Original Research Article

Comparison between Buprenorphine and Clonidine as an adjuvant to intrathecal bupivacaine for abdominal hysterectomy

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Abstract

Background: This study was planned to compare the block characteristics, intraoperative haemodynamic changes, duration of postoperative analgesia and perioperative complications between buprenorphine and clonidine when used as an adjuvants to intrathecal hyperbaric bupivacaine. **Methodology:**This was randomized comparative study on 108 females who underwent hysterectomy. Hemodynamic parameters, onset and duration of sensory and motor block were noted and also intra as well as post operative complications were noted and the findings were compared between 3 groups. **Results:** The time of onset of Sensory Block, motor block , duration of sensory and motor block were significantly higher in buprenorphine group as compared to clonidine and bupivacaine alone group. In present study, incidence of bradycardia as well as hypotension was significantly higher in group C as compared to group B and group A ($p<0.05$). However, intraoperative pain was significantly higher in group A as compared to other 2 groups ($p<0.05$). **Conclusion:**Buprenorphine is preferable than clonidine as an adjuvant with hyperbaric bupivacaine in patients posted for abdominal hysterectomy under spinal anaesthesia for better intraoperative haemodynamic stability and prolonged period of postoperative analgesia.

Keywords: Buprenorphine, clonidine, bupivacaine, hysterectomy, sensory block, motor block, post operative analgesia.

Introduction

Hysterectomy is frequently done procedure usually performed under spinal anesthesia .Although most of patients are comfortable under spinal anesthesia, nearly fifty percent patient report pain or discomfort as demonstrated by Alahuhta et al[1]. At times it needs to supplement with either iv analgesics or general anesthesia or by increasing dose of bupivacaine. Pederson et al[2] found pain in one third of patients even after increasing dose of bupivacaine. Also postoperative analgesia is limited when a bupivacaine is used alone.

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Few patients report nausea while uterine exteriorization and putting clamps. All of these disadvantages can be overcome by addition of intrathecal additives which improves quality of subarachnoid block intra-operatively as well as postoperatively. Many of these additives have been studied including Fentanyl, ketamine, alpha 2 adrenergic agonists along with local anaesthetic drugs to improve quality of perioperative analgesia and to prolong duration of action. We aimed to study effects of intrathecal adjuvants clonidine and buprenorphine along with Bupivacaine in patients undergoing hysterectomy in terms characteristics of block, duration of postoperative analgesia , intraoperative hemo-dynamics and peri-operative complications if any.

Material and methods

This randomized double blind study was conducted in tertiary care institute during January 2018 to December

2019. A total of 108 female patients posted for elective abdominal hysterectomy under spinal anaesthesia, requiring 1 to 3 hours duration and level of anaesthesia T4 to T6 belonging to 40 to 70 years of age with ASA grade I or II and giving consent for the study were included. Patients with bleeding/ coagulation disorders, vertebral column deformities, with other associated co morbidities such as uncontrolled hypertension, ischemic heart disease, respiratory diseases, CNS disorders were excluded from the study. After obtaining ethical clearance from Institute's ethical committee, written consent was obtained from all the participants. All the selected patients were randomly allocated into 3 groups using predetermined computer generated random allocation plan. Group A received intrathecal hyperbaric bupivacaine 3ml + 0.2ml normal saline (this was a control group). Group B received intrathecal hyperbaric bupivacaine 3ml + 0.2ml buprenorphine (60µg). Group C -received intrathecal hyperbaric bupivacaine 3ml + 0.2ml clonidine (30µg). Separate Anesthesiologist was allotted to prepare drugs and for measuring postoperative parameters.Patients were investigated according to institutional protocol. Patient was taken on table and all the monitors including NIBP cuff, ECG, SpO2 probe and temperature probe was attached. Patient was explained the procedure and lateral position was given to patient. Under all aseptic precautions patient was given spinal anesthesia using 25 gauge spinal needle in L2-L3 or L3- L4 space. Drug was injected intrathecally after obtaining clear flow of CSF.Onset of sensory block was determined by pinprick method every 30 seconds from 0 hour at one fixed dermatome level i.e. L1. The maximum level of sensory block achieved in each patient within initial 30 minutes was noted and also time required to achieve it was recorded in minutes. The highest dermatome showing sensory analgesia was taken as the maximum level of block when it remained same even after 5 minutes. Total duration of sensory block was defined as loss of pinprick sensation at L1 up to reappearance of pinprick sensation at L1. Motor block was assessed at every 30 seconds from '0 'hour as per the modified Bromage scale till grade 1 block achieved and after that every 15minutes. Onset of motor block was noted when the patient was unable to raise extended legs but able to move knees and feet (grade 1 MBS), that time was noted as the time for onset of motor block in seconds. The duration of motor block was defined as the time period between onset of motor block (grade1) up to time for reappearance of feet/ankle movement (grade 2). It was recorded in minutes. Overall intraoperative quality of surgical anesthesia noted as - excellent: patient was comfortable, no supplementation required - satisfactory: some discomfort, sedation plus analgesics required - poor: severe discomfort and pain, general anaesthesia required. Intraoperative haemodynamic parameter such as pulse rate, mean blood pressure, systolic blood pressure, SPO2 was monitored intraoperatively as follows at baseline after 2minutes of injecting drug, then every 3minutes for first 20 minutes, then - every 5minutes for up to 60 minutes, then every 15minutes interval till the end of surgery. Incidence of side effects and requirement of analgesics or supplementation with general anesthesia was noted. After completion of surgery, patients were observed in recovery room at the interval of 1hour for 12hours and at the interval of 2hours for next 12hours, for following complications and treated if any complications developed. Patient was observed in recovery room for 12 hours at 1hour interval for Visual Analogue Scale (VAS) score. Duration of postoperative analgesia was time from injection of intrathecal drug that is 0 hour till demand of 1st analgesic or VAS score 4 or more.

Statistical analysis: Data was analyzed in statistical software STATA, version 10.1, 2011. Quantitative variables were expressed as mean, standard deviation (SD) and range (minimum-maximum value), while frequency and percentages were used to summarize categorical (qualitative) variables. Between-the-group differences in mean change from baseline in three intervention groups were tested with One-way Analysis of variance (ANOVA). Pearson's Chi-square test was performed for comparing difference in proportions of qualitative variables. A p-value <0.05 was considered statistically significant.

Observations and result

Three groups were comparable in terms of demographic characters (Table 1).The time of onset of Sensory and motor Block was significantly delayed in group B and C as compared to A and it was maximum in Group B (p=0.0001). Similarly mean fixation time and duration of sensory and motor block was significantly higher in group B followed by group C and A (p<0.01) (Table 2). Quality of sensory and motor block was significantly better in patients in group B and C as compared to A (P<0.05).The requirement of sedation and analgesia (grade II SB) and GA (grade III SB) was significantly more in group A when compared with group B and C(P<0.05).None of the patient from group B and C required GA (Table 3) Mean pulse rate was decreased at 20 minutes in all the three groups when compared with their respective baseline. However it was not statistically significant in group A

(0.2546*) and B (0.9035*) but was highly significant in group C (P=0.0001*).The pulse rate was almost stable in group A and B after 20 minutes. However in group C decrease was sustained up to 45minutes and then it was stabilized (p<0.05) (graph 1) Mean of MBP was decreased at 20 minutes in all the three groups when compared with their respective baselines. This fall was statistically significant in all the three groups (P=0.0001*).The MBP was almost stable in group A and B after 20 minutes. However in group C decrease was sustained up to 45 minutes and then it was stabilized (p<0.05).(graph 2) Mean duration of postoperative analgesia was maximum in group B (343.47 ± 53.90), followed by group C (279.64 ± 31.85) and group A (171.25 ± 36.67) and the observed difference was statistically highly significant (P=0.0001).In present study, incidence of bradycardia as well as hypotension was significantly higher in group C as compared to group B and group A (p<0.05). However, intraoperative pain was significantly higher in group A as compared to other 2 groups (p<0.05). The incidence of postoperative complications was almost negligible in all the three groups and all the three groups were found to be comparable regarding postoperative complications (p>0.05).

Table 1:Distribution according to Baseline variables

Baseline variables	Group A	Group B	Group C	P value
Age in years(Mean ± SD)	49.14± 8.36	50.94±9.9	48.5± 6.95	0.44
Height in cms(Mean ± SD)	156.3±3.96	155.8±4.3	156.5±5.6	0.82
Weight in kg(Mean ± SD)	56.36 ±6.77	57.25±7.1	58.5± 7.74	0.46
Duration of surgery (min) (Mean ± SD)	100.42±29.7	111.7± 29.7	115.4±28.2	0.08

Table 2: Comparison of block characteristics between

Block characteristics	Group A	Group B	Group C	P value
Onset of sensory block in minutes(Mean ± SD)	101.25± 33.7	186.7±59.2	162.5±66.3	0.001
Fixation time in Minutes (Mean ± SD)	11.17±2.4	21.42±2.4	13.56±2.8	0.001
Duration of sensory block in min (Mean ± SD)	170.64 ±30.9	319.0±50.7	261.9±26.6	0.001
Onset of motor block in min(Mean ± SD)	181.7± 50.7	281.9±98.4	259.2±75.9	0.001
Duration of motor block in min(Mean ± SD)	140.1±29.4	270.7±51.0	225.3±29.5	0.001

Table 3:Comparison of quality and dermatome level achieved

		Group A		**Group B**		**Group C**		**p value**
		No.	**%**	**No.**	**%**	**No.**	**%**	
Maximum dermatome level achieved	T4	14	38.89	18	50	18	50	0.668
	T5	2	5.56	3	8.33	1	2.78	
	T6	20	55.56	15	41.67	17	47.22	
Quality of sensory block	I	4	11.1	0	0	0	0	**0.001**
	II	13	36.1	2	5.56	0	0	
	III	19	52.78	34	94.4	36	100	
Quality of motor block	I	4	11.11	0	0	0	0	**0.001**
	II	13	36.11	5	13.89	0	0	
	III	19	52.78	31	86.11	36	100	

Table 4:Incidence of complications among three groups

Intra-operative complications	Group A		Group B		Group C		p value
	No.	%	No.	%	No.	%	
No complications	16	44.44	28	77.78	18	50	**0.009**
Nausea/ vomitting	-	-	-	-	-	-	-
dizziness	-	-	-	-	-	-	-
Only Bradycardia	0	0	1	2.78	6	16.68	**0.016**
Hypotension with Bradycardia	0	0	1	2.78	2	5.56	0.771
Only Hypotension	5	13.89	2	5.56	10	27.78	**0.04**
Intraoperative Pain	13	36.11	2	5.56	0	0	**0.001**
Shivering	2	5.56	2	5.56	0	0	0.327
Total	**36**	**100**	**36**	**100**	**36**	**100**	

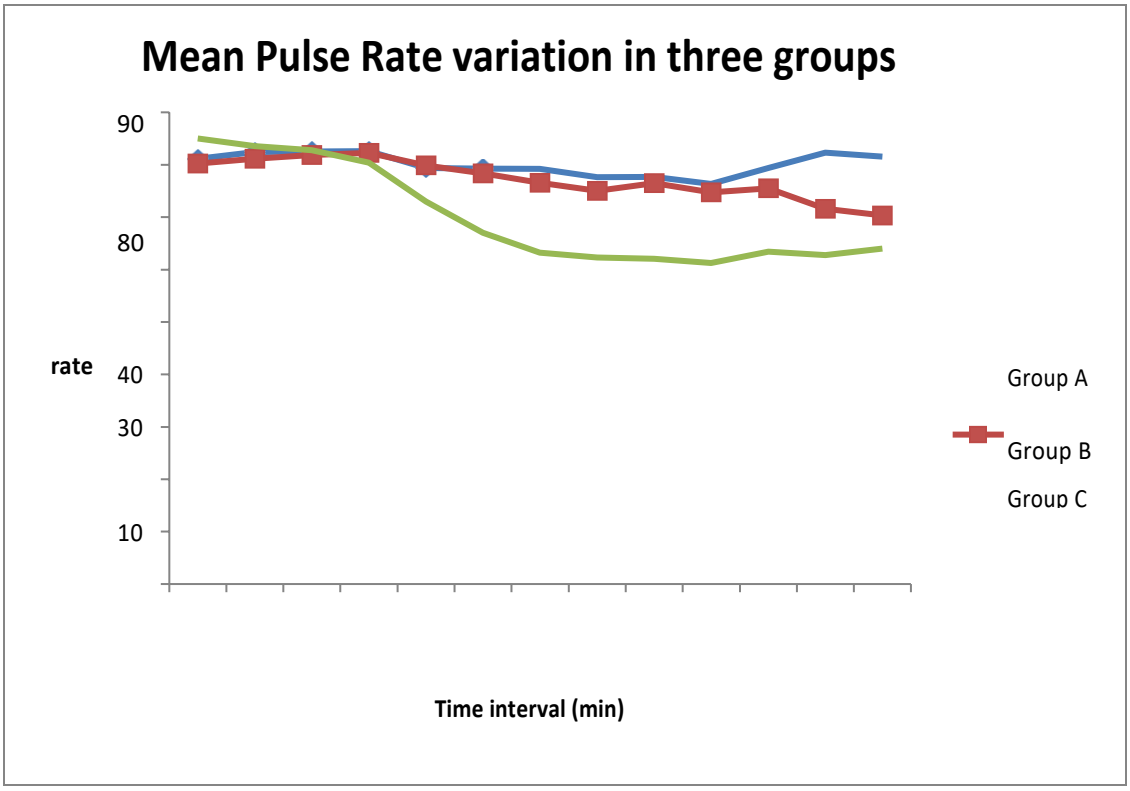

Fig 1: Comparative Mean Pulse Rate at different time interval

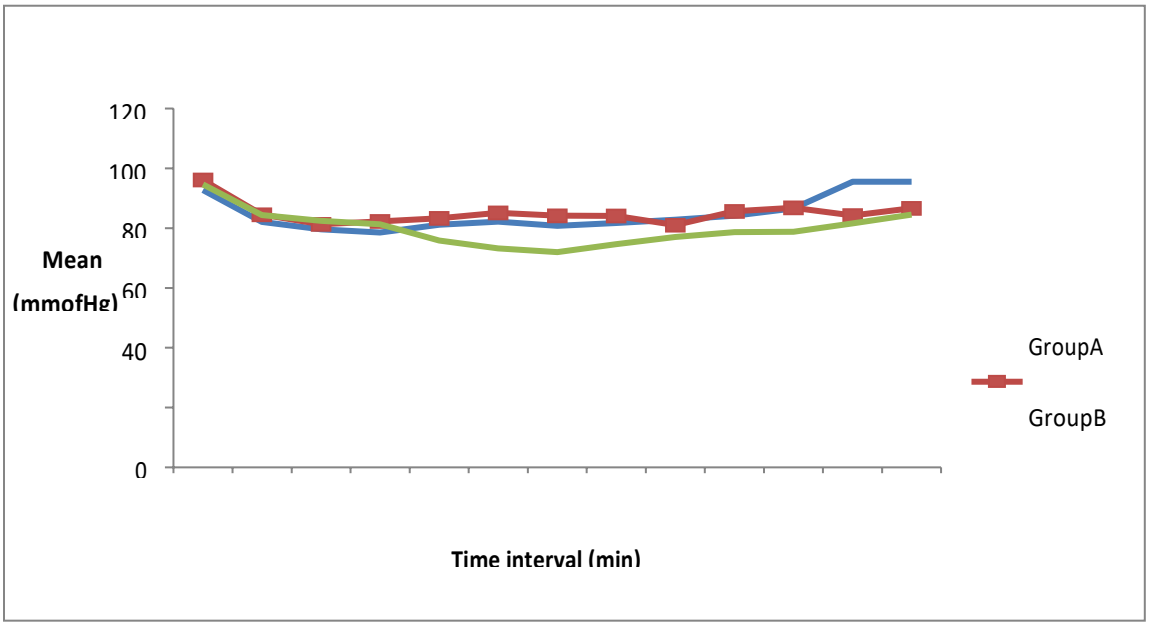

Fig 2:Comparison of mean blood pressure variation in three groups

Discussion

Spinal Anesthesia is commonly employed technique for various lower abdominal surgeries including hysterectomy. Most of patients undergoing hysterectomy are elderly having some or other respiratory or cardiac co morbidities. Level of sensory blockade required for hysterectomy is usually up to T6 dermatome and duration of surgery last for about one to two hours. Using high doses of Bupivacaine can lead to various complications like hypotension, myocardial depression and cardiac dysrhythmias. Addition of adjuvant will not only help to reduce dose of Bupivacaine and hence reducing side effect but also will provide prolong postoperative analgesia than alone will local anaesthetic will do. Hence we evaluated effect of intrathecal buprenorphine and clonidine along with Bupivacaine for abdominal hysterectomy. We decided to use 30µ of clonidine based on study of Khandelwal et al[3] and Chopra et al[4]. The direct acting alpha-adrenergic agonists have long been used as adjuvants to spinal local anesthetics in order to prolong the spinal blockade. Their effect is mainly attributed to spinal vasoconstriction and subsequent decrease of systemic absorption of drug, while a direct antinociceptive action via spinal alpha-adrenergic receptors, especially the alpha- 2 type, may also exist. The central alpha-2-adrenergic agonists activate alpha-2-adrenergic receptors in substantia gelatinosa and also spinal opioid receptors. Anti nociception is probably related to the suppression of C-fiber neurotransmitters 'release and increased potassium conductance leading to hyperpolarisation of post-synaptic dorsal horn neurons[5].Buprenorphine, a thebaine derivative, has got strong opioid agonist effect on µ opioid receptor as well as weak antagonistic effect which prevent its addiction and physical dependence. When added intrathecally due to its highly lipophilic nature, it remains attached to spinal opioid receptors for prolonged duration providing longer duration of analgesia and prevents its rostral spread so side effects like vomiting and respiratory depression are reduced. It is also found to have local anaesthetic effect which may be responsible for its prolonged duration of analgesia[6].In present study, mean duration of sensory block was observed to be 319.03±50.72 minutes in group B and it was statistically higher as compare to group C (261.9±26.6) and group A(170.64 ±30.9). Arora et al also documented similar findings and duration of sensory blockade was significantly higher ($p<0.05$) with addition of buprenorphine as compared to Bupivacaine alone and bupivacaine clonidine[7].

.The longer duration of action of buprenorphine can be attributed to its high affinity for opioid receptor and high lipid solubility[8].

Mean duration of motor block was significantly prolonged ($p<0.05$) with addition of buprenorphine (270.69±51.03) than that with clonidine-bupivacaine (225.25±29.54) and bupivacaine alone. This observation in the present study supported by observation of Arora et al who also compared buprenorphine and clonidine and observed statistically significant prolonged duration of motor block with buprenorphine (262±46.7) than clonidine (228.6±46.7) [7]. We found delay in onset of sensory block in buprenorphine bupivacaine group (186.66±59.18) than in clonidine- bupivacaine and Bupivacaine alone (101.25±33.70) which was statistically significant. Arora et al also observed similar delayed onset of sensory block with addition of buprenorphine to bupivacaine (438±192) as compared to bupivacaine alone (384±180), although this difference was not statistically significant ($p>0.05$)[5]. Negi et al[9] observed statistically significant ($p<0.05$) difference i.e. addition of buprenorphine to bupivacaine delayed onset of sensory block significantly (714±286.8) as compared with addition of clonidine (552±341.4).

We also observed delay in onset of motor block in buprenorphine group which was statistically significant as compared to clonidine-Bupivacaine and Bupivacaine only group. This finding was similar to findings of Negi et al[9]. There was significant drop in mean pulse rate and blood pressure from 20 minutes to 45 minutes following block in clonidine Bupivacaine group as compared to other two groups. Observations of Gujar et al[10], Manuraj et al[11], Arora et al[8] also supports this finding i.e. sustained decrease in the pulse rate with the addition of clonidine. This finding correlates with the observations of Sonya et al[8],Arora et al[7] also observed fall in heart rate and MAP more with clonidine than that with buprenorphine added to bupivacaine and bupivacaine alone. Action of clonidine on α2 adrenoceptors which are inhibitory and causes decrease in outflow from vasomotor centers and sympathetic center explains this finding as this effect is lacking with the buprenorphine[10].The overall incidence of significant hypotension and bradycardia was minimal with bupivacaine (13.89%) and bupivacaine with buprenorphine (11.12%) and was comparable. However the incidence of significant hypotension and bradycardia was significantly higher (50%) with clonidine as an adjuvant to bupivacaine ($p<0.05$) when compared with bupivacaine alone and with adjuvant buprenorphine. This higher incidence of hypotension and bradycardia in present study with clonidine is clearly attributable to α1 agonistic action of clonidine[10].Mean duration of postoperative analgesia was maximum in group B (343.47 ± 53.90), followed by group C (279.64 ± 31.85) and group A (171.25 ± 36.67) and the observed difference was statistically highly significant (P=0.0001).Prolonged analgesia of buprenorphine is because of its highly lipophilic nature, high affinity for opiate receptor. It remains attached to spinal opioid receptors for long duration as it has slow dissociation constant of drug receptor complex[9,12]. Analgesic properties of clonidine are due to activation of α2 receptors located in dorsal horn. Presynaptic stimulation of α2 receptor inhibits neurotransmitter release and postsynaptic stimulation of substantia gelatinosa prevents neuronal transmission through hyperpolarization. It also block the conduction of C and Aδ fibers[13-15].

Conclusion

Both buprenorphine and clonidine added as adjuvant to hyperbaric Bupivacaine provides prolonged duration and better quality of sensory & motor block, excellent surgical conditions with advantage of prolonged postoperative analgesia and minimal postoperative complications. However buprenorphine provides significantly stable intraoperative hemodynamics and more prolonged duration of block and postoperative analgesia as compared to clonidine. The only limiting factor is delayed onset and prolonged fixation time than clonidine. Hence, buprenorphine is preferable than clonidine as an adjuvant with hyperbaric Bupivacaine in patients posted for abdominal hysterectomy under spinal anaesthesia for better intraoperative haemodynamic stability and prolonged period of postoperative analgesia.

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