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ORIGINAL ARTICLE

EFFECT OF INTRATHECAL ROPIVACAINE WITH DEXMEDETOMIDINE FOR OPERATIVE AND POST OPERATIVE ANALGESIA: A PROSPECTIVE RANDOMIZED STUDY

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ABSTRACT BACKGROUND: This prospective randomized double blind study was conducted to evaluate the effect and safety of intrathecal dexmedetomidine added to isobaric ropivacaine. **MATERIALS AND METHODS:** 120 adult female patients, who underwent vaginal hysterectomies, were randomly allocated to receive intrathecally either 3 ml of 0.75% isobaric ropivacaine + 0.5 ml normal saline (Group R) or 3 ml of 0.75% isobaric ropivacaine +5 µg dexmedetomidine in 0.5 ml of normal saline (Group D). Following intrathecal administration, duration of onset of sensory and motor blockade, maximum dermatomal level achieved, duration of analgesia, hemodynamic parameters and incidence of side effects were observed. **RESULTS:** Duration of onset of sensory block upto T10, T8 and the highest level of block achieved i. e. T6 were similar in both the groups. The mean time of sensory regression to S2 was 297.71±34.11 min in group D and 221.35±22.70 min in group R. Time to achieve Bromage score 0 was significantly slower with the addition of dexmedetomidine (229.37±28.74 min in group R vs. 258.55±30.46 min in group D). Duration of postoperative analgesia was significantly greater in group D (270.00±38.75 min) as compared to group R (174.77±22.31 min). The maximum VAS score for pain was less in group D (4.42±0.69) as compared to group R (7.03±0.78). There were no significant difference in hemodynamic parameters and incidence of side effects in both the groups. **CONCLUSION:** The addition of dexmedetomidine to ropivacaine intrathecally produces significantly longer sensory and motor blockade along with better postoperative analgesia, and excellent hemodynamic stability without any significant side effects.
KEYWORDS: Dexmedetomidine, Ropivacaine, Intrathecal, Hysterectomy.

INTRODUCTION: Spinal anaesthesia is a an established mode of anaesthesia for lower abdominal surgeries because it blunts the "stress response" to surgery, decreases intraoperative blood loss and lowers the incidence of postoperative thromboembolic events.[1-3] Bupivacaine is the most commonly used local anesthetic for neuraxial anaesthesia, however it is associated with cardiotoxic side effects.[4] As a result, an enantiomer-specific amide type local anesthetic, ropivacaine, which has lower potential for cardiac and central nervous systemic toxicity and shows greater differentiation between sensory and motor blockade along with improved hemodynamic stability was introduced in 1996 and approved for spinal anesthesia in the European Union in 2004.[5]

Various adjuvants have been used intrathecally to improve the quality and duration of the spinal anaesthesia along with better postoperative analgesia. The most commonly used agents have been opioids, such as morphine, fentanyl and sufentanil. However addition of opioids has been associated with undesirable side effects like respiratory depression, pruritis, nausea and vomiting.

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Various other drugs like and other drugs such as clonidine, magnesium sulfate, neostigmine, ketamine and midazolam, have also been used but none is without associated adverse effects.[6, 7] Dexmedetomidine, is a novel and highly selective alpha-2 adrenoceptor agonist, having antinociceptive action for both somatic and visceral pain.[8] Various studies have reported the efficacy and safety of intrathecal dexmedetomidine in combination with bupivacaine.[9-11] However very little data is available on usage of dexmedetomidine in spinal anaesthesia with ropivacaine. Therefore this study was planned to study the synergistic effect and safety between dexmedetomidine and isobaric ropivacaine in spinal anesthesia and compare this with isobaric ropivacaine alone in the patients undergoing vaginal hysterectomy.

MATERIALS AND METHODS: After getting institutional ethics committee approval this prospective randomised double blind study was conducted on 120 patients aged between 18-65 years with ASA grade I or II, undergoing vaginal hysterectomy under spinal anesthesia. Patients, who refused for spinal anesthesia, were ASA grade III & IV, age less than 18 years or greater than 65 years were excluded from the study. Patients with known history of head injury, psychiatric diseases, weight more 70 kg, height less than 145 cm**,** patients with a known history of intake of beta blocker's, alpha-2 adrenergic receptor antagonists, calcium channel blockers, ACE inhibitors**,** patients with known history of allergy to any test drugs, patients suffering from major hepatic, renal or cardiovascular system dysfunction, contraindications to spinal anesthesia or any patient who has received any analgesic drugs within the past 24 hours were also exclude from the study.

After a well informed consent and thorough pre-anesthetic evaluation, all patients were cannulated in the preoperative room. In operating room they were preloaded with 15 ml/kg of lactated Ringer's solution and noninvasive blood pressure (NIBP), pulse oximeter, electrocardiogram (ECG) were attached to all patients. Lumber puncture was performed in L_3-L_4 or L_4-L_5 intervertebral space in sitting position through a midline approach using 25G Quincke's needle under all aseptic precautions. Patients were randomized on the basis of sealed envelope technique to receive one of the following drug (drug was made by an anesthesiologist blinded to the study protocol).

GROUP R: 3 ml volume of 0.75% isobaric ropivacaine (22.5 mg) and 0.5 ml of normal saline.

Group D: 3 ml volume of 0.75% isobaric ropivacaine (22.5 mg) with 5µg dexmedetomidine in 0.5 ml of normal saline.

The drug was injected intrathecally over approximately 10 to 15 seconds. Immediately after intrathecal injection, patient was then made to lie in supine position. The Anesthesiologist performing the block was blinded to the study drug and intraoperative vitals were recorded. The level of sensory block was checked by loss of pinprick sensation by 23 G hypodermic needle and dermatomal levels were tested every 2 minutes until the highest required level was stabilized for four consecutive tests. Testing was then conducted every 10 minutes until the time of two segment regression of block. Further testing was performed every 20 minutes intervals until the recovery to S_2 dermatome.

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Simultaneously motor block was evaluated using the Bromage Scale as follows:

BROMAGE 0 - The patient is able to move the hip, knee and ankle.
BROMAGE 1 - The patient is unable to move the hip, but is able to move the knee and ankle.
BROMAGE 2 - The patient is unable to move the hip, and knee, but is able to move the ankle.
BROMAGE 3 - The patient is unable to move the hip, knee, and ankle.

Hemodynamic parameters were recorded every 3 minutes after spinal administration of selected drug for first 15 minutes and subsequently every 5 minutes for half an hour after spinal anesthesia then at every 10 minutes till the end of surgery. Any fall in BP below 100 mm Hg or more than 20% of base line was treated with administration of oxygen, fast iv fluids and vasopressor (mephentermine 3 to 6mg iv) as needed. Any fall in heart rate less than 60 beats or more than 20% of base line was treated with injection atropine 0.3 mg increments iv, as needed. Data regarding the highest dermatomal level of sensory blockade, the time to reach this level from the time of spinal injection, time to S_2 sensory regression were recorded. All durations were calculated considering the time of spinal injection as time zero. After commencement of surgery, patient's anxiety and sedation level was evaluated by Modified Ramsay Sedation Score as follows-

Modified Ramsay Sedation score is as below:

1. Patient is anxious, agitated or restless.
2. Patient is co-operative, oriented and tranquil alert.
3. Patient responds to Commands.
4. Asleep, but brisk response to light glabellar tap or loud auditory stimulus.
5. Sluggish response to light glabellar tap or loud auditory stimulus.
6. No response.

The incidence of adverse effects such as nausea, vomiting, shivering, itching, pruritus, respiratory depression, sedation and hypotension were recorded. Postoperatively, pain scores was recorded by using Visual Analogue pain scale (VAS) between 0-10 (0= no pain, 10= the most severe pain), initially every 1 hour for 2 hours, every 2 hours for next 8 hours and then after every 4 hours till 24 hours. Injection tramadol in the dose of 2 mg per kg IV (max 100mg) was given as rescue analgesia when VAS≥4. All data was analysed using IBM SPSS Statistics 21.0 software. The qualitative data between two groups was compared using Chi Square test and for comparison of the continuous variable independent t- test was used. $P < 0.05$ was considered statistically significant. Power of study was 80 at 95% confidence interval.

RESULTS: Initially 120 patients were included in the study. All the patients achieved adequate level of anesthesia except one patient in each group. Both patients required general anesthesia because of inadequate sensory blockade so these patients were excluded from the study. Finally 59 patients in Group R and 59 patients in Group D were included in the statistical analysis. The groups were comparable with respect to demographic characteristics (Table 1). The results regarding the characteristics of sensory as well as motor block are summarized in (Table 2). Block regression was significantly slower with the addition of intrathecal dexmedetomidine (Group D) as compared to ropivacaine alone (Group R). Both, time to two segment regressions and time to S2 regression were significantly more with

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intrathecal dexmedetomidine. On statistical analysis, the maximum VAS score in the group D was lower as compared to group R up to 24 hours postoperatively (Table 3). The duration of analgesia was also significantly prolonged with the addition of dexmedetomidine as compared to ropivacaine alone (270.00±38.75 min and 174.77±22.31 min, respectively). There were no serious adverse effects in the study patients. Only 3 patients in group R and 2 patients in group D had hypotension which required treatment with a single dose of 6mg mephentermine, while none of the patients in both groups suffered from nausea, vomiting, sedation and bradycardia.

DISCUSSION: In this study we have tried to evaluate the efficacy and safety of intrathecal dexmedetomidine in combination with ropivacaine. α_2 adrenoceptor agonist like clonidine has been extensively used in anaesthetic practice for their sympatholytic, sedative, analgesic, and anesthetic-sparing effects.[12, 13] Dexmedetomidine is a highly selective α_2 agonist with a 10 times greater $\alpha 2/\alpha 1$ selectivity than clonidine α_1 receptors.[12-14] Dexmedetomidine has most commonly been used for ICU sedation, however there is a growing body of evidence which supports its use as an adjuvant to local anaesthetic agents in neuraxial blocks.

Al-Ghanem et al[9] and Al-Mustafa et al[10] in their studies observed that the effect of dexmedetomidine is dose dependent and that the onset of sensory blockade was more rapid with the use of dexmedetomidine. However in our study we observed that addition of dexmedetomidine did not enhance the speed of onset of sensorimotor blockade. This can be attributed to the fact that the above authors added dexmedetomidine to bupivacaine as compared to ropivacaine in our study.

In a study conducted by Kanazi et al[15] they observed that 3 μg dexmedetomidine or 30 μg clonidine added to 13 mg spinal bupivacaine equally prolonged the duration of sensory and motor block with minimal side-effects in urologic surgical patients. Similar findings were observed in our study where we observed that there was a significant prolongation in duration of both sensory as well motor blockade in the group receiving intrathecal dexmedetomidine along with ropivacaine. Similar sensory block characteristics were found by Gupta et al.[16] In another study conducted by Gupta et al,[11] they observed that the total duration of motor blockade was prolonged in dexmedetomidine group as compared to fentanyl group (421±21 min vs. 149.3±18.2 min, P value<0.0001).

The mechanism of action by which intrathecal alfa-2 adrenoceptor agonist prolong the motor and sensory block of local anaesthetics is not well known. The local anaesthetics act by blocking sodium channels, whereas the alfa-2 adrenoceptor agonist acts by binding to pre-synaptic C-fibres and post-synaptic dorsal horn neurons. The analgesic action of intrathecal alfa-2 adrenoceptor agonist is by depressing the release of C-fibre transmitters and by hyperpolarisation of post-synaptic dorsal horn neurons.[17] It may be an additive or synergistic effect secondary to the different mechanism of action of the local anaesthetic and the alfa-2 adrenoceptor agonist as studied by Salgado et al.[18] This antinociceptive effect may explain the prolongation of sensory block when added to spinal anaesthetics. The prolongation of the motor block of spinal anaesthetics may result from the binding of alfa-2 adrenoceptor agonists to motor neurons in the dorsal horn.[19, 20]

In a dose-finding study by Khaw et al[21], different doses (10, 15, 20 and 25 mg) of ropivacaine were evaluated (after dilution to a total volume of 3 ml with normal saline) in caesarean section. The effective dose (ED50 and ED95) for spinal ropivacaine was calculated to be 16.7 mg (ED50) and 26.8 mg (ED95). In a study by Kessler et al[22], the authors concluded that isobaric ropivacaine (22.5 mg)

was suitable for spinal anesthesia for lower abdominal gynaecological surgery. Various studies have reported that 5 μg intrathecal dexmedetomidine is safe and devoid of any neurotoxic side effect, hence, we used 5 μg dexmedetomidine along with 22.5mg isobaric Ropivacaine (0.75%).[9, 10, 15]

There was a significant reduction delay in the time to fist rescue analgesia in group receiving intrathecal dexmedetomidine. Also there was a significant reduction in the analgesic consumption and the highest VAS score recorded in the first 24 hours. Similar findings are observed by Mahendru et al[23], Gupta et al[16] and Al-Mustafa et al.[10]

Talke et al[24], observed in their study that α-2 adrenergic agents also have anti-shivering property. In our study shivering was noted in 3 patients in Group R and in one patient in Group D. This is in agreement with the above mentioned study. The combination of ropivacaine and dexmedetomidine provided excellent hemodynamic stability. We also did not observe any hemodynamic side effect in our study. Bradycardia, hypotension and sedation which are the most dreaded side effects of alpha adrenoceptors agonist were also not observed in our study which can be attributed to the usage of low dose of dexmedetomidine. Our study adds to the growing body of evidence that dexmedetomidine can be effectively and safely used as an intrathecal adjunct to ropivacaine however our study was limited by its small sample size and larger randomized controlled studies are recommended to firmly establish the efficacy and safety of intrathecal dexmedetomidine.

To conclude our study reveals that 22.5 mg of isobaric ropivacaine (3 ml of 0.75%) when administered intrathecally along with 5μg dexmedetomidine for lower abdominal surgery it provides significantly longer sensory and motor blockade, better postoperative analgesia, reduced requirement of rescue analgesic in first 24 hour and excellent haemodynamic stability with minimal side effects.

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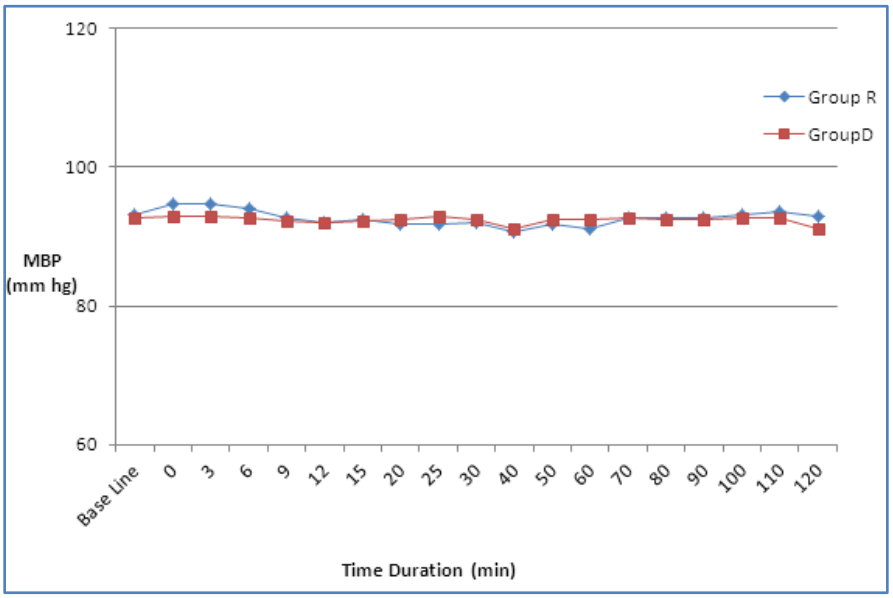

Fig. 1: Comparison of Mean BP (mmHg) between two study groups

Group R – Ropivacaine + Normal saline, Group D – Ropivacaine + Dexmedetomidine

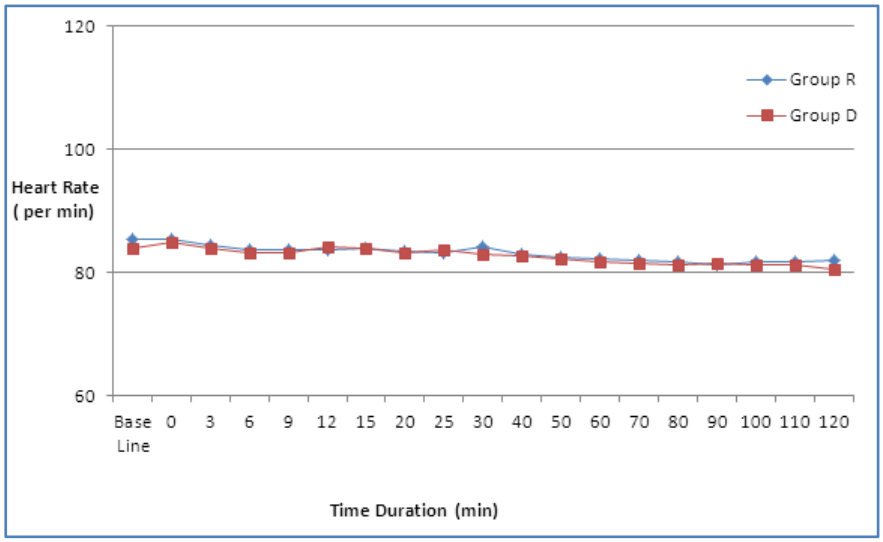

Fig. 2: Comparison of heart rate (per minute) between the two study groups

Group R – Ropivacaine + Normal saline, Group D - Ropivacaine + Dexmedetomidine

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Patient Characteristics	Group R (59) Mean±SD	Group D (59) Mean±SD	P Value
Age (Yrs)	45.59±8.34	44.23±7.70	0.36
Weight (Kg)	51.06±4.34	49.91±5.18	0.10
Height (cm)	152.06±8.08	151.61±7.41	0.37
BMI	21.99±2.45	21.66±2.26	0.355
ASA Grade I/II	24/35	29/30	0.35
Duration of Surgery	114.74±15.60	118.16±17.86	0.68

Table 1: Demographic characteristics of patients

*P<0.05-interaction is found to be significant between the groups.

†Group R-Ropivacaine+Normal saline, Group D-Ropivacaine+Dexmedetomidine, BMI-Body Mass Index, ASA-American Society of Anesthesiologists.

Block Characteristics	Group R (59) Mean ±SD	Group D (59) Mean ± SD	P value
Onset of sensory block upto T10 (min)	3.96± 0.64	4.03±0.69	0.58
Onset of sensory block upto T8 (min)	7.44 ± 0.87	7.35±0.86	0.59
Onset of sensory block upto T6 (min)	13.76 ± 1.89	13.55±1.85	0.21
Time of two segment regression from highest sensory block level (min)	117.00 ± 15.65	172.37±18.97	<0.001
Time of regression to S2 level (min)	221.35± 22.70	297.71±34.11	<0.001
Time to achievement of maximum motor blockade (min)	5.46 ± 0.91	5.54±0.85	0.60
Total duration of motor blockade (min)	229.37 ± 28.74	258.55±30.46	<0.001

Table 2: Block Characteristics of patients

*P<0.05-interaction is found to be significant between the groups.

†Group R-Ropivacaine+Normal saline, Group D-Ropivacaine+Dexmedetomidine

	Group R (59) Mean ±SD	Group D (59) Mean ± SD	P value
Time of rescue analgesia (min)	174.77± 22.31	270.00±38.75	<0.001
Highest pain score on VAS Scale	7.03 ± 0.78	4.42±0.69	<0.001
Total number of analgesic injections given in 1st 24 hours	4.25 ± 0.75	2.89±0.66	<0.001
Total dose of analgesic consumed in 1st 24 hours (mg)	421.86 ± 80.03	283.89± 64.32	<0.001

Table 3: Comparison of Postoperative analgesia between the two study groups

*P<0.05-interaction is found to be significant between the groups.

†Group R-Ropivacaine+Normal saline, Group D-Ropivacaine+Dexmedetomidine

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