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Effects of Intrathecal Clonidine on Spinal Analgesia during Elective Cesarean Delivery: A Randomized Double Blind Clinical Trial

Houshang Talebi[1]*, Afsaneh Norouzi[2], Khadijeh Nasri[3], Atefe Alaee[4] and Saran Lotfollahzadeh[5]

[1]Assistant Professor of Anesthesiology, Department of Anesthesiology, Arak University of Medical Sciences, Arak, Iran
[2]Assistant Professor of Anesthesiology, Department of Anesthesiology, Arak University of Medical Sciences, Arak, Iran
[3]Assistant Professor of Gynecology, Department of Gynecology, Arak University of Medical Sciences, Arak, Iran
[4]MSc. Department of Medical Information Sciences, Tehran University of Medical Sciences, Tehran, Iran
5. Student of Medicine, Arak University of Medical Sciences, Arak, Iran
Corresponding Email: drtaleby1000@gmail.com

ABSTRACT

In order To investigate the effect of addition of clonidine to lidocaine on duration of spinal analgesia and need for postoperative analgesics after Caesarean section delivery, this randomized case-controlled double-blind clinical trial was designed and conducted. 166 eligible women were randomly allocated to either case or control group (n=83), Spinal anesthesia was done by 75-100 mg lidocaine 0.5% in control group and by 75-100 mg lidocaine 0.5% plus 75µg clonidine in case group. Onset of analgesia, Blood pressure, Hypotension, Bradycardia, and Neonates Apgar scores were recorded during surgery. After surgery, duration of sensory and motor functions, Intensity of post-operative nausea and vomiting, Total analgesic consumption and time to first analgesic request were assessed. Data were analyzed by SPSS and an alpha level < 0.05 was considered to be statistically significant. Onset of analgesia, Duration of Motor and sensory block, mothers' systolic blood pressure and pulse rate in different recorded times, and Total Analgesic consumption in case group showed a statically significant difference in comparison to the control group. Analgesia demanding, Time of first request for analgesics, Intensity of Nauseas and vomiting, Apgar score showed no significant difference. We have demonstrated that addition of 75 µg clonidine to lidocaine extends spinal analgesia along with sensory and motor block after Caesarean section and improves early analgesia without clinically significant maternal or neonatal side-effects. This single 75 µg intrathecal clonidine dose also reduced the amount of subsequent analgesic consumption during the first 12 hours after delivery.

Keywords: Cesarean Section; clonidine; Anesthesia, Spinal.

INTRODUCTION

Neuraxial anesthesia has become the most preferred technique for caesarean sections. Although epidural, spinal, continuous spinal, and combined spinal epidural techniques have all been advocated, most caesarean sections are performed under single-shot spinal anesthesia. It is simple to perform, economical, produces rapid onset of anesthesia and complete muscle relaxation [1-2].

Even when a long acting local anesthetic like bupivacaine is used, the duration of spinal anesthesia [SA] is short and higher doses of analgesics are required in the postoperative period. Pain control after cesarean section delivery improves breastfeeding and mothers' satisfaction. In addition, inadequate analgesia leads to elevated plasma catecholamine concentrations, resulting in adverse effect on all organ systems [3-4]. Therefore, achieving a

subarachnoid block that provides high quality postoperative analgesia of consistently prolonged duration is an attractive goal. Opioids such as morphine, fentanyl, and sufentanil have been administered intrathecally as adjuncts to increase the duration of postoperative analgesia. Although they ensure superior quality of analgesia, they are associated with many side effects such as pruritis, nausea, vomiting, urinary retention, and especially late and unpredictable respiratory depression [5].

Hypotension is a common clinical problem following neuraxial blockade and is associated with morbidity for both mother [nausea, vomiting] and fetus [acidosis]. Techniques used to prevent hypotension include intravenous fluids and sympathomimetic drugs. Based on current evidence, intravenous prehydration has poor efficacy, probably because of rapid distribution [1]. It has been shown that administration of a fluid bolus starting at the time of injection of neuraxial anaesthetic [cohydration] is more effective because maximum effect can be achieved at the time of the block and consequent vasodilatation [6].

This has directed the research toward the use of newer and better local anesthetic additives for SA such as neostigmine, ketamine, midazolam, and clonidine [5]. Analgesic properties of clonidine have been shown to depend on the activation of α2 receptors located in the dorsal horn. Presynaptic stimulation of α2 receptors inhibits neurotransmitter release and postsynaptic stimulation prevents neuronal transmission through hyperpolarisation [7]. Although prolongation of the effects of local anesthetics has been reported for oral and intravenous clonidine, the intrathecal route is more effective; clonidine prolongs the duration of action of intrathecal administered local anesthetics and has potent antinociceptive properties [8]. The addition of clonidine is better than the opiods when side effects on the maternal physiology as well as the fetal Apgar scores are considered [4].

In order To investigate the effect of addition of clonidine to lidocaine on duration of spinal analgesia and need for postoperative analgesics after Caesarean section delivery, this randomized case-controlled double-blind clinical trial was designed and conducted. In previous labor studies It was observed that intrathecal clonidine added to local anesthetic in doses of 150 μg prolongs spinal anesthesia and analgesia but hemodynamic instability was reported [9], in our study intrathecal doses of clonidine was titrated to 75 μg in order to achieve adequate analgesia and ensure hemodynamic stability.

MATERIALS AND METHODS

This prospective double blinded case-controlled randomized clinical trial was conducted on 166 ASA I&II parturient candidate for elective cesarean delivery that were admitted to a university hospital during April-October 2010.

Study protocol was registered in Iranian registry of clinical trials (IRCT) under number IRCT138901212080N3. Ethical approval was obtained from the Institutional Review Board and the Hospital Research Ethics Committee (under number 88-65-2). All patients signed the informed consent forms prior to recruitment in the study.

Sample size was acquired using the 'Two means comparison' formula. The power value was determined to be 80%, with an assumed dropout rate of 20%. Considering d=4, sample size of 83 for each group is obtained.

Inclusion criteria for this study was specified as ASA I&II women aged between 15-45 years appropriate for elective cesarean section under spinal anesthesia.

Exclusion criteria was defined as history of preeclampsia, chronic hypertension, diabetes; using β-blockers or anti-psychotic agents. Also mothers of neonates with decollement placenta; respiratory distress or hypoxia due to meconium aspiration; or Apgar score less than 7 were excluded from the study.

Simple random sampling was performed and 166 women recruited in the study. After pairing homogenization regarding age and gravidity, Patients were randomly allocated to either case or control group (n=83), using randomized blocks. Primary data profile (age, weight, height, ASA, parity and gravidity) for each women was completed.

Lactated Ringer's solution (500 mL) was administered IV for all patients prior to the surgery. Spinal anesthesia was done by 75-100 mg lidocaine 0.5% in control group and by 75-100 mg lidocaine 0.5% plus 75μg clonidine in case group, both of which were brought to equal volume with maximum of 2.5 ml distilled water and were injected

through a 25-gauge spinal needle at L3-L4 or L4-L5 intervertebral interspace. Motor block was confirmed by inability to lift the leg, followed by testing of sensory block to stimuli (pin prick) at T4 level, and their onset was recorded in their profile.

During surgery, 100-1500 mL Lactated Ringer's solution was infused for all patients.

Blood pressure was monitored with an automated cuff blood pressure monitor at 5-minutes intervals for 20 minutes, at 10-minutes intervals until leaving the recovery room and then at 4-hours intervals for 12 hours.

Hypotension, a decline of more than 20% from baseline pressure or systolic blood pressure of less than 90 mmHg, was managed with 5mg ephedrine which was repeated if needed.

Bradycardia, a decline of pulse rate of less than 50 bpm was managed with 0.5 mg IV atropine.

An oxytocin infusion of 20 U/h was instantly started upon umbilical cord clamping.

In order to evaluate the effect of clonidine on neonates, their Apgar scores were measured and recorded upon delivery, and 5-minutes intervals until 10 minutes.

After transferring to the recovery room and along with pulse and blood pressure monitoring, recovery of sensory and motor functions were assessed and recorded by retrieval of pinprick perception and ability to lift the leg respectively.

For 12 hours after transferring the subjects to the ward, Post-operative complications such as headache, chills or emesis was recorded profile in case of any. Intensity of post-operative nausea and vomiting were assessed using a 4 items scale (None, mild, moderate, severe). Total analgesic consumption and time to first analgesic request were also recorded.

All medications and syringes were prepared and covered according to the random number list by an anesthesia assistant who was blinded to the study. All the parameters were evaluated and recorded by an anesthesiologist who was blind to the study.

Demographic data and other study parameters were analyzed by SPSS software version 18.0 (Statistical Product and Service Solutions, SSPS Inc., Chicago). Descriptive analysis, chi-square test and between-groups assessments were used for analyzing and presenting the results. An alpha level < 0.05 was considered to be statistically significant.

RESULTS

Eighty three patients completed the trial in each group. Both groups were similar with regard to maternal demographic factors (Table 1).

Mean time of Onset of analgesia in case group was lower and it showed a statically significant difference in comparison to the control group.

Duration of Motor and sensory block was statistically higher in case group, but Analgesia demandant and Time of first request for analgesics showed no statistically significant difference in two groups.

Total Analgesic consumption in two groups were also compared and case group showed a lower amount of Analgesic consumption which was significantly different.

Intensity of Nauseas and vomiting among mothers was recorded but its statistical analysis revealed no significant difference between the two groups.

Details of these outcomes are demonstrated in table 2.

Systolic and diastolic blood pressure were separately measured. Although diastolic blood pressure didn't appear to be statistically different in two groups, but hoteling multivariate t-test showed that mothers' systolic blood pressure and pulse rate in different recorded times was statistically lower in case group than the control group ($p > 0.05$).

Apgar score was measured upon delivery, and 5-minutes intervals until 10 minutes, In order to evaluate the effect of clonidine on neonates which showed no significant difference between case and control group (Table 3).

No clinically relevant maternal or neonatal side-effects were detected.

DISCUSSION

Based on the findings from this study, it was determined that administration of intrathecal clonidine 75μg reduced the onset of spinal analgesia while prolonged duration of motor block and the time to first analgesic request after cesarean delivery compared to control groups. Because of the importance of rapidity in cesarean section surgery, a decrease in commencement of analgesia improves the surgeon's convenience; while extending the offset of sensory and motor block increase mothers' convenience and safety. Also low cost per vial of clonidine for enhancement of analgesia can be recommended for routine obstetric pain control in developing countries.

Apgar score was measured upon delivery, and 5-minutes intervals until 10 minutes, In order to evaluate the effect of clonidine on neonates which showed no significant difference between case and control group. This ineffectiveness is considered important because well-being of the infant is a major factor for evaluating the anesthetic management of pregnant women [10].

These outcomes are consistent with previous studies. In 2006, the effect of addition of 75μg clonidine to hyperbaric bupivacaine on postoperative morphine consumption after Caesarean section was investigated in a randomized controlled double-blind clinical trial which prolonged spinal anesthesia after Caesarean section and improved early analgesia, but did not reduce the postoperative morphine consumption during the first 24 hours [11]. In our study duration of sensory block was prolonged for 11 minutes which is a statically significant difference toward the control group. But unlike that, post-operative analgesics consumption was statistically less than the case group in our study, despite the shorter follow up period.

In a different study, researchers evaluated the efficacy of spinal clonidine combined with ropivacaine and sufentanil and its effects on maternal and fetal outcome. Patients receiving spinal clonidine had significantly longer lasting analgesia compared to patients treated without clonidine [12], supporting longer lasting analgesia which was confirmed in the present study. But in the mentioned study, Clonidine-treated patients experienced a more pronounced decrease in mean arterial pressure as compared to patients treated without clonidine. The groups also differed in ephedrine requirement and number of new onset fetal heart rate abnormalities. In our research, systolic and diastolic blood pressure were separately measured. Although diastolic blood pressure didn't appear to be statistically different in two groups, but hoteling multivariate t-test showed that mothers' systolic blood pressure and pulse rate in different recorded times was statistically lower in case group than the control group. Maternal hypotension is associated with neonatal acidemia and base excess correlates with neonatal outcome and should be prevented as much as possible [10 , 13].

In another study in 2008, the postoperative antihyperalgesic effect of intrathecal clonidine after caesarean delivery was evaluated. Findings revealed that Intrathecal clonidine 150 mug combined with bupivacaine had a postoperative antihyperalgesic effect at 48 hours after elective cesarean delivery [12] which is also consistent with our study.

By conducting another study in Indonesia, researchers evaluated maternal satisfaction with single-dose spinal analgesia for the management of obstetric pain. The overall maternal satisfaction for labor analgesia was high, concluded that single-dose spinal analgesia with a combination of bupivacaine, morphine, and clonidine provided effective labor pain control, and maternal satisfaction with this technique was very high [14].

In 2009, oxford university researchers evaluated the analgesic effect of epidural clonidine after spinal surgery. Findings from their study indicated significantly lower morphine consumption in those who received epidural infusion of clonidine. It significantly reduced the demand for morphine and reduced postoperative nausea with few side effects [15]. Our results are in agreement with mentioned study, except for postoperative nausea, which showed

no statistically significant difference between two groups. This difference can be explained by proper pre-operative hydration and well-homogenization of the parturients in our study.

Table 1. Demographics of Study Participants

Variable/Mean±SD	Control Group (N=83)	Case group (N=83)	p-value
Mean Age (yrs.)	28.56±5.6	28.24±5.4	> 0.05
BMI (kg/m^2)	31.9±5.4	32.2±5.9	> 0.05
ASA (I/II) (n)	82 (98.7%)	81 (97.5%)	> 0.05
Gravidity			> 0.05
I	21 (25.2 %)	20 (24.1%)	
II	41 (49.4%)	36 (43.4 %)	
III	15 (18.1%)	17 (20.5 %)	
IV	4 (4.8 %)	10 (12)	
Parity			> 0.05
Primiparity	27 (32.5 %)	28 (33.8 %)	
Previous NVD	5 (6 %)	14 (16.9 %)	
Previous C-section	51 (61.4 %)	39 (47 %)	
Both NVD & C-section	0 (0%)	2 (2.4 %)	

Table 2. Primary outcome measures in two groups of case and control

Variable/Mean	Control Group (N=83)	Case group (N=83)	p-value
Onset of analgesia (min)	6.2±4.81	4.9±4.48	<0.05
Duration of Motor block (min)	118.08±46.04	168.78 ±47.50	<0.001
Duration of sensory block (min)	39.15±14.05	50/00±15.21	<0.001
Time of first request for analgesics (min)	4.5± 0.61	3.3 ± 0.77	>0.05
Analgesia demandant (n)	4 (4.8 %)	6 (7.2 %)	> 0.05
Analgesic consumption (n)			<0.05
Nil	68 (81.9%)	74 (89.2 %)	
50 mg pethidine plus 1 supp diclofenac	12 (14.4 %)	9 (10.8 %)	
50 mg pethidine plus 2 supp diclofenac	3 (3.6 %)	0	
Nausea &vomiting (n)			> 0.05
None	49 (59%)	48 (57.8%)	
Mild	23 (27.7 %)	31 (37.3%)	
Moderate	10 (12%)	4 (4.8%)	
Severe	1 (1.2%)	0 (0 %)	

Table 3. Apgar score of neonates upon delivery and 5 & 10 minutes after

Apgar score	Case group (n=83)	Control group (n=83)	p-value
Minute 1	8.78±0.73	8.74±0.53	> 0.05
Minute 5	9.69±0.57	9.74±0.53	> 0.05
Minute 10	9.90±0.40	9.19±0.38	> 0.05

Due to limitations of time and hospital facilities, we could not evaluate the study parameters for a period longer than 12 hours. Further studies with longer periods of post-operative follow up are recommended to evaluate the possible adverse effects of intrathecal clonidine and analgesic consumption more precisely. Also, it is recommended to evaluate other adverse effects such as sedation and pruritus in future, so that in case of not significant side effects, intrathecal clonidine can be routinely recommended for cesarean section delivery.

We have demonstrated that addition of 75 μg clonidine to lidocaine extends spinal analgesia along with sensory and motor block after Caesarean section and improves early analgesia without clinically significant maternal or neonatal side-effects. This single 75 μg intrathecal clonidine dose also reduced the amount of subsequent analgesic consumption during the first 12 hours after delivery.

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