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A Randomised Double-Blinded Dose Response Study of the Fentanyl with Hyperbaric Ropivacaine in Cesarean Section

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Abstract

Background: Much research work has been done to know the minimum required concentration of local anaesthetic agents, employing various adjuvants for cesarean section. The present study states that Fentanyl addition to heavy Ropivacaine reduced the dose of later, thereby its side effects related to higher doses in cesarean sections.

Patients: Three groups of thirty parturient each were made randomly. Group I received 15 mg 0.6% Ropivacaine; Group II received 12 mg 0.6% Ropivacaine and 12.5 µg Fentanyl and Group III received 10 mg 0.6% Ropivacaine and 25 µg Fentanyl. Sensory and motor block properties, hemodynamics, intraoperative visceral pain, sedation, shivering, nausea and vomiting, postoperative analgesia; foetal outcomes and side effects were evaluated. ANOVA, chi-square and Mann-Whitney-U tests were used where appropriate ($p<0.05$).

Results: Intrathecal hyperbaric Ropivacaine and its combination with Fentanyl provided effective sensory and motor block (1.73-2.1 min, p value<0.001), S2 dermatome regression time was longer in Ropivacaine- Fentanyl combination as compared to Ropivacaine alone. Umbilical venous pH and APGAR score was similar (9-9.4) in all groups. Postoperative analgesic effect (monitored as a secondary end-point) was prolonged by addition of Fentanyl; here intraoperative ephedrine requirement was significantly increased in group I (30 mg) as compared to group II (8 mg) and III (6 mg).

Conclusions: S2 dermatome regression time taken as the primary end point was longer in Ropivacaine-Fentanyl combination as compared to Ropivacaine alone. Addition of 12.5 and 25 µg Fentanyl significantly reduced the dose of heavy Ropivacaine resulting in longer, complete and effective analgesia with hemodynamic stability and less side-effects. It is concluded that intrathecal hyperbaric Ropivacaine provides efficient and safe anaesthesia for cesarean section delivery and that this effect is further enhanced by the addition of Fentanyl. Hence the best effective and safe combination, as per this study is 12 mg of Ropivacaine with 12.5 µg Fentanyl (Group II).

Keywords: Cesarean section; Hyperbaric ropivacaine; Intrathecal fentanyl

Introduction

Spinal anaesthesia is well known safe, effective, economical, easy to perform technique which provides rapid and reliable anaesthesia with muscle relaxation for cesarean section. It reduces the risk of aspiration pneumonitis with early return of intestinal motility with minimal maternal and neonatal side effects [1,2]. Ropivacaine is the first single enantiomer-specific compound, structurally related to bupivacaine has a reduced risk of cardiotoxicity, neurotoxicity and rapid recovery of motor function [3-5]. Ropivacaine is available in isobaric form which when used for intrathecal block may cause intraoperative visceral pain, because of variable sensory and motor response [6-9]. There has been two good studies on intrathecal Fentanyl with hyperbaric Ropivacaine they are: addition of Fentanyl 10 µg, to hyperbaric Ropivacaine 15 mg, for spinal anaesthesia increased the duration of analgesia in the early postoperative period in patients undergoing caesarean delivery [10], and the second one is about finding the lowest effective local anaesthesia effect of Ropivacaine and Bupivacaine [11], here we postulate that the addition of fentanyl to hyperbaric Ropivacaine may allow reduction of heavy dose of Ropivacaine, providing hemodynamic stability and prolonged post-operative analgesia. The aim of this prospective, randomized, double-blinded study was to observe the effect of intrathecal heavy Ropivacaine alone and in combination with intrathecal two doses of Fentanyl 12.5 and 25 µg. The primary outcome(s) studied were onset of motor and sensory blockade, hemodynamic variables, sedation, use of additional fluid and ephedrine requirements, time to regression of spinal blockade below level S1. Secondary outcome measures studied were time to first analgesic request, Comparison of the degree of the postoperative analgesic effect [change in VAS (Visual Analogue Scale) at 6 and 24 hours post-surgery] as well as post-operative cumulative analgesic consumption. This study comprises of the maiden findings about the co-administration of Ropivacaine with Fentanyl, which not only act synergistically but also significantly reduces the side-effects associated with the former. We are putting forth statistically significant, supporting null hypothesis (n=90) data to prove the same.

Patients and Methods

A randomized double blind study was performed after obtaining the approval of Ethical Committee of Chattrapati Shahuji Maharaj Medical

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University, Lucknow, India. 93 full term pregnant females of American Society of Anaesthesiologist (ASA) grade I, II, aged >20 years were included for the study. Patients were randomized into three groups of 30 each using computer generated random number table. These groups were further classified based on intrathecal drug combination used.

Group I:	15 mg 0.6% hyperbaric Ropivacaine
Group II:	12 mg 0.6% hyperbaric Ropivacaine+12.5 µg Fentanyl
Group III:	10 mg 0.6% hyperbaric Ropivacaine +25 µg Fentanyl

All patients were explained about the intrathecal use of drug; written and informed consent was taken. Patients included in the study were not aware of the drug combination, which they received for spinal anaesthesia. Exclusion criteria was any contraindication for spinal anesthesia, complicated pregnancies such as multiple pregnancy, pregnancy-induced hypertension, placenta previa, acute fetal distress, patients with previous abdominal surgeries, patients having body weight >70 kg. All Patients received oral ranitidine 150 mg and metoclopramide 10 mg; the night before and on the morning of surgery 30 ml sodium citrate were given orally; before arrival to the operation room, patients were preloaded with 10-15 ml/kg body of ringer lactate via 18 gauge venous catheter. Base line standard monitoring included continuous electrocardiogram, pulse oximetry, non-invasive blood pressures and urine output. Sensory and motor assessment methods were described to all patients before start of anaesthesia. The solution was prepared aseptically by the anaesthetist administering the block, by mixing Ropivacaine 4 ml 7.5 mg/ ml with 1 ml 25% dextrose making the solution 5ml, each ml contain Ropivacaine 6 mg/ml and glucose 50 mg/ ml to give solutions with density of 1.01949 g at 37°C [12]. Spinal anaesthesia was given in left lateral position between L_3 and L_4 vertebrae using 25 gauges, Whitacre needle taking complete aseptic precautions. In group I intrathecal Ropivacaine (15 mg), in group II intrathecal Ropivacaine (12 mg) with Fentanyl (12.5 µg), Ropivacaine 10 mg with Fentanyl 25 µg in the third group was given over 10–15 s; immediately after the block, each parturient was placed supine with a wedge under right hip [13]. Non-invasive blood pressure and pulse were measured every 5 min for first 30 min and there after every 10 min. Patients were given supplementary O_2 with the help of venturi mask. Sensory block was tested by cold, touch, and pinprick along the midclavicular line till the block reached T6 level and then the surgical incision was allowed [14]. Motor block using a modified Bromage scale (0=no block, 1=inability to raise extended leg, 2=inability to flex knee and 3=inability to flex ankle and foot) was also recorded at the 5, 10, 15, 20, 25 and 30 minutes. The following variables were recorded: time to initial onset of analgesia, highest level of sensory analgesia, the time to complete motor block, time to two-segment regression of analgesic level from T6 dermatome to T8, regression of analgesic level to S1 dermatome, motor recovery (ability to move lower limbs) and first request for analgesic were recorded. The total duration of analgesia was considered from the time of injection of spinal anaesthetic, until the first request for analgesic by the patient. The surgical anaesthesia was graded as "excellent"- if there were no complaints from patient or surgeon, "Good" - if there was complaint of pain which was relieved by IV opioid analgesics and "Poor" - if more than one dose of analgesic or rescue general anaesthesia was required [2]. Maternal hemodynamic parameters, which included heart rate, ECG, NIBP (both systolic and diastolic), respiratory rate and SpO_2, were monitored continuously. Hypotension (defined as systolic arterial pressure falling more than 20%) was treated with injection ephedrine 3-6 mg in bolus doses and heart rate <55 beats/minute was treated with 0.4 mg of injection atropine. Intravenous fluids were given as per operative loss with blood transfusion if required. During the surgical procedure, side effects like sedation, nausea, vomiting, pruritus, shivering, bradycardia or hypotension were recorded. Nausea and vomiting were treated with 4-6 mg of i.v. ondansetron. The pruritis was assessed as mild, moderate and severe stages. Urinary bladder was catheterized in all patients before the start of surgery, until 24 hours postoperatively. Postoperatively, pain scores were recorded by using VAS between 0 and 10 (0=no pain, 10=the most severe pain), initially every 1 hour for 2 hours, then every 2 hours for next 8 hours and then after every 4 hours till 24 hours. Injection diclophenac 75 mg intramuscular was given as rescue analgesia when VAS ≥ 4. Follow-up was carried out 1 week postoperatively by the blinded anaesthetist who asked about postoperative headache as well as postoperative pain and dysesthesia in the buttock, thighs, or lower limbs. Apgar score of neonate was recorded at 1, 5 and 10 min [15].

Statistical Analysis

Data were analysed by using statistical software namely SPSS 15.0. The sample size, based on α risk of 0.05 and β risk of 0.9 showed that 30 patients per study groups were needed. Results were presented as median (range), mean (SD) or frequencies as appropriate. Block characteristics were compared using the two-tailed Mann–Whitney U-test. Three groups were compared by using one-way ANOVA with the Bonferroni multiple comparison tests. Data were considered significant with $P<0.05$. The proportion of side effects was compared using the chi-square test ($\chi^2=57.24$, 10) and statistical significance was observed at $P<0.001$ [16].

Results

Adequate anaesthesia for surgery was achieved in patients of all three groups. The groups were comparable with respect to age, height and weight, sex, and ASA status (Table 1).

One patient in each group was withdrawn because of total block failure (no muscle weakness or loss of sensation) and given a general anaesthesia, so leaving 29 patients in each group. There was approximately no difference in the duration of surgery, although its duration was somewhat longer in the II group (Table 1) as compared to I and III. Hyperbaric Ropivacaine produced a more rapid onset of block, which ultimately regressed more quickly (Table 2).

The onset of analgesia to pinprick at T6 was earlier in group I as compared to group II and III and the maximum block height was greater in group I as compared to II and III (Table I). Median time to maximum block height was the faster in group I as compared to II and III (Tables 1 and 2).

The quality of anaesthesia was excellent in all patients but patients of II and III groups were thermodynamically more stable as compared to group I in which hypotension was detected in (66.6%) patients. Intraoperative ephedrine requirements (mg) were more in group I (30 ± 6) as compared to group II (8 ± 2) and III (6 ± 2). Motor blockade was excellent in all patients but onset is slightly earlier in group I as compared to II and III (Table 2).

Parameters	Group I	Group II	Group III
Age (years)	27.7 ± 2.9	26.8 ± 2.5	27.5 ± 3
Height (cm)	156.6 ± 3.3	157.2 ± 3.7	157.1 ± 3.97
Weight (kg)	62 ± 2.8	61.9 ± 3.3	62.67 ± 2.38
ASA I/II	20/10	22/8	19/11
Duration of surgery (min)	48 ± 15.8	57 ± 10.6	52 ± 12.9

Values are Mean ± SD of 29 patients

Table 1: Patient characteristics.

Parameters		Group I	Group II	Group III	P Value
Onset to T6 (min)		5.71 ± 0.13	5.81 ± 0.13	5.82 ± 0.14	>0.05
Onset to T4 (min)		10.27 ± 0.14	12.1 ± 0.21	15.87 ± 0.15*	<0.01*
Motor Block (min)	B1	1.73 ± 0.05	1.8 ± 0.14	2.1 ± 0.17	>0.05
	B2	4.68 ± 0.11	5.27 ± 0.13*	5.53 ± 0.09*	<0.001*
	B3	8.93 ± 0.12*	9.97 ± 0.12*	11.37 ± 0.13*	<0.001*
Total Power Regain (min) B0		153.67 ± 2.51	132.06 ± 1.76*	121.0 ± 2.11*	<0.001*
Demand of Rescue Analgesia (min)		133.66 ± 1.89	165.00 ± 1.84*	188.67 ± 1.64*	<0.001*
Maximum Block Height		T2(T2-T4)	T4 (T3-T6)	T5 (T3-T5)	-
Time (min) of Two Segment Regression (T4-T6)		70 ± 17.94	80 ± 18.56	86 ± 19.86	-

*P<0.01 **P<0.001

Table 2: Onset of Motor and sensory block (time in minutes).

Side Effects	Group I		Group II		Group III	
(n=90)	No.	%	No.	%	No.	%
Nausea	7	23.33	2	6.67	1	3.33
Hypotension*	20	66.67	12	40	5	16.67
Bradycardia**	4	13.33	1	3.33	1	3.33
Itching**	-	-	1	3.33	2	6.67
Headache*	5	16.67	3	10	1	3.33
Shivering	5	16.67	2	6.67	1	3.33

***P<0.01 **P<0.001**

Table 3: Side Effects.

Median time to regression of sensory block to T10 was longer in group III as compared to I and II (Table 2). The median times to complete regression of both sensory and motor block were earlier in the I group as compared to II and III groups. Therefore, in the patients mobilized earlier in the hyperbaric group I as compared to II and III groups, demand for rescue analgesia (Table 2).

Umbilical venous pH and APGAR score at every minute was similar in all the groups (II: 9.2, III: 9.0 and I: 9.4). Postoperative analgesia was prolonged by addition of Fentanyl in dose dependent manner.

Hypotension, Bradycardia, Nausea and vomiting was more in group I as compared to groups II and III. Intraoperative sedation was not found in group I where as patients of groups II and III were drowsy but arousable. The sedation score was less in group I (2.8 ± 0.6), than group II (3.2 ± 0.1) and III (3.8 ± 0.7). Itching was more but headache and backache was less in III group as compared to groups II and I. No neurologic symptoms were found at 24 h and during follow up of patients (Table 3).

Discussion

Now-a-days regional anaesthesia has gain increased popularity for caesarean because of reduced incidence of morbidity and mortality as compared to general anaesthesia [1]. However, regional anaesthesia has its own complication like sudden hypotension, bradycardia, nausea and vomiting, high spinal and visceral pain. These complications can be avoided by careful monitoring, reduction in doses of local anaesthetic agents, addition of various adjuvants with local anaesthetics [1]. Keeping all these factors in mind we have performed this study. In present study heavy Ropivacaine was used due to reduced risk of cardiac and CNS toxicity, addition of glucose to isobaric Ropivacaine provide adequate depth of anesthesia without any intraoperative visceral pain, the maximum block height was greater and more consistent and had a faster onset and recovery [17-20], considered clinically important in emergency cases in which there may be some urgency to deliver the fetus. Episodes of hypotension, nausea and vomiting, however, were more frequent as a consequence of the hyperbaric block characteristics but this did not cause any adverse fetal outcomes, because all hypotensive episodes were promptly corrected with fluids and ephedrine. In our study, IV prehydration was done, and better control of blood pressure may have been achieved with ephedrine [21,22]. In Fentanyl group all patients has rapid recovery from anaesthesia, so that all patients become ambulatory much earlier as compared to Ropivacaine group. A number of studies have previously reported the use of hyperbaric [6,19] Ropivacaine for spinal anesthesia. In the present study we found that 15 mg heavy Ropivacaine provided sufficient intra operative anaesthesia but incidence of hypotension were found 66.67%, nausea and vomiting were more in group I, so we added an adjuvant Fentanyl in two doses (12.5 and 25 µg) with Ropivacaine, to minimize the dose of heavy Ropivacaine [23]. Fentanyl augment analgesia produced by heavy Ropivacaine through direct binding with specific spinal receptors [1], hence reduce the dose of Ropivacaine to achieve adequate surgical anaesthesia [2], obliterate the visceral pain caused due to traction on peritoneum and intra parietal organs in minimum dose of ropivacaine during caesarean deliveries. Low dose of spinal anaesthesia has the advantage of providing cardiovascular stability. Harsoor et al. [2] observed that 8 mg hyperbaric Bupivacaine is preferable to 10 mg in spinal anaesthesia for cesarean section to obtain adequate analgesia and avoid maternal hypotension in asian race. Danelli et al. [24] recommended a low dose of 0.06 mg/cm height of women for spinal block in elective caesarean section. In our study all intrathecal injection were given in the lateral position but patients of group I got higher cephalic spread, whereas, patients of group II and III received lower cephalic spread it may be due to lower amount of dose of heavy Ropivacaine [19]. When a hyperbaric solution is injected in the lateral position, the tendency would be for it to spread by gravity in the cephalic direction. When the patient is turned supine, gravity would also spread the solution cephalad down the lumbar curvature. The synergistic action of fentanyl and local anaesthetics in central neuraxial blocks (CNB) improves the quality of intraoperative analgesia and also prolongs the postoperative analgesia. A dose of injection Fentanyl 12.5 µg produces peak effects, with higher doses increases the incidence of side effects. Study by Fan et al. [25] also suggest tramadol as a safe alternative to fentanyl for labor analgesia due to its similar analgesic efficacy.

It is concluded that intrathecal hyperbaric Ropivacaine provides efficient and safe anaesthesia for cesarean section delivery. The addition of 12.5 and 25 μg Fentanyl reduces the dose of heavy Ropivacaine resulting in longer, complete and effective analgesia with hemodynamic stability with less side-effect. Hence the best effective and safe combination, as per this study is 12 mg Ropivacaine with 12.5 μg Fentanyl (Group II).

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