ORIGINAL RESEARCH

The effect of addition of neostigmine on dose requirement of ropivacaine 0.1% and on duration of labour in labouring patients receiving lumbar epidural analgesia

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ABSTRACT
Neostigmine (acetyl cholinesterase inhibitor) is a parasympathomimetic agent that has been investigated for use as an adjunct analgesic agent in the perioperative and peripartum period. Intrathecal injection of neostigmine increases extracellular acetylcholine levels in spinal cord leading to increased stimulation of spinal muscarinic and possibly nicotinic receptors to produce analgesia. The study was conducted in 50 Primiparous patients in active phase of labour in the labour ward of Department of Obstetrics and Gynecology. Patients were randomized into two groups using computer generated random numbers:**Group A:**Received 0.1% Ropivacaine with fentanyl2µg/ml in 10 ml total volume.**Group B:**Received 0.1% Ropivacaine with fentanyl 2µg/ml and neostigmine 500µg in 10 ml total volume.As far as number of supplements are concerned, in group A 44% and group B 88% patients needed 1 supplement at 2nd hour, where as 56% patients in group A and 12% patients in group B needed 2 supplements at 2nd hour, which was statistically significant (p value 0.002). 80% of the patients in group A and 96% patientsin group B did not require any supplements at 1st hour, whereas 20% patients in group A and 4% patients in group B required 1 supplemental dose at 1st hour, which was statistically insignificant (p value 0.189).With regard to number of supplements at 3rd hour, in group A 60% patients and group B 76% patients did not require any supplements, while 40% patients in group A and 24% patients in group B needed 1 supplement, which was statistically insignificant (p value 0.225).

Key words: Neostigmine, ropivacaine 0.1%, lumbar epidural analgesia

INTRODUCTION

Labour may be the most painful experience many women ever encounter. The experience is different for each woman and different methods chosen to relieve pain depend upon the techniques available locally and the personal choice of the individual. Hence, providing effective and safe analgesia during labour has remained an on-going challenge.

Central neuraxial analgesia is the most versatile method of labour analgesia and the gold standard technique for pain control in obstetrics [1]. In the early 1960s, the lumbar epidural replaced caudal analgesia as the preferred technique. In 1967 Beazley *et al.* published a classic study of the efficacy of different forms of analgesia in labour[2]. Since then epidural analgesia has been widely introduced for pain relief in labour even for routine practice. The use of lumbar epidural catheters in the 1970s permitted administration of pain relief early in labour, rather than only at the time of delivery.[2]

Bupivacaine has been used traditionally for epidural labour analgesia but Ropivacaine, a new local anaesthetic may be superior to bupivacaine for epidural analgesia because of decreased potency for motor block and greater safety.[3] Ropivacaine as a sole epidural analgesic, however, requires relatively concentrated solutions (0.2%-0.3%) and is often unsatisfactory because of inadequate analgesia or excessive motor block. The addition of epidural fentanyl improves analgesia and allows the use of 0.1% and 0.05% solutions of epidural Ropivacaine with decreased risk of motor block.[3] The amount by

which fentanyl reduces local anaesthetic dose requirement depends on dose of fentanyl and the modern day mixtures include low concentration of local anaesthetics with opioids.[4]

Neostigmine (acetyl cholinesterase inhibitor) is a parasympathomimetic agent that has been investigated for use as an adjunct analgesic agent in the perioperative and peripartum period. Intrathecal injection of neostigmine increases extracellular acetylcholine levels in spinal cord leading to increased stimulation of spinal muscarinic and possibly nicotinic receptors to produce analgesia. While intrathecal administration is limited by a high incidence of nausea and vomiting in this patient population, the epidural route is more promising[5]. Epidural administration of neostigmine is found to be safe in the obstetric population, with no reported adverse effects in the mother or foetus.[6]

METHODOLOGY

SOURCE OF DATA: The study was conducted in 50 Primiparous patients in active phase of labour in the labour ward of Department of Obstetrics and Gynecology.

STUDY DESIGN: Prospective, randomized, double blinded, controlled study.

SAMPLE SIZE: 50.

INCLUSION CRITERIA

1. ASA II, Consenting primigravida in labour, gestational age ≥ 36 weeks.
2. Age 18-35 years, singleton pregnancy with vertex presentation.

EXCLUSION CRITERIA

1. Allergy to any of the study drugs.
2. Significant coagulopathy.
3. Patients with history of significant disorders (Pregnancy induced hypertension, diabetes mellitus, obstetric haemorrhage, other cardiovascular, respiratory, central nervous system or renal system disorders).
4. **OTHER CONTRAINDICATIONS:** Localized sepsis, raised ICP etc.

METHODS OF COLLECTION OF DATA

Patients were explained about the procedure and informed/written consent was obtained.

- Thorough pre anaesthetic evaluation was performed.
- Routine investigations obtained.
- Foetal status, labour status (frequency and duration of labour pain and cervical dilatation) assessed and noted both clinically and with Cardiotocography (CTG).
- Patients were randomized into two groups using computer generated random numbers:
- **GROUP A:**Received 0.1% Ropivacaine with fentanyl 2µg/mlin 10 ml total volume.
- **GROUP B:**Received 0.1% Ropivacaine with fentanyl 2µg/mland neostigmine 500µg in 10 ml total volume.
- Baseline hemodynamic parameters likematernal heart rate, oxygen saturation, ECG, non-invasive blood pressure, wererecorded.
- Under strict aseptic precautions epidural space identified with patient in left lateral position by midline approach using 18 G Tuohy's needle in L_{3-4} or L_4-L_5 interspace with loss of resistance to saline technique and catheter is threaded cephalad 3 to 4 cms into epidural space. After negative aspiration for blood and CSF, a test dose of 3ml of lignocaine 2% with 1:2, 00, 000 adrenaline was administered through the catheter.
- Ten ml of study drugof either 0.1% Ropivacaine with fentanyl 2µg/mlor 0.1% Ropivacaine with fentanyl 2µg/ml and Neostigmine 500µg was administered as per group allotment.
- Analgesia maintained by top up of 5 ml solution of 0.1% Ropivacaine with fentanyl 2µg/ml with NRS≥4, not earlier than 15 min of previous dose.
- Patients who experienced inadequate analgesia (NRS≥4) during the process were supplemented with additional 5 ml solution at least 15min later.

RESULTS

Table 1: Comparison of total dose of Local anaesthetic used in the study subjects among the two groups

Total dose of LA used (mg)	Group A, n=25	Group B, n=25	P value
Mean ± SD	20.8 ± 2.77	16.8 ± 2.45	<0.001

The mean total dose of Local anaesthetic i.e. Ropivacaine 0.1%used in group A was 20.8 mg (±SD 2.77) and in group B was 16.8 mg (±SD 2.45), which was statistically significant (p value <0.001).

Table 2: Comparison of dose of local anaesthetic required per hour in the study subjects among the two groups

Comparison of dose of local anaesthetic required per hour in the study subjects among the two groups			
LA dose (mg/hour)	Group A, n=25	Group B, n=25	P value
Mean ± SD	6.52 ± 0.69	5.68 ± 0.65	<0.001

The mean dose of LA anaesthetic required per hour in group A was 6.52mg (±SD 0.69) and in group B was 5.68mg (±SD 0.65), which was statistically significant (p value was <0.001).

Table 3: Comparison of duration of labour in the study subjects among the two groups

Comparison of duration of labour in the study subjects among the two groups			
Duration of labour (min)	**Group A, n=25**	**Group B, n=25**	**P value**
Mean ± SD	191.2 ± 15.23	177.8 ± 16.4	0.004

The mean duration of labour in group A was 191.2 min (±SD 15.23) and in group B was 177.8 min (±SD 16.4), which was statistically significant (p value 0.004).

Table 4: Comparison of duration of analgesia in the study subjects among the two groups

Comparison of duration of analgesia in the study subjectsamong the two groups			
Duration of analgesia (min)	Group A, n=25	Group B, n=25	P value
Mean ± SD	73.8 ± 9.61	93 ± 12.99	<0.001

The mean duration of analgesia in group A was 73.8 min (±SD 9.61) and in group B was 93 min (±SD 12.99), which was statistically significant (p value <0.001)

Table 5: Comparison of onset of sensory block among the two groups

Onset of SB	**Group A,n=25**	**Group B,n=25**
	Frequency (%)	**Frequency (%)**
20 min	11 (44%)	13 (52%)
25 min	9 (36%)	10 (40%)
30 min	5 (20%)	2 (8%)
Mean ± SD	23.8 ± 3.89	22.8 ± 3.25

P value: 0.471

The mean onset of sensory blockade in group A was 23.8min (±SD 3.89) and in group B was 22.8min (±SD 3.25), which was statistically insignificant. (P value 0.471)

Table 6: Comparison of degree of motor block among the two groups

Degree of Motor block	**Group A,n=25**	**Group B,n=25**
	Frequency (%)	Frequency (%)
Degree 0	23 (92%)	23 (92%)
Degree 1	2 (8%)	2 (8%)

P value: 1

The degree of motor blockade was similar in both the groups.92% patients in group A and B had 0 degree blockade, 8% patients in group A and B had 1 degree blockade, which was statistically insignificant (p value 1).

Table 7: Comparison of requirement of supplements at different intervals of time among the two groups

Comparison of requirement of supplements at different intervals of time among the two groups						
Intervals of supplementation		**Group A, n=25**		**Group B, n=25**		**P value**
		Frequency	**(%)**	**Frequency**	**(%)**	
Supplements at 1st hour						
	0	20	(80%)	24	(96%)	0.189
	1	5	(20%)	1	(4%)	
Supplements at 2nd hour						
	1	11	(44%)	22	(88%)	0.002
	2	14	(56%)	3	(12%)	
Supplements at 3rd hour						
	0	15	(60%)	19	(76%)	0.225
	1	10	(40%)	6	(24%)	

As far as number of supplements are concerned, in group A 44% and group B 88% patients needed 1 supplement at 2nd hour, where as 56% patients in group A and 12% patients in group B needed 2 supplements at 2nd hour, which was statistically significant (p value 0.002).

80% of the patients in group A and 96% patientsin group B did not require any supplements at 1st hour, whereas 20% patients in group A and 4% patients in group B required 1 supplemental dose at 1st hour, which was statistically insignificant (p value 0.189).
With regard to number of supplements at 3rd hour, in group A 60% patients and group B 76% patients did not require any supplements, while 40% patients in group A and 24% patients in group B needed 1 supplement, which was statistically insignificant (p value 0.225).

DISCUSSION

Labour, also called as parturition, is the process by which frequent and sufficiently strong uterine contractions cause thinning (i.e., effacement) and dilation of the cervix, thereby permitting passage of the foetus from uterus through the birth canal.
Melzack and Wall described the gate control theory of pain[7],which has led to better understanding of mechanisms involved in perception of pain and analgesia. There is considerable variability in the intensity of pain experienced by women during labour. Nulliparous women rate labour pain as more severe when compared to multiparous women.
Various techniques are available for administering labour analgesia. Neuraxial analgesia is the most effective method of intrapartum pain relief and the only form of analgesia that provides complete analgesia for both stages of labour.Previous studieshave shown that satisfaction of the birth experience was greater in patients who received epidural analgesia[8].Studies that compared epidural analgesia with systemic opioids and/or inhalational analgesia (i.e., nitrous oxide) have found that pain scores were lower and patients were more satisfied with neuraxial analgesia[9].Additionally, the presence of an epidural catheter and effective epidural analgesiafacilitate rapid initiation of epidural anaesthesia for emergency caesarean delivery.
The ideal analgesic drug for labour would provide rapid onset of effective analgesia with minimal motor blockade, long duration of action, minimal maternal toxicityand negligible effect on uterine activity and uteroplacental perfusion. It would undergo limited transplacental transfer and thus have minimal direct effect on the foetus. Although this perfect analgesic drug does not exist, the combination of a local anaesthetic with an opioid can be used to achieve this goal.
Racemic Bupivacaine has been the most commonly used amide local anaesthetic for epidural labour analgesia. Its transplacental transfer is limited as it is highly protein bound. After epidural administration of Bupivacaine (without opioid) during labour, the patient experiences pain relief within 8-10 min, but peak effect is achieved after about 20 min and duration of analgesia is approximately 90 minutes.
Ropivacaine, a relatively newer amide local anaesthetic, is similar to bupivacaine in structure and pharmacodynamics. It is a homologue of Bupivacaine and Mepivacaine, and is formulated as a single-levorotatory enantiomer rather than a racemic mixture. Studies have shown that Ropivacaine is less cardiodepressant and arrhythmogenic than Bupivacaine[10]. It is more selective for sensory fibres when compared to other local anaesthetics, thus produces less motor block which allows for increased maternal ambulation and normal progression of labour, resulting in fewer instrumental deliveries and more vaginal deliveries. All these factors indicate that Ropivacaine might be superior to Bupivacaine in obstetric analgesia. The side-effects of Ropivacaineare hypotension, bradycardia, nausea, paraesthesia, and urinary retention, which are considered mild and transient. Ropivacaine concentrations used to initiate epidural analgesia range from 0.08% to 0.2%.[20] In our study we used Ropivacaine in the concentration of 0.1%.
Though contemporary practice of epidural labour analgesia includes administration of a long-acting amide local anaesthetic combined with a lipid-soluble opioid, other drugs may be added as adjuvants. These adjuvants may prolong the duration of analgesia or decrease the local anaesthetic dose required.
Neostigmine used as adjuvant along with local anaesthetic-opioid combination, prevents the breakdown of acetylcholine within the spinal cord, which in turn binds to muscarinic receptors leading to reduced neurotransmitter release and subsequent analgesia. Roelants*et al*. randomly assigned parturient to receive either epidural Ropivacaine (20 mg) alone or epidural Neostigmine (4 μg/kg) combined with Ropivacaine (10 mg), with or without Sufentanil (10 μg). The magnitude and duration of analgesia in the Ropivacaine/Neostigmine group was similar to that of the plain Ropivacaine group but less than in the Ropivacaine/Sufentanil group. Neostigmine is hydrophilic, and the researchers hypothesized that only a small portion of the epidural dose penetrates the spinal cord[11]. In a subsequent study, the same researchers compared epidural Sufentanil 20 μg with Sufentanil 10 μg combined with Neostigmine 250, 500, or 750 μg[12]. They found that Neostigmine 250 μg with Sufentanil was ineffective, but both 500 and 750 μg of Neostigmine produced effective analgesia similar in duration to that obtained with Sufentanil alone. In our study we used Neostigmine in the dose of 500 μg to determine the effect of adding Neostigmine on dose requirements of Ropivacaine 0.1% and on duration of labour in labouring patients receiving lumbar epidural analgesia.

CONCLUSION

We conclude that the addition of Neostigmine to the combination of Ropivacaine-Fentanyl during epidural labour analgesia significantly reduces the dose requirement of the local anaesthetic, Ropivacaine 0.1% and also reduces the duration of labour. Hence Neostigmine can be routinely used as an adjuvant to

the local anaesthetic-opioid combination for epidural labour analgesia.

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