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Original Article

A Comparative Prospective Study of Intrathecal Dexmedetomidine-Fentanyl for Labor Analgesia

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***ABSTRACT*:**

Background: Pain relief during maternal labor is one of the main goals of maternity care. Combined spinal epidural analgesia is an accepted technique to alleviate labor pain with minimal side-effects to mother and fetus. **Aims:** To evaluate the effect of combination of intrathecal dexmedetomidine and fentanyl on maternal and neonatal outcomes during labor in comparison to dexmedetomidine or fentanyl alone. **Materials and Methods:** We carried out a prospective study on 120 consecutive parturients over a period of 1-year from June 2017 to December 2017 at a tertiary care hospital. Patients were randomly divided to three groups of 40 each: Group D (n=40): Patients received 5 µg intrathecal dexmedetomidine in 1 ml of normal saline; Group F (n=40): Patients received IT 20 µg fentanyl in 1 ml of normal saline and Group DF (n=40): Patients received IT 5 µg dexmedetomidine plus 10 µg fentanyl in 1 ml of normal saline. Maternal heart rate and non invasive blood pressure were recorded every 5 minutes following the intrathecal injection. Other side effects such as pruritus, nausea and vomiting and respiratory depression were recorded. **Results:** Demographic findings were comparable in all the groups. Onset of analgesia was faster and duration of analgesia was longer in group DF than in the two other groups. There was no statistical difference between the three groups as regard the mode of delivery. Regarding to maternal side-effects; hypotension and bradycardia were recorded in group D (6 patients (15%), 5 patients (12.5%) respectively) more than the two other groups; the fentanyl group showed significant increase in pruritus 10 patients (25%); lastly nausea and vomiting were detected only in DF group one patient (2.5%). **Conclusion:** Addition of 5 µg intrathecal dexmedetomidine to 10 µg fentanyl prolonged the duration of analgesia. The combination decreases the incidence of side effects in comparison to IT 10 µg dexmedetomidine or IT 20 µg fentanyl alone.

Key words: Analgesia, Dexmedetomidine, Fentanyl, Labor, Neonatal.

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INTRODUCTION:

Pain relief during maternal labor is one of the main goals of maternity care. Labor pain is excruciating and leads to a spectrum of adverse physical and psychological stress to mother and fetus. Labor pain and painful uterine contractions cause hyperventilation and high catecholamine levels resulting in maternal and fetal hypoxemia.[1, 2] Pain relief provides patient's comfort and attenuates the release of stress hormones.[3]

Combined spinal epidural (CSE) analgesia is a widely accepted technique to alleviate labor pain with minimal side-effects to mother and fetus.[4] The use of intrathecal opioids for labor analgesia continues to gain popularity, but there are limited data to guide this use. Fentanyl, a Phenyl piperidine derivative, is a short-acting and potent synthetic narcotic. Due to its short half-life, fentanyl is considered a good option for labor pain relief. Fentanyl can safely provide effective, long-lasting labor analgesia without motor block, at a reasonable cost. Fentanyl has been used along with bupivacaine for labor analgesia extensively to decrease motor block, however the addition of opioids to local anesthetics has disadvantages of pruritus and respiratory depression.

Dexmedetomidine, a highly selective and potent alpha 2 adrenergic agonist has intrinsic analgesic properties and has been used with spinal bupivacaine to prolong postoperative analgesia. Recent reviews of use of dexmedetomidine in pregnancy have shown that it does not cross the placenta significantly due to its high placental retention. Several studies have used dexmedetomidine intravenously and epidurally in labor without any adverse effects on mother or fetus.[7, 8]

However, in pregnancy, dexmedetomidine intrathecally or intravenously, still remains an off label use. Dexmedetomidine has an analgesic-sparing effect, significantly reducing opioid requirements and has a sympatholytic effect that can attenuate the stress response to surgery.[9, 10]

The aim of this observational comparative study was to evaluate the effect of combination of IT dexmedetomidine and fentanyl on maternal and neonatal outcomes during labor in comparison to IT dexmedetomidine or IT fentanyl alone.

MATERIALS AND METHODS:

After obtaining clearance from the Institutional Research and Ethics Committee, we carried out a prospective study on 120 consecutive parturients over a period of one year from June 2017 to December 2017 at Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana State, India. Our methodology and criteria was based on Mohamed AA and Salem RA (2015).[1]

The expectant mothers were explained about procedure of labor analgesia and its benefits. Obstetrician concurrence was obtained for inclusion of any patient in the study. Written and informed consent after explaining the effects of drugs being used for labor analgesia was obtained from the patient for their participation in the observational study.

Inclusion Criteria:

1. Patients aged 19-39 years
2. Patients with ASA physical status I-II
3. Patients scheduled for normal vaginal delivery with uncomplicated pregnancy, cephalic presentation not in fetal distress, single fetus and in active labor

Exclusion Criteria:

1. Patients with cardiac, liver, or kidney diseases,
2. Patients allergic to local anesthetics or study drugs,
3. Any contraindication of regional anesthesia,
4. Intrauterine growth retardation or fetal compromise
5. Patient refusal.

Randomization and enrollment was done by closed envelop. Patients were randomly divided to three groups of 40 each:

1. Group D (n=40): Patients received 5 µg intrathecal dexmedetomidine in 1 ml of normal saline;
2. Group F (n=40): Patients received IT 20 µg fentanyl in 1 ml of normal saline and
3. Group DF (n=40): Patients received IT 5 µg dexmedetomidine plus 10 µg fentanyl in 1 ml of normal saline.

With the patient in the sitting position an intrathecal injection of the study drug was administered using a combined spinal epidural set (CSE) at L3-L4 intervertebral space. An epidural catheter was inserted 5 cm into the epidural space using the CSE set and secured for future administration of 10-12 ml of 0.125% bupivacaine required when the VAS was recorded above 3 and repeated top-ups of the same dosage were administered as and when the VAS for pain was recorded above 3 till delivery of the baby. 10-15ml of 0.5% bupivacaine was administrated if emergency cesarean section was indicated.

Data collection and measurements:

Hemodynamic data non invasive blood pressure, heart rate, oxygen saturation, and respiratory rate were recorded. The obstetrician showed the cervical dilatation, stage and progress of labor, and fetal heart rate. The onset of administration of intrathecal analgesia was considered when the patient was in active labor. The baseline was defined as time before intrathecal injection of drugs. Analgesia onset was the time from intrathecal injection to time of recording a VAS less than 3. VAS was recorded thereafter every 1 minute for 10 minutes and then every 10 minutes till VAS reached more than 3. Duration of analgesia was defined as the time from intrathecal injection to the time when VAS reached more than 3 and needed additional analgesia through the epidural catheter.

Maternal heart rate and non invasive blood pressure were recorded every 5 minutes following the intrathecal injection. Occurrence of hypotension which was defined as decrease in blood pressure more than 20% from baseline and bradycardia defined as heart rate less than 60 were immediately treated with intravenous fluids, ephedrine or atropine as appropriate. Fetal bradycardia was monitored by cardiotocograph and was initially treated by giving oxygen to mother and ensuring lateral position to avoid aortocaval compression. Other side effects such as pruritus, nausea and vomiting and respiratory depression were recorded. pruritus was treated by i.v diphenhydramine 50 mg and 10 mg oral loratidine and nausea and vomiting were treated with ondansetron 4 mg. Modes of delivery were recorded. Neonatal outcome like; neonatal Apgar score and umbilical cord blood pH were recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, Chicago, IL). Data are presented as mean±SD, or numbers as appropriate. Patient characteristics (age, weight, height, parity and gestational age), onset and duration of analgesia and pH of umbilical artery were analyzed using the independent two sample t-test. Other parameters were studied using the Chi square test or Fisher's exact test as appropriate. The linear mixed model was used for comparison of MAP and HR between the three groups. P values of <0.05 were considered significant.

RESULTS:

Demographic findings were comparable in all the three groups (Table 1). Onset of analgesia was faster and

duration of analgesia was longer in group DF than in the two other groups (p-value <0.001), 12 patients in D group, 15 patients in group F and 11 patients in group DF needed top-ups of 10 ml of 0.125% bupivacaine till delivery of baby (Table 2).

Regarding to maternal side-effects; hypotension and bradycardia were recorded in group D (6 patients (15%), 5 patients (12.5%) respectively) more than the two other groups; the fentanyl group showed significant increase in pruritus 10 patients (25%); lastly nausea and vomiting were detected only in DF group one patient (2.5%). The other side effects like shivering, respiratory depression or postdural puncture headache were not noticed in the three study groups (Table 3). There was no statistical difference between the three groups as regard the mode of delivery (Table 4).

All patients in the three groups had baseline VAS ranged from 7-10, at 5 minutes reading VAS became less than 3 in the three groups and reached the lowest level (0-1) at 30 minutes reading and started to increase in the next readings. VAS became more than 3 earlier in the group F than group D and group DF (Table 5).

Table 1: Demographic data in the three groups

Characteristic	Group D	Group F	Group DF	P value
Age (year)	23.46±4.13	25.78±5.86	24.56±4.92	>0.05
Weight (Kg)	83.57±7.05	81.98±5.43	83.95±6.12	>0.05
Height (Cm)	164.13±7.13	164.87±6.24	163.24±6.02	>0.05
Primapara (n,%)	30 (75%)	34 (85%)	32 (80%)	>0.05
Multipara (n,%)	10 (25%)	6 (15%)	8 (20%)	>0.05
Gestational age (weeks)	39.30±1.36	39.62±1.09	39.45±1.08	>0.05
ASA grade I	32 (80%)	34 (85%)	34 (85%)	>0.05
ASA grade II	8 (20%)	6 (15%)	6 (15%)	>0.05

Table 2: Labor characteristics in the three groups

Characteristic	Group D	Group F	Group DF	P value
Rupture of membrane (n, %)	14 (35%)	15 (37.5%)	18 (45%)	>0.05
Cervical dilatation (Cm)	3.65±0.81	3.94±0.72	3.96±0.83	>0.05
Progress of labor (cm/h)	1.5±0.6	1.7±0.8	1.8±0.5	>0.05
Induced labor (n, %)	16 (40%)	14 (35%)	12 (30%)	>0.05
Onset of analgesia (min)	4.31±0.75	4.86±1.34	2.98±0.86	>0.05
Duration of analgesia (min)	128.68±15.84	109.16±14.12	141.76±12.18	<0.05
Number of patients needed epidural analgesia (n, %)	14 (35%)	15 (37.5%)	12 (30%)	>0.05

Table 3: Adverse events in the three groups

Characteristic	Group D	Group F	Group DF	P value
Hypotension (n, %)	6 (15%)	1 (2.5%)	4 (10%)	<0.05
Bradycardia (n, %)	5 (12.5%)	1 (2.5%)	2 (5%)	>0.05
Nausea or Vomiting (n, %)	0 (0)	0 (0)	1 (2.5%)	>0.05
Pruritus (n, %)	0 (0)	10 (25%)	2 (5%)	<0.05

Table 4: Mode of delivery in the three groups

Characteristic		Group D	Group F	Group DF	P value
Vaginal delivery (n, %)		30 (75%)	28 (70%)	26 (65%)	>0.05
Assisted vacuum vaginal delivery (n, %)		5 (12.50%)	6 (15%)	8 (20.0%)	>0.05
	Total	5 (12.5%)	6 (15%)	6 (15%)	>0.05
C&S (n %)	Due to Fetal distress	1	1	1	>0.05
	Due to Failure of progress	4	5	5	>0.05

Table 5: VAS During Contractions

VAS during contractions	Group D	Group F	Group DF	Total	P value
0	8 (20%)	23 (57.5%)	30 (75%)	61 (50.83%)	
1	15 (37.5%)	14 (35%)	8 (20%)	37 (30.83%)	
2	16 (40%)	3 (7.5%)	2 (5%)	21 (17.5%)	<0.001
3	1 (2.5%)	0 (0)	0 (0)	1 (0.83%)	
Total	40 (100)	40 (100)	40 (100)	120 (100)	

DISCUSSION:

Pain relief in labour has always been surrounded with myths and controversies. Hence, providing effective and safe analgesia during labour has remained an ongoing challenge. Labor analgesia has been evolved over the years to minimize motor blockade, enable walking epidurals and avoid prolongation of labor. Lipophilic opioids like fentanyl have been used extensively intrathecally and epidurally for labor analgesia along with local anesthetics. Dexmedetomidine, a selective alpha 2 adrenoreceptor agonist has been used in spinal and epidural anesthesia as an adjuvant and has several advantages of increased duration of analgesia compared to local anesthetics alone with no adverse neurological effects.[1, 2, 11, 12]

Niu et al (2013) in their metaanalysis showed that intrathecal dexmedetomidine prolonged the duration of spinal anesthesia and improved postoperative analgesia and did not increase the incidence of hypotension and adverse events.[13]

We used a preservative free dexmedetomidine intrathecally in labor and no adverse effects of intrathecal administration on the mother or newborn were noted. Recent studies showed that dexmedetomidine has been used very sparingly for labor analgesia but however has potential uses. Most of the case reports and studies that described the use of dexmedetomidine in parturients have mentioned that babies delivered were with normal APGAR scores which proves that even if there is any uteroplacental transfer, it doesn't affect the fetal well-being.[7, 8] We also observed similar findings.

Studies showed that dexmedetomidine has high placental retention and increases the frequency and amplitude of uterine contractions directly and in a dose-dependent fashion suggesting advantages for use as an analgesic adjunct during labor.[14-16] Hence excellent analgesia along with absence of motor block was expected on intrathecal administration of dexmedetomidine, thus making it a suitable drug for labor analgesia. However its intrathecal use in labor remains an off label use. The dose of 10 μg used in this study was lesser than intravenous doses previously used in pregnancy and no adverse effects on the newborn were anticipated. Dexmedetomidine acts on the receptors of the substantia gelatinosa of the dorsal horn of the spinal cord which inhibit the firing of nociceptive neurons stimulated by peripheral Aδ and C fibers. It also inhibits the release of the nociceptive neurotransmitter substance P.[17]

Dexmedetomidine has a spinal mechanism thus making it a viable stand-alone analgesic agent when administered intrathecally. Hence we used intrathecal dexmedetomidine without bupivacaine for the initiation of labor analgesia with the CSE technique. Doses of dexmedetomidine of 10 μg and 15 μg have been used intrathecally in studies and have shown prolongation of analgesic effects of spinal hyperbaric bupivacaine in a dose-dependent manner.[18]

We used 5 μg dexmedetomidine plus 10 μg fentanyl intrathecally in labor with minimal adverse effects on the mother or newborn were noted. Our results are in accordance with that of Niu et al (2013) who found that intrathecal dexmedetomidine prolonged the duration of spinal anesthesia and improved postoperative analgesia and did not increase the incidence of hypotension and adverse events.[13]

Combination of dexmedetomidine and fentanyl (Group DF) showed a quicker onset of analgesia than dexmedetomidine or fentanyl alone. Duration of analgesia was better in group DF compared to groups D and F. All patients achieved a VAS <3 after 5 minutes. The present study showed that addition of spinal 5 μg dexmedetomidine to fentanyl significantly prolonged duration of analgesia compared with either use of intrathecal 20 μg fentanyl or 10 μg dexmedetomidine. Our findings are in accordance with Gupta et al (2011) who found significantly improved analgesic efficacy with combination of dexmedetomidine and fentanyl when compared with dexmedetomidine and fentanyl as intrathecal adjuvant ($P<0.001$).[6]

Al-Mustafa et al (2009) and Hala et al (2011) observed dose dependent prolongation of duration of action of analgesia with reduced analgesic requirement when intrathecal dexmedetomidine dosages increased (5, 10 and 15 μg).[19, 20] Similar to our findings Mahdy et al (2011) found that after intrathecal dexmedetomidine and fentanyl injection there were no adverse effects on mothers or babies in any group.[21] Fyneface-Ogan et al (2012) found no significant differences in the Apgar score, pH of umbilical venous blood, baseline fetal heart rate.[22]

When side effects were recorded, hypotension and bradycardia were markedly observed in D group than in the other two groups. Fyneface-Ogan et al (2012) agreed with our results by observing minimal change of maternal blood pressure after intrathecal administration of dexmedetomidine. Clinical studies have demonstrated the safety of intrathecal dexmedetomidine in humans.[22]

However it has been shown that dexmedetomidine in relatively high doses can lead to hypotension when administered either neuraxially or intravenously.[19] Hence a lower dose (5 μg) of dexmedetomidine was used in our study and the parturient remained hemodynamically stable. It is well known that intrathecal administration of local anesthetics reduce blood pressure by decreasing sympathetic outflow.[23]

Imarengiaye (2005) successfully used dexmedetomidine 1 μg/kg followed by 1 μg/kg/h for 10 minutes before cesarean delivery to facilitate awake fiberoptic endotracheal intubation patient with spinal muscular atrophy type III with provided adequate sedation, without respiratory compromise.[24] Similarly, Palanisamy et al (2009) used i.v. dexmedetomidine successfully as an adjunct to opioid-based PCA and general anesthesia for the respective provision of labor analgesia and cesarean delivery anesthesia in a parturient with a tethered spinal cord, with favorable maternal and neonatal outcome.[25]

Hence we suggest that with the prolonged period of analgesia demonstrated by intrathecal

dexmedetomidine and fentanyl, with lack of adverse effects (such as sedation, respiratory depression, hypotension in the mother, and neonatal depression) could be considered an attractive alternative for labor analgesia.

LIMITATIONS OF THE STUDY

1. Smaller sample size
2. lack of thorough ling term follow-up

CONCLUSION

Addition of intrathecal dexmedetomidine to fentanyl prolongs the duration of analgesia and decreases the incidence of side effects in comparison to dexmedetomidine or fentanyl alone.

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