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STUDY OF EFFICACY AND SAFETY OF ORAL CLONIDINE AS AN ADJUVANT TO BUPIVACAINE SPINAL ANAESTHESIA

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ABSTRACT

During the past two decades clonidine-α 2 agonist has been investigated as an adjuvant to general and regional anesthesia and postoperative pain relief. The aim of study was to evaluate the effect of oral clonidine premedication on the duration of motor and sensory blockade and post-operative analgesia during bupivacaine spinal anesthesia.60 patients, aged 30-60 years scheduled to undergo abdominal hysterectomy included in prospective randomized single blind study. Preoperative assessment with routine investigation done for all the patients. After obtaining informed and written consent, patients were divided into Group B and Group CB. Oral clonidine was given as premedication in Group CB. All patients were preloaded with inj. Ringer Lactate 10ml/kg. Lumbar puncture performed. Bupivacaine heavy 0.5% 3 cc. NIBP, pulse rate, Spo2, ECG were monitored perioperatively. Group CB patients has faster onset of sensory and motor blockade. Total duration of both sensory and motor blockade was prolonged in group CB. There was no significant change observed in NIBP and Spo2.Patients in Group CB had reduction in pulse rate as compared to Group C. Post-operative analgesia was of prolonged duration in group CB. Chances of dryness of mouth and bradycardia were more in group CB as compared to group B. Oral clonidine produce sedation without respiratory depression. Oral clonidine given 60 minutes before spinal anesthesia with bupivacaine heavy 0.5%produce significant prolongation of sensory and motor block, sedation and adequate post-operative analgesia and also decreases post spinal shivering with minimal hemodynamic disturbances.

Key words: Oral clonidine, spinal anesthesia, bupivacaine heavy 0.5%.

INTRODUCTION

Spinal anesthesia is widely used for both elective and emergency` surgical procedures, particularly gynecological operations, caesarean operations, orthopedic surgeries, urological operations and lower abdominal surgeries. It lessens the risk of vomiting & pulmonary aspiration in patients with full stomach and also helpful in patients with chronic pulmonary and airway disease. Spinal anesthesia also reduces operative site bleeding and decreases the incidence of deep vein thrombosis. Sometimes, some surgeries may last little longer than the predictable duration, which may limit the use of single shot spinal anesthesia. So, now a day many drugs are used as an adjuvant to bupivacaine spinal anesthesia for prolongation of its action and post-operative analgesia. These includes opioids like morphine, fentanyl, tramadol, butorphanol etc. and non-opioids drugs like ketamine, benzodiazepine, neostigmine and clonidine.

Intrathecal opioids have adverse effects like sedation, pruritus, urinary retention, nausea, vomiting and risk of late respiratory depression which may limit their usefulness.

Clonidine, α2 adrenergic agonist being an antihypertensive agent produces sedation, anxiolytic, sympatholytic, antisialogue effect, abolition of endocrine stress, analgesia, antiemesis, decreases oxygen consumption and reduction in post-operative shivering. The α2 agonist also has ability to potentiate the effect of local anesthetics. Studies show that unlike intrathecal opioids, Clonidine does not cause pruritis or respiratory depression.

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Both oral and subarachnoid administration of Clonidine may improve the quality and duration of spinal anesthesia and have potent analgesic and sedative effects, with stable hemodynamics.

With this concept in mind and with the aim of providing cost effective, easy administration and better quality and pain free recovery period to the patients undergoing lower abdominal surgeries, this study was undertaken. This study evaluates the effect of intrathecal bupivacaine with oral clonidine versus intrathecal bupivacaine alone.

AIMS OF STUDY

Aim of study was to evaluate the effect of oral clonidine premedication on the duration of motor and sensory blockade, postoperative analgesia, sedation, post spinal shivering and its complication during bupivacaine spinal anesthesia.

MATERIAL AND METHOD

In a prospective randomized single blind study. 60 patients of ASA Physical Status I & II, aged between 30-60 years scheduled to undergo abdominal hysterectomy were selected for the study.

All the patients underwent a thorough preanesthetic checks up. Complete Hemogram, Urine examination, RBS, Blood Urea; Serum creatinine, ECG and Chest X-ray. The patients were explained regarding the procedure of pain assessment with the help of Visual Analogue Scale [VAS] system, a day prior to operation. VAS is a 10 cm scale with marks from 0 to 10 with 1cm spacing. Mark 0 no pain, Mark 10 Worst pain. Patients were explained about the plan of anesthetic procedure in details and informed written consent was taken.

Patients with spinal anesthesia refusal, cardiorespiratory compromise, hepatic and renal disease, h/o drug allergy, chronic backache, neurological deficit, epilepsy, endocrine disorders were excluded from the study.

RANDOMISATION

Patients were randomly divided in to two groups by computer generated randomization. Group B receive inj. Bupivacaine heavy 0.5% 3ml intrathecally. Group CB receive tab. Clonidine 150mcg orally 60 min. prior to spinal anesthesia with bupivacaine heavy 0.5% 3 ml intrathecally.

One anesthetist gave the tablets according to randomization technique. Another anesthetist unaware of study drug, performed and evaluated the intrathecal anesthesia and post-operative course. The level of the sedation was assessed as per the following scoring system [Verbal Rating Score], before giving spinal anesthesia.

Sedation Score

1. No sedation
2. Drowsy
3. Sleeping but arousable by using verbal command
4. Sleeping but not arousable by using verbal stimuli but arousable to a drowsy state by using light tactile stimuli
5. Sleeping and difficult to arouse by using a tactile stimulus.

All the patients were preloaded with inj. Ringer Lactate 10 ml/kg of body weight, 20 minutes prior to subarachnoid injection of drug. Under all aseptic and antiseptic precautions. lumbar puncture was performed in lateral position in L3-4 space by a midline approach with 23 G disposable spinal needle. With appearance of free flow of CSF inj. Bupivacaine heavy 0.5% 3 cc was injected. After performing the block and until the end of study, the patients were kept in supine position. Pulse rate, blood pressure were recorded immediately after spinal anesthesia. The sensory level of anesthesia was assessed by the patient's response to pinprick, using a 24 G hypodermic needle along the anterior axillary line.

The parameters noted for assessment of sensory block were as follows:

1. Onset of sensory block in seconds
2. Time to achieve peak [T6] level in seconds
3. Two segment regression time in minutes
4. Time for sensory regression to L1 in minutes

The degree of motor blockade was assessed as per the following MODIFIED BROMAGE SCALE. After the drug administration

Grade 0: Able to move hip. knee. ankle and toes

I: Unable to move hip. able to move knee, ankle and toes.

II: Unable to move hip and knee. able to move ankle and toes.

III: Unable to move hip, knee. ankle and toes

The parameters noted for the assessment of motor block were as follow:

1. Onset of motor block i.e. time to reach Bromage grade in seconds
2. Time to achieve Bromage grade III in seconds
3. Duration of motor block i.e. recovery to Bromage grade O in minutes

Intra operatively, NIBP every 5 minutes, heart rate, Spo2, ECG were monitored continuously. Sensory and motor levels were also measured at 1, 3, 5, 10, 15, 30, 60, 90, 120 minutes and then half hourly till complete resolution of sensory anesthesia. Time for two segments regression of sensory blockade was also noted intra operatively.

Complications like hypotension, bradycardia, shivering, dryness of mouth, nausea and vomiting were also noted. Bradycardia was treated when pulse rate decreased below 60 beats/min, with inj. Atropine 0.6 mg IV. Hypotension was treated when SBP fall by 30% below the preanesthetic value, initially with I.V. fluids and then with vasopressor [inj. Mephenteramine 5Mg IV] if required. Intra-operatively sedation was given in form of inj. Midazolam 1 mg IV when required.

Post operatively, all the patients were shifted to recovery room. Pulse. Blood pressure, Spo2 total duration and level of sensory and motor block was observed at 30 minutes interval time, till sensory block wear off. Post operatively, patients were also asked to mark a point on the visual analogue scale according to their intensity of pain. Total duration of anesthesia was counted from the time of injection of spinal drug to VAS 4/10 in post-operative period. At this time patients were given inj. Diclofenac Sodium 1.5 mg / kg I.M. as rescue analgesic.

Complications like bradycardia, nausea, vomiting, dryness of mouth, post spinal shivering was noted. As all the patients were catheterized, retention of urine could not be evaluated.

RESULTS

Results were compared using the student's unpaired 't' test after calculating the mean, standard deviation in both the groups for the respective scores. A 'p' value >0.05 was considered not significant, p <0.05 significant and p <0.001 was considered as highly significant.

The mean time for onset of sensory block was 101.50±14.08 seconds in group B while in group CB it was 93.33±16.52 seconds. Onset of sensory block was faster in group CB. Time to achieve peak level [T_6] in group B was 288.10±0.34 seconds while in group CB it was 245.87±52.30 seconds which was faster as compare to group CB and the difference was highly significant[p<0.001].

Time for two segment regression was longer in group CB 138.97±20.02 min. more than group B 99.66±6.75 min, which was statistically highly significant [p<0.001].Time for sensory regression to L_1 from peak sensory level T_6 was also longer in group CB 250.56±17.48 min than group B 171.46±15.47 min [p<0.001].

The onset of motor block was shorter in group CB115±15.16 seconds than group B 128.6±14.32 seconds [p<0.001].Time to achieve bromage grade III was shorter in group CB 206.87±46.7 seconds as compare to group B 260.26±8.21 seconds [p<0.001].Total duration of motor block was longer in group CB 212.83±16.52 minutes than group B 151.57±5.11 minutes [p<0.001].

On intragroup comparison, after premedication, a significant reduction in pulse rate was observed in group CB compare to group B throughout the study [p<0.05].

A significant reduction in SBP was noted 30 minutes after the block in both the groups, compared to baseline value.[p<0.05].Intergroup comparison showed no significant difference. Both intragroup as well as intergroup comparison showed no significant difference.[p>0.05].

. Both intragroup as well as intergroup comparison showed no significant difference throughout the study[p>0.05]

Considering oxygen saturation in intragroup and intergroup, both groups were comparable.

Mean duration of analgesia in group B was 230.50±27.90 minutes while in group CB it was 313.53±23.87 minutes. The duration of analgesia was longer in group CB [p<0.001].

Incidence of bradycardia was more in group CB. 33.33% patients in group CB had dryness of mouth.20% patients in group B and only 3.33%patients in group CB had postspinal shivering.

Table 1. Demographic Data [Mean ±SD]

Characteristics	Group B [n=30]	Group CB [n=30]	p value
Age [yrs]	45.53±8.60	45.43±7.25	p>0.05
Weight [kg]	52.27±6.70	53.53±6.88	p>0.05
Height[cm]	157.8±5.01	157.8±6.05	p>0.05
ASA physical status no [%] I II	 20[66.66%]] 10[33.33%]	 18[60%] 12[40%]	

Both the groups were comparable for age, height and weight.

Table 2. Assessment of Sedation

Sedation Score	GROUP B		GROUP CB	
	No.	%	No.	%
1	30	100	4	13.33
2	-	-	21	70.00
3	-	-	5	16.66
4	-	-	-	-
5	-	-	-	-

All the patients in Group B and 13.33% patients in Group CB had sedation score 1[no sedation].Majority of patients in Group CB i.e.70% had sedation score 2.

Table 3. Assessment of Sensory Block & Motor Block [Mean ± SD]

Parameter	Group B	Group CB	pValue
Onset of Sensory block[sec]	101.50 ± 14.8	93.33 ± 16.52	p<0.05
Time to achieve Peak T6 level [sec]	288.10 ± 0.34	245.87 ± 52.30	p <0.001
Two Segment regression time[min]	97.66 ± 6.75	138.97 ± 20.02	p <0.001
Time for sensory regression to L1[min]	171.46 ± 15.47	250.56 ± 17.48	p <0.001
Onset of motor block	128.6 ± 4 .32	115.00 ± 15.16	p<0.001
Time to achieve bromage grade III [sec]	260.26 ± 8.21	206.87 ± 46.70	p <0.001
Duration of motor block [min]	151.57 ± 5.11	212.83 ± 16.52	p<0.001

Table 4. Complications

Parameter	Group B		Group CB	
	No.	%	No.	%
Bradycardia	2	6.66	5	16.66
Hypotension	6	20.00	5	16.66
Nausea	2	6.66	1	3.33
Dryness of mouth	-	-	10	33.33
Shivering	6	20.00	1	3.33

Incidence of bradycardia was more in group CB. 33.33% patients in group CB had dryness of mouth.20% patients in group B and only 3.33%patients in group CB had postspinal shivering.

Fig 1.

Fig 2.

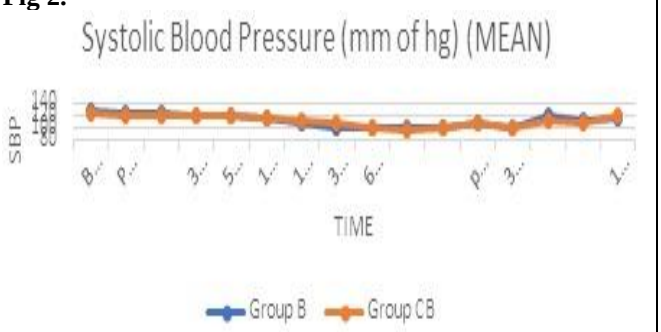


Fig 3.

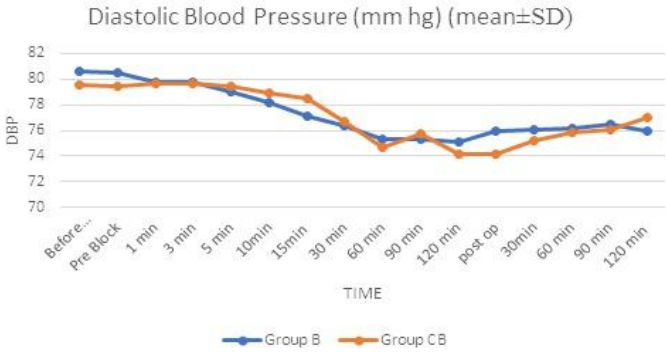
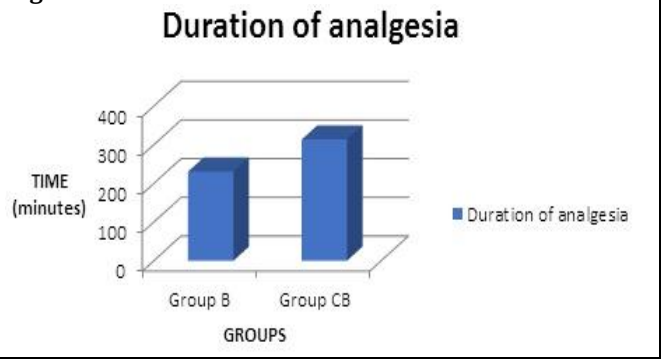


Fig 4.



DISCUSSION

For last several years Clonidine is used as an adjuvant to regional and general anesthesia in various routes like oral, Epidural, intrathecal, intravenous, intramuscular [3]. Oral administration is both simple and cheaper than other routes. Therefore we carried out this study to evaluate the effect of oral Clonidine as an adjuvant to spinal anesthesia with hyperbaric Bupivacaine 0.5% in patients undergoing elective abdominal hysterectomy.

α2 agonists as premedication, have ability to potentiate the anesthetic action of other agents and also reduce anesthetic requirement during surgery. This effect is observed universally, regardless of the type of anesthetic, I.V., volatile or regional block.

In our study, we did not use any other premedication in any case as we wanted to study the exact effect of the drug Clonidine.

Koichi et al used oral Clonidine in different doses ranging from 75 mcg to 300 mcg to evaluate a dose effect relationship to enhance tetracaine spinal anesthesia, and he found a plateau effect at a dose of 150 mcg and suggested that 150 mcg was the optimal dose for prolongation of tetracaine spinal anesthesia without adverse cardiovascular effects[5]. Aftab et al. Dobrydnjov et al. Wichai et al and Dziubdziela et al had also used dose of 150 mcg oral Clonidine as premedication. So we had selected 150 mcg oral Clonidine as a premedication in our study.

Majority of the patients, [70%] in group CB had sedation score 2,while not a single patient had sedation score of 4 & 5.

Dobrydnjoy et al[10]in their study found a greater degree of sedation after orally administered Clonidine than spinal route and he found no sedation with plain bupivacaine group, which is in accordance with our results.

Spencer et al[8]had also found greater incidence of sedation with oral Clonidine than with plain lidocaine [50% vs 0%].

Neimi L, De negri et al, Dobrydnjoy I et al found a higher level of sedation with intrathecal administration of Clonidine along with bupivacaine.

The hypnotic and sedative effect of α2 agonists have been attributed to the stimulation of locus ceruleus a brain stem nucleus which is associated with regulation of sleep and wakefulness.

Presynaptic activation of α2 receptor inhibits the release of norepinephrine and post synaptic activation of α2 receptor results in inhibition of synaptic activity via G protein mediated mechanism that involves inhibition of adenylate cyclase[2,3]. Both these mechanisms produce analgesia, sedation and anxiolysis.

Oral Clonidine as premedication used with hyperbaric bupivacaine, spinal anesthesia resulted in early onset of sensory anesthesia, less time to achieve peak sensory level and prolonged duration of sensory anesthesia. These findings confirm that oral Clonidine acts synergistically with local anesthetic Bupivacaine.

The early onset of sensory anesthesia due to Clonidine had also been reported in study of Dobrydnjoy et al[10].

Prolongation of sensory blockade due to oral Clonidine with bupivacaine was also supported by studies of Dziubdziela et al[9], Dobrydnjoy et al[10]. Azad et al, Spencer Luie et al and Aftab et al had also found that the oral Clonidine prolonged the sensory blockade induced by lidocaine spinal anesthesia. Koichi Ota et al. had found the dose related prolongation of tetracaine spinal anesthesia by oral Clonidine in humans[5], while Bunnet et al studied that only intratheral but not the oral Clonidine prolonged the duration of spinal anesthesia[4].

Oral Clonidine used as premedication to hyperbaric bupivacaine spinal anesthesia in our study resulted in significant reduction in onset time of motor blockade and prolongation of duration of motor blockade as compared to plain bupivacaine alone. These results were also supported by Dobrydnjoy I et al. Liu Spencer et al. Aftab et al noted the similar results while using oral Clonidine in lidocaine spinal anaesthesia.

Direct Spinal activation by oral Clonidine is due to spread of drug via systemic circulation into spinal cord. The substantia getatinosa of dorsal horn of spinal cord contains receptors which when stimulated, block the conduction of A delta and C fibres and increases potassium conductance.

Large doses of Clonidine causes local vasoconstriction[2]which reduces vascular removal of local anesthetic and there by prolongs the sensory block[3].

Our study shows that 150 mcg oral Clonidine given 60 minutes before spinal anesthesia resulted in significant reduction in heart rate and it remained at low stable level till 2 hours post operatively compared to baseline values.

In our study no patient needed more than one bolus dose of atropine for the treatment of bradycardia.

Aftab et al, Koichi Otta et al had observed no incidence of bradycardia with 150 mcg of oral Clonidine in their study. Dobrydynjoy et al observed decreased in heart rate during first 2 hours and atropine was used in only 13% of total patients without any significant intergroup differences. All these authors considered bradycardia in their studies when pulse rate < 55 beats /min.[5,10,15]

The bradycardia effect of Clonidine is caused by presynaptically mediated inhibition of norepinephrine or by a vagomimetic action at nucleus solitarius [2].

Kochi Otta et al [5] in his study showed that hemodynamic depression induced by Clonidine is dose related and he suggested that150 mcg oral Clonidine is safe for prolonging spinal anesthesia asthis dose does not produce hypotension or bradycardia. Similarsuggestions have appeared from the study conducted by Poutta et al. Liu Spencer et al in their study found that, though 200 mcg Clonidine decreased heart rate and SBP no subject had hypotension or bradycardia.

Centrally, post synaptic activation of α2 adrenoreceptors in locus ceruleus and nucleus tractus solitarius reduces sympathetic drive. Activation of nonadrenergic imidazoline preferring binding sites in the lateral reticular nucleus by Clonidine produces hypotension as well as antiarrythmogenic action[3]. Peripherally, activation of presynapticαsub-2- adreno receptors at sympathetic terminals, reduces their release of norepinephrine by the sympathetic nerve terminals, which causes vasorelaxation and reduced chronotropic drive result in hypotension[3].

In our study, the mean duration of post-operative analgesia was prolonged in group CB [313.53± 23.87 minutes] than group B [230.50±27.90 minutes]. The difference was highly significant. In group Band group CB, rescue analgesic was supplemented at 4 and 6 hrs respectively. Thus Clonidine provides sufficient post-operative analgesia upto 6hrs without any supplementation.

Dobrydnjoy et al in their study reported duration of effective analgesia in oral Clonidine group [313±29 minutes] and plain bupivacaine group was [236±27 minutes][10].

Similar findings have been noted in the study of Aftab et al [15]. Our results are supported by Park et al in orthopaedic surgery[14]. Goyagi T et al had shown in study that oral Clonidine not only had a good analgesic effect but it also has a synergistic effect with opioids for post-operative pain relief.

Clonidine exerts the antinociception by interacting centrally as well as peripherally located α2 adrenoreceptors. Interaction of Clonidine to these sites causes activation of inwardly rectifying G protein gated potassium channel, which results in membrane hyperpolarization and decreases the firing rate of excitable cells in CNS. Clonidine also causes reduction of calcium conductance into cell thus inhibiting neurotransmitter release. These two mechanisms produce different ways of effective analgesia [2].

The antinociceptive effect produced by orally administered alpha2adrenergic agonists is mainly caused by direct spinal activation due to spread of drug via the systemic circulation into spinal cord as Clonidine is highly lipid soluble and crosses tissue barrier rapidly [10].

Study shows that blood pressure decreases more in hypertensive patients than in normotensive patients.

Clonidine decreases salivary secretion which causes dryness of mouth and it may be uncomfortable in some cases [2].So, whenever clonidine is used as oral premedication and when antisialogue effect is not desired, one can avoid antisialogue drugfor premedication.

Impaired autonomic thermoregulation during neuroaxial anesthesia results in intra operative core hypothermia, which finally decreases the vasoconstriction and shivering thresholds. Thus, shivering is a very common event during spinal anesthesia.

How Clonidine arrests shivering is unclear, but it was believed that Clonidine acts on the central thermoregulatory centers mainly rather than peripheral and there by prevents shivering[16].

Mao CC et al in their study found that premedication with 150mcg Clonidine is effective to prevent post spinal shivering during30 minutes, immediately after spinal anesthesia [12].

CONCLUSION

We concluded that 150 mcg oral Clonidine given 60 minutes before institution of spinal anesthesia with bupivacaine heavy 0.5% produces significant prolongation of sensory and motor block, sedation and adequate post-operative analgesia and also decreases the post spinal shivering with minimal hemodynamic disturbances.

Though intrathecally administered Clonidine provides best results Clonidine can be used orally as an adjunct to Bupivacaine spinal anesthesia where intrathecal preparation of Clonidine is not available.

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