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Research Paper

Abdominal Hysterectomy Under Epidural Block: Comparison Between Bupivacaine with Clonidine Versus Ropivacaine with Clonidine

Medical Science

KEYWORDS : abdominal hysterectomy, epidural block, ropivacaine, bupivacaine, clonidine

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ABSTRACT

CONTEXT: *Abdominal hysterectomy is one of the most common non-pregnancy related gynecological surgeries performed. Regional anesthesia (spinal/epidural/combined) offers several advantages for these surgeries lowering the risk associated with general anesthesia. Bupivacaine used to be the most common anesthetic agents for epidural block, however, in recent years; ropivacaine has increasingly replaced bupivacaine because of its similar analgesic properties, lesser motor blockade and decreased propensity of Cardio toxicity. Neuraxial adjuvant like Clonidine augments the action of local anesthetics.*

AIMS: *Comparison of onset, duration of sensory and motor block and any adverse effects between 0.5%bupivacaine with clonidine versus 0.5% ropivacaine with clonidine (75microgram /kg).*
Setting and Design: This Prospective randomized study was carried out in 50 patients (25 in each group) of ASA grade 1 and 2 scheduled for abdominal hysterectomy.

Materials and Methods: *Epidural block was administered GROUP-1 (BC): Epidural bupivacaine 20 ml (0.5%) with 0.75 µg/kg clonidine GROUP-2 (RC): Epidural ropivacaine 20 ml (0.5%) with 0.75 µg/kg clonidine*
Onset, duration of sensory-motor block, heart rate, blood pressure, oxygen saturation and respiratory rate were recorded.
Statistical analysis: The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0.Chi-square test, ANOVA , Student's t-test and Paired t-test were used.

Results: *Groups were comparable with regard to demographic data, hemodynamic stability.*

Onset of sensory and motor blockade was faster in RC Group as compared to BC group. Recovery of motor block was early in RC Group. No potential side effect like bradycardia or hypotension was seen in either group.

Conclusion: *Although clonidine as adjuvant can be used safely to both bupivacaine as well as ropivacaine in abdominal hysterectomy under epidural block, but on account of faster onset, hemodynamic stability and early recovery of motor block ropivacaine with clonidine seems to be a better option.*

INTRODUCTION

Abdominal hysterectomy is one of the most common non-pregnancy related gynecological surgery performed (Wilcox *et al.*, 1994; Lepine *et al.*, 1997)[1,2]. In recent years, regional blocks such as spinal / epidural or a combination of spinal / epidural blocks have gained widespread popularity among the surgical fraternity and have been well accepted by both the patient as well as the surgeon. Regional blocks, by lowering the side effects associated with general anesthesia contribute in reducing the post-operative duration of hospital stay. Bupivacaine is one of the most common anesthetic agents used for gynecological surgeries, however, in recent years, ropivacaine has increasingly replaced bupivacaine for the said purpose because of its similar analgesic properties, lesser motor blockade and decreased propensity of Cardio toxicity (McClellan and Faulds, 2000)[3]. Although ropivacaine is claimed to have lower Cardio toxicity yet some researchers have concluded that it has a limited or no superiority in epidural analgesia (Beilin and Harper, 2010)[4]. Clonidine, a α-2 adrenergic agonist that produces analgesia via a non-opioid mechanism, is used as an adjuvant in regional anesthesia in various settings (Hayashi *et al.*, 1993; Eisenach *et al.*, 1996)[5,6]. The co- administration of clonidine and local anesthetic produces better analgesia than either drug alone (Acalovschi *et al.*, 1997; D'Angelo *et al.*, 1999; Syal *et al.*, 2011) [7,8,9]. The combination of epidural clonidine with bupivacaine for analgesia has been extensively studied. Clonidine has shown to improve analgesia when added to epidural ropivacaine. There are numerous studies, which have shown comparison of bupivacaine and ropivacaine, but there is lesser literature available comparing addition of clonidine as an adjuvant to bupivacaine and ropivacaine, which has dose sparing effect, which consequently reduces the incidence of side effects, associated with larger doses of these anesthetics and hence there is an urgent need to fill this void based on empirical evidence (Benhamou *et al.*, 1998; Sia *et al.*, 2000)[10,11].

Thus, the present study was conducted to evaluate the Efficacy of epidural bupivacaine (0.5%) with clonidine versus ropivacaine (0.5%) with clonidine in abdominal hysterectomies.

MATERIAL AND METHODS

After approval from institutional ethical committee, a total of 50 female patients aged between 40-60 years of American Society of Anesthesiologist (ASA) physical status 1 and 2 , scheduled for elective abdominal hysterectomy under epidural block were enrolled in this randomized double-blind study .

Patients with significant cardiovascular disease, renal failure, hepatic dysfunction and chronic pulmonary disease, neuromuscular disorder, morbid obesity, bleeding disorders, infections, history of allergy or sensitivity to any of the studied local anesthetics on operative patients, were excluded from the study.

Study Groups

After obtaining written informed consent, the enrolled patients were randomized in two groups of 25 patients each (n=25) using random number table.

GROUP-1 (BC): Epidural bupivacaine 20 ml (0.5%) with 0.75 µg/kg clonidine

GROUP-2 (RC): Epidural ropivacaine 20 ml (0.5%) with 0.75 µg/kg clonidine

Patient were asked to nil per oral for solid food 10 hours before surgery and nil per oral for clear liquid for 2 hours before surgery

All the patients were administered premedication with tablet ranitidine 150mg a night prior to surgery.

On the day of surgery, the patients were wheeled into the operation theatre and connected to all noninvasive monitors. Baseline hemodynamic parameters, heart rate, Non-Invasive blood pressure (NIBP), ECG and oxygen saturation were recorded.

Women were randomly assigned in a double-blinded fashion to one of the two groups with computer-generated codes.

Patients were placed in the sitting position and under strict aseptic precautions; local infiltration of lignocaine hydrochloride 2ml was performed at Lumbar level L2-3. Epidural space was localized and confirmed by the Loss of Resistance to saline technique using an 18 –gauge Tuohy's needle. An epidural catheter was then inserted into the space in a cephalic direction and aspirated for detection of cerebrospinal fluid or blood and secured to skin.

After 5 minutes of institution of test dose (3ml of 2% lignocaine with 1 in 2 lakh adrenaline solution) Group **(BC) received** Epidural bupivacaine 20 ml (0.5%) with 0.75 µg/kg clonidine whereas **GROUP (RC) received** Epidural ropivacaine 20 ml (0.5%) with 0.75 µg/kg clonidine.

The anesthesiologist performing the block recorded the baseline value of vital signs (BP, HR, SpO_2,) before performing the procedure, and once in every 5 minutes inside the OT, then after every 15 minutes in the Post Anesthesia Care Unit (PACU) till the recovery of sensory and motor function.

The sensory level was checked and confirmed with pinprick method bilaterally for onset. Motor block was assessed using a modified Bromage Scale (0=No motor block, 1=Unable to raise extended legs, 2=Unable to flex knees, 3 =Unable to flex ankle and foot).

Times for Recordings
Heart rate (HR), non-invasive blood pressure (NIBP), respiratory rate (RR) and peripheral oxygen saturation (SpO_2) was recorded at:

- T0- Before administration of drug
- T1-5 mins after administration of the drug
- T3-10 mins after administration of drug
- T4-15 mins after administration of drug
- T5-30 mins after administration of drug
- T6-60 mins after administration of drug
- T7- T9 Every hour till 240 mins

Pain was assessed by using 10 point Visual Analog Scale (VAS) in which a score of "0" indicated "no pain" and a score of "10" "worst pain imaginable".

Motor block duration was the time for return to Bromage scale 1. Adverse effects like nausea, vomiting and shivering were also documented and managed symptomatically.

Hypotension was defined by decrease in MAP below 20% of baseline or SBP <90 mm Hg and was treated with Inj. Mephentermine 6 mg/ml.

STATISTICAL TOOLS EMPLOYED

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean ± standard deviation. To compare the change in a parameter at two different time intervals paired "t" test was used.

OBSERVATIONS AND RESULTS
The enrolled patients were randomized in two groups of 25 patients each (n=25) using random number table as given in Table 1.

At baseline, both the groups were matched for age, body weight and ASA grade, showing no statistically significant intergroup difference (p>0.05). (table 2)

At baseline, both the groups were matched for all the Hemodynamic parameters (heart rate, diastolic blood pressure, systolic blood pressure, mean arterial blood pressure) and did not show a significant Intergroup difference (p>0.05)(table 3) Mean SBP values in Group 1 were found to be lower than Group 2 from baseline to 60 min interval and higher than Group 2 from 120 min to 240 min intervals but the Difference was not significant statistically at any time interval. (table 4)

With respect to diastolic blood pressure, Group 1 had lower mean value as compared to Group 2 from baseline till 60 min and higher mean value as compared to Group 2 from 120 to 240 min intervals but the difference between two groups was not significant statistically at any of the time intervals (p>0.05)(table5)

Mean time taken for onset of motor as well as sensory block was less in Group 2(RC) as compared to Group 1 (BC), thus showing early onset of sensory and motor block in ropivacaine group as compared to bupivacaine group. Mean Duration of motor as well as sensory block was more in Group 1 as compared to group 2, thus showing early recovery in ropivacaine group. For the block characteristic, the differences between both the groups were statistically Significant (p<0.05). Mean duration of analgesia

was higher in Group 2. The demand for rescue analgesic was early in bupivacaine-clonidine group as compared to ropivacaine-clonidine group. The difference between two groups was statistically significant (p<0.001). (table 6)

The two groups were almost comparable as far as side effects were concerned. Dry mouth and Nausea/vomiting were the most common side effects observed in both the groups. Sedation was the next most common side effect. None of the patient had respiratory depression. There was no significant difference among the groups with respect to different side effects (p >0.05). (table 7)

DISCUSSION
In recent years, regional blocks such as spinal, epidural /combination of spinal and epidural blocks have gained widespread popularity among the surgical fraternity and

have been well accepted by both the patient as well as the surgeon. Regional blocks, by lowering the side effects associated with general anaesthesia contribute in reducing the post-operative duration of hospital stay (Grant, 2008) [12]. Abdominal hysterectomy is one of common procedures suitable for use of regional anaesthesia. For many years, bupivacaine has been used for epidural block because of its long duration of action. Ropivacaine, an amide local anesthetic produced in the pure levorotatory form addresses some of the concerns related to bupivacaine (Beilin and Halpern, 2010)[13]. However, some studies have reported less motor blockade produced by Ropivacaine (Eddleston *et al.*, 1996; Campbell *et al.*, 2000)[14,15]. To attain an equal or better potency and to enhance the post-operative analgesic effect, use

of adjuvants is common in anaesthetic practice nowadays. Clonidine, an alpha-adrenergic agonist, is one of the main drugs that can be used for this purpose owing to its production as a preservative-free preparation.

In present study, we evaluated the efficacy of bupivacaine with Clonidine versus ropivacaine with clonidine for hemodynamic stability, onset and duration of sensory / motor blockade and reduction in post-operative analgesic requirement.

For this purpose a prospective randomized controlled trial study was planned in which a total of 50 ASA Grade I/II female patients aged 40 to 60 years, scheduled for abdominal hysterectomy were enrolled and randomly allocated to two study groups *viz.* Patients who received epidural 0.75 µg/kg clonidine with 20ml (0.5%) bupivacaine (Group 1(BC)), Patients who received epidural 0.75 µg/kg clonidine with 20ml (0.5%) ropivacaine (Group 2(RC)). All these doses have been reported to be optimum and safe for use as a local anaesthetic with or without use of epinephrine (Cox *et al.*, 2003)[16]. The groups were matched for demographic, anthropometric characteristics and baseline hemodynamic parameters. With respect to heart rate during the study period, statistically no significant difference was observed between both the groups. Clonidine has a potent regressive effect on heart rate within 15-90 minutes of epidural administration (Rockermann *et al.*, 1995)[17]. In a study by Bajwa *et al.* (2010)[18] while using clonidine in combination with ropivacaine during epidural block as compared to Ropivacaine alone, similar variations in heart rate were observed but at different time intervals. De Beer *et al,* (2003) [19] also reported that epidural clonidine carries a hypotensive risk among humans and is associated with a reduction in heart rate and arterial pressure among adults.

This typically occurs within 15-30 min of administration and persists for 3 h. In a Doppler evaluation of epidural analgesia through bupivacaine, Chen *et al.* (2006)[20] have also observed that Bupivacaine increases the heart rate during epidural .

Thus in present study, clonidine addition either to Bupivacaine or Ropivacaine had a regulating effect on the heart rate. The pattern of change and intergroup differences observed for blood pressure variables *i.e.* SBP and DBP were also similar to those observed for heart rate.

Clonidine suppresses sympathetic outflow resulting in lower blood pressure. Addition of clonidine either as a fixed dose or as an infusion has been shown to have a lowering effect on arterial pressure as observed in present study (Landau *et al.*, 2002; Topcu *et al.*, 2005;) [21,22.] However, in some studies no significant impact of clonidine addition has been reported on the blood pressure (Laha *et al.*, 2011; Gecah-Gashi *et al.*, 2013) [23,24] Despite reduction in mean blood pressure levels, no event of hypotension was noticed in any group thus highlighting that the given dosages of adjuvant use of clonidine did not reduce the arterial pressure substantially.

With respect to onset of motor and sensory block, both the blocks were achieved early in Group 2 (RC) as compared to group 1(BC). Regression of sensory and motor blockade took longer in Group 1 (BC) as compared to group2 (RC). The results are in agreement with the observation in previous studies that addition of clonidine reduces the onset time for blocks and enhance the duration of block when added to Ropivacaine and Bupivacaine respectively. Faster sensory and motor blockade using Ropivacaine in combination with clonidine as compared to Bupivacaine with clonidine has been documented by Erlacher *et al.* (2001) [25] .

The reason for shorter onset time of block in Ropivacaine with clonidine group could be explained as ropivacaine being less potent than bupivacaine in blocking A beta fibers, but it was more effective than bupivacaine in the blockade of A gamma and C-fibers. The two agents have almost identical dissociation constants with a pKa of 8.0 and 8.1 and similar apparent protein-binding capacity, but ropivacaine is less lipid soluble than bupivacaine. It would be reasonable to expect that a weaker binding to extra neural fat and tissues with ropivacaine might also contribute to greater availability of ropivacaine for transfer to the site of action. These factors could have explained the tendency towards a more rapid block onset and its sustenance with ropivacaine+clonidine combination.

Regarding the side effects concerned, Dry mouth and Nausea/vomiting were the most common side effects observed in both the groups. None of the patient had respiratory depression. None of the side effects had a significant intergroup difference.

Clonidine is associated with specific side effects, especially cardiovascular (*e.g.* bradycardia, hypotension), and bupivacaine is known for its potential cardiotoxicity and cerebral convulsant activity. Ropivacaine appears well suited to achieve long lasting nerve block without having to resort to adjuvant medications yet addition of clonidine enhanced its efficacy without any potential side effect.

The findings in present study show that Ropivacaine in combination with clonidine provides a haemodynamically stable, faster and prolonged epidural block and a longer analgesic effect. Both Bupivacaine as well as Ropivacaine in combination with Clonidine provide a significantly better block characteristics and haemodynamic stability. No potential side effect or Brady cardiac or hypotensive event took place thus showing that the adjuvant use of clonidine can be done safely.

There are limited studies in literature evaluating the epidural block using Ropivacaine and Bupivacaine in combination with Clonidine for abdominal hysterectomies; the present study is amongst one of the pioneering studies regarding this issue.

CONCLUSION

On the basis of present study the following conclusions can be drawn: Ropivacaine with clonidine provided a faster onset of a sensory and motor block as compared to Bupivacaine with Clonidine. Both the groups, Bupivacaine with clonidine (BC) and Ropivacaine with clonidine (RC) provided hemodynamic stability. Ropivacaine with clonidine provided a faster recovery of sensory and motor block as compared to Bupivacaine with Clonidine. Duration of analgesia was more in Ropivacaine with clonidine group as compared to Bupivacaine with clonidine group. Both the supplemented group had significantly longer duration of analgesia.

Dry mouth and Nausea/vomiting were the most side effects observed in both the groups. Sedation was the next most common side effect. None of the patient had respiratory depression. Statistically, there was no significant difference between both groups with respect to different side effects. No event of bradycardia or hypotension took place in any of the groups.

The findings of the study suggest that adjuvant use of clonidine helps in achieving a better haemodynamic stability, faster block onset, longer duration of block and analgesia and manageable side effects. Ropivacaine in combination with clonidine provided the best block characteristics, haemodynamic stability and analgesic effect. Given the relative superiority of Ropivacaine as compared to Bupivacaine in terms of cardiotoxicity and cerebral convulsant activity, it may be recommended for use in epidural block in cases of abdominal hysterectomy after a thorough validation through larger studies in variable environments.

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TABLES

Group	No. of patients	Description
Group 1(BC)	25	Patients who received epidural 0.75 µg/kg clonidine with 20ml (0.5%) bupivacaine
Group 2(RC)	25	Patients who received epidural 0.75 µg/kg clonidine with 20ml (0.5%) ropivacaine

Table 1: Groupwise Distribution of Subjects

SN	Characteristic	Group 1 (n=25)		Group 2 (n=25)		Significance of difference (ANOVA)	
		Mean	SD	Mean	SD	F	p
1.	Age	49.2	4.9	50.2	5.2	0.887	0.416
2.	Body weight	48.1	6.8	49.4	6.7	0.301	0741
3.	ASA I:II	16:9		14:11		p=0.683	

Table 2: Baseline demographic characteristics

Hemodynamic Variables	Group 1		Group 2		Statistical Significance (ANOVA)	
	Mean	SD	Mean	SD	F	p
Heart rate (per min)	84.92	7.91	82.80	8.25	0.556	0.576
Diastolic Blood pressure (mm Hg)	81.52	4.94	82.32	3.45	0.533	0.589
Systolic Blood Pressure (mm Hg)	126.32	6.60	126.72	5.56	1.211	0.304
Mean arterial pressure (mm Hg)	96.52	4.09	97.12	3.09	0.156	0.855

Table 3: Baseline Hemodynamic Variables in Study Population

Time interval	Group 1 vs 2		
	MD	SE	p
Baseline	-0.4	1.54	0.963
5 min	-1.44	1.56	0.626
10 min	-1.84	1.66	0.512
15 min	-0.32	1.26	0.965
30 min	-0.72	1.75	0.911
60 min	-0.72	1.82	0.917
120 min	0.16	1.17	0.990
180 min	0.88	1.34	0.788
240 min	0.24	1.49	0.986

Table 4:Between Group Comparison of Systolic Blood Pressure

Time interval	Group 1 vs 2		
	MD	SE	p
Baseline	-0.8	1.47	0.850
5 min	-1.92	1.63	0.470
10 min	-2.64	1.77	0.302
15 min	-1.52	1.77	0.669
30 min	-0.4	2.04	0.979
60 min	-0.72	2.18	0.942
120 min	0.24	2.33	0.994
180 min	3.68	2.35	0.266
240 min	3.68	2.26	0.241

Table 5: Between Group Comparison of Diastolic Blood Pressure

Characteristic	Group 1 (n=25)		Group 2 (n=25)		Statistical Significance (ANOVA)	
	Mean	SD	Mean	SD	F	p
Onset of motor block (min)	16.08	2.08	11.20	2.42	149.98	<0.001
Total duration of motor block (min)	123.76	2.96	117.76	2.60	281.78	<0.001
Onset of sensory block (min)	11.40	1.76	8.56	2.47	81.10	<0.001
Total duration of sensory block (min)	110.24	2.18	109.04	2.01	85.31	<0.001
Mean duration of analgesia (hrs)	5.24	0.93	5.48	0.82	29.08	<0.001

Table 6: Block characteristics in different groups

Characteristic	Group 1 (n=25)		Group 2 (n=25)		Statistical Significance	
	No.	%	No.	%	χ^2	p
Nausea/vomiting	4	16	6	24	1.303	0.521
Sedation	3	12	4	16	4.097	0.129
Shivering	0	0	1	4	2.083	0.363
Respiratory depression	0	0	0	0	-	-
Headache	2	8	1	4	2.083	0.363
Dry mouth	7	28	6	24	2.066	0.356

Table 7: Side Effects

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