision of a trained professional (31). In this study, none of the complications reported with remifentanil infusion were observed. As this study was performed under the guidance of a trained anesthesiologist and the patients and fetus were fully monitored.

Many patients in current medical center did not have the consent to use neuroaxial pain management techniques, so in patients with refusal for epidural analgesia (21), spinal cord disorder (16) or contraindications to the regional analgesia (17), the use of Dexmedetomidine which is an α2 agonist drug with appropriate pain relief and sedation, no maternal or neonatal complications and, were indicated as suitable alternatives to pain management. Dexmedetomidine accelerated the first stage of labor and maintain a sense of childbirth, mobility and force, but is associated with fewer maternal and neonatal complications than other intravenous drugs used to manage labor pain. More extensive studies on the effect of Dexmedetomidine on labor pain management and maternal and neonatal complication are needed.
Conclusion

Based on results, it seems that administration of Dexmedetomidine to manage labor pain with careful monitoring of mother and fetus is recommended. Due to limited studies, further larger and multicenter studies are needed to be performed.

Abbreviations

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PR: Pulse Rate; RR: Respiratory Rate; SPO2: Saturation Peripheral Oxigen; FHR: Fetal Heart Rate; VAS: Verbal Analogue Scale; RSS: Ramsay Sedation Scale

Declarations

Ethics approval and consent to participate

This research project was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (number: IR.BMSU.REC.1397.250 date: 2019-02-15) and it was registered in the Iranian registry of clinical trials (IRCT20161022030421N5 date: 2019-07-20). Consent letters were obtained from participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are not any competing interests.

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There is not any funding in this study.

Authors' contributions

Conceptual: AD and ML, Data gathering: AD, AE, MD and ML, Data analyzing and Drafting: AD, AE, MD and ML. All authors read and revised and approved the final version of the manuscript.

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References


**Figures**

![Comparison of mean systolic and diastolic blood pressure (mmHg) in the intervention group during the study](image)

**Figure 1**

Comparison of mean systolic and diastolic blood pressure (mmHg) in the intervention group during the study I=Primary SBP and DBP; II= during bolus dose of Dexmedetomidin; III= during labor; IV=after placental expulsion
Figure 1

Comparison of mean systolic and diastolic blood pressure (mmHg) in the intervention group during the study I=Primary SBP and DBP; II= during bolus dose of Dexmedetomidin; III= during labor; IV=after placental expulsion

Figure 2

Comparison of mean systolic and diastolic blood pressure (mmHg) in the control group during the study I=Primary SBP and DBP; III= during labor; IV=after placental expulsion
Figure 2

Comparison of mean systolic and diastolic blood pressure (mmHg) in the control group during the study
I=Primary SBP and DBP; III= during labor; IV=after placental expulsion

Figure 3

Comparison of the mean VAS score in the intervention group during the study VAS1=Primary VAS; VAS2=after bolus dose of Dexmedetomidin; VAS3= during labor; VAS4=after placental expulsion
Figure 3

Comparison of the mean VAS score in the intervention group during the study VAS1=Primary VAS; VAS2=after bolus dose of Dexmedetomidin; VAS3= during labor; VAS4=after placental expulsion